Efficacy of venlafaxine extended release in major depressive disorder patients: effect of baseline anxiety symptom severity

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Effects of baseline anxiety on the efficacy of venlafaxine extended release versus placebo were examined in a post hoc pooled subgroup analysis of 1573 patients enrolled in eight short-term studies of major depressive disorder. Anxiety subgroups were defined based on baseline 17-item Hamilton Rating Scale for Depression Item 10 score <3 (low) versus ≥3 (high). Change from baseline to final visit in Montgomery–Åsberg Depression Rating Scale total score and Montgomery–Åsberg Depression Rating Scale response and remission rates were analyzed. Change from baseline in Montgomery–Åsberg Depression Rating Scale total score and response and remission rates was significantly greater for venlafaxine extended release versus placebo in both low and high anxiety subgroups (all $P < 0.0001$). A statistically significant baseline anxiety by treatment interaction was observed for Montgomery–Åsberg Depression Rating Scale total score only ($P = 0.0152$). The adjusted mean change from baseline in Montgomery–Åsberg Depression Rating Scale total score was significantly greater in the high anxiety subgroup versus low anxiety subgroup for patients treated with venlafaxine extended release (−6.27 versus −3.89; $P = 0.0440$) but not placebo. These results support the efficacy of venlafaxine extended release for major depressive disorder treatment in patients with anxiety symptoms. *Int Clin Psychopharmacol* 34: 110–118 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Symptoms of anxiety are common in patients with major depressive disorder (MDD) (Fava *et al.*, 2008; Wiethoff *et al.*, 2010). A recent review reported rates of co-occurring anxiety in depressed patients as high as 78% (Gaspersz *et al.*, 2018). The prevalence of current or lifetime comorbid anxiety disorders is estimated at 51–57% in outpatients with depression (Fava *et al.*, 2000; Zimmerman *et al.*, 2002a). Anxious depression has been associated with a greater severity of illness, longer duration of illness, increased incidence of suicidal thoughts or behaviors, and more severe functional impairment compared with non-anxious depression (Altamura *et al.*, 2004; Fava *et al.*, 2006; Wiethoff *et al.*, 2010), and MDD patients with comorbid anxiety at baseline are likely to have poorer clinical outcomes than those without anxious symptoms (Souery *et al.*, 2007; Fava *et al.*, 2008; Gaspersz *et al.*, 2018).

Although antidepressant medications have generally similar efficacy within and between classes when used to treat depression (Gelenberg *et al.*, 2010), and a range of antidepressant drugs have been shown to be effective in treating depression with anxiety (Tollefson *et al.*, 1994; Bandelow *et al.*, 2007; Nelson, 2010; Kornstein *et al.*, 2014; Stein *et al.*, 2013), several studies suggest that there may be efficacy differences among drugs in MDD patients with symptoms of anxiety. For example, in analyses of depressed patients with high levels of anxiety symptoms at baseline, patients treated with selective serotonin reuptake inhibitors (SSRIs) had greater response rates than in those treated with bupropion (Papakostas *et al.*, 2008), and patients treated with the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine (extended release or immediate release) had significantly greater rates of remission compared with patients treated with fluoxetine (Davidson *et al.*, 2002).

The antidepressant venlafaxine extended release has demonstrated efficacy for treating both MDD (Thase *et al.*, 2017) and anxiety disorders in double-blind, placebo-controlled clinical trials (Rickels *et al.*, 2000; Davidson *et al.*, 1999; Allgulander *et al.*, 2004b) and is approved for the treatment of generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder in addition to MDD (Effexor package insert, 2017). Venlafaxine extended release also significantly improves symptoms of depression in MDD patients with comorbid anxiety (Silverstone and Ravindran, 1999; Silverstone and

Salinas, 2001); however, results of anxiety subgroup analyses based on clinical trial data for other antidepressant drugs have suggested that antidepressant efficacy may be reduced in MDD patients with high baseline anxiety compared with patients with lower anxiety (Joliat *et al.*, 2004; Fava *et al.*, 2008; Wiethoff *et al.*, 2010; Papakostas *et al.*, 2012). This has not previously been examined with venlafaxine extended release in patients treated for MDD. The objective of this analysis was to determine the effect of baseline anxiety symptoms on improvement in depression symptoms in MDD patients treated with venlafaxine extended release or placebo. We therefore conducted a post hoc meta-analysis of data from eight clinical trials of venlafaxine extended release versus placebo for the treatment of MDD.

Methods
Data set
Patient-level data were pooled from eight short-term (6–12 weeks), randomized, placebo-controlled studies of venlafaxine extended release for the treatment of MDD. This data set includes all available short-term, Wyeth/Pfizer sponsored phase II, III, or IV, double-blind, placebo-controlled studies in adult patients with MDD that included at least one venlafaxine extended release treatment arm and that administered the Hamilton Rating Scale for Depression (HAM-D) at baseline and included a change from baseline in Montgomery–Åsberg Depression Rating Scale (MADRS) score as an efficacy outcome. Study characteristics are listed in Table 1. Venlafaxine extended release dose ranged from 75 to 375 mg/day. Six studies used flexible dosing, one used fixed dosing, and one included fixed- and flexible-dose arms. Five of the studies included an active control treatment arm and one included a venlafaxine immediate release arm; only data from venlafaxine extended release and placebo arms were included in the analysis.

Protocols and any amendments received Institutional Review Board/Ethics Committee approval before the study began, and all patients were required to provide written informed consent prior to enrollment.

Patients
All eight studies included in the post hoc analysis enrolled adult outpatients (≥18 years; ≥20 years for one study) who met *Diagnostic and Statistical Manual of Mental Disorders* (DSM; Third Edition-Revised, Fourth Edition, or Fourth Edition-Text Revision) (American Psychiatric Association, 1987; American Psychiatric Association, 1994; American Psychiatric Association, 2000) criteria for major depression, severe depression, or MDD. Enrolled patients had symptoms of depression of at least 30 days duration and a $HAM-D_{21}$ total score of 20 or greater [or MADRS total score ≥ 27 (1 study)] at screening and baseline. The HAM-D total score was calculated as the sum of items 1–17 (Hamilton, 1960), equivalent to the

17-item HAM-D ($HAM-D_{17}$) total score. HAM-D items 18–21 were not scored or considered in the current analysis. Exclusion criteria were designed to select a sample of medically stable patients with a principal diagnosis of MDD (excluding bipolar and psychotic depression). Patients with recent treatment with the study drug, a history of drug or alcohol dependence within a year of study entry, or acute suicidality were also excluded.

Measures
The measure of efficacy in this analysis was change from baseline in MADRS total score at last visit (last observation carried forward). Other outcomes assessed were rate of response, defined as at least 50% reduction from baseline in MADRS total score, and rate of remission (MADRS total score ≤ 10) at the last visit.

Baseline anxiety symptoms were assessed using the HAM-D psychic anxiety item (item 10), scored from 0 (no difficulty) to 4 (fears expressed without questioning). Subgroups were defined using a HAM-D item 10 threshold score of 3 (low anxiety < 3; high anxiety ≥ 3), which has been used as a proxy for one of the criterion symptoms ('Fear that something awful may happen') for DSM (5th Edition; DSM-5) depressive disorder with anxious distress (McIntyre *et al.*, 2016; American Psychiatric Association, 2013). Analyses were also conducted using two additional definitions for baseline anxiety subgroups; one based on the HAM-D item 11 (somatic anxiety) score, scores from 0 (absent) to 4 (incapacitating), and another based on the HAM-D anxiety/somatization factor score (sum of HAM-D items 10, 11, 12, 13, 15, and 17), which incorporates both psychic and somatic anxiety symptoms (Cleary and Guy, 1977). Somatic anxiety subgroups were defined using a baseline HAM-D item 11 threshold value of 3 (low anxiety < 3; high anxiety ≥ 3), as was used for HAM-D item 10. HAM-D anxiety/somatization score subgroups were defined using less than 7 (low anxiety) versus 7 or greater (high anxiety) as described previously (Tollefson *et al.*, 1993).

Statistical analysis
Statistical analyses were based on the full analysis set (FAS), defined as all patients in the pooled studies who took at least 1 dose of the study drug during the double-blind treatment period. To examine the effect of baseline anxiety symptoms on venlafaxine extended release efficacy, change from baseline in MADRS total score was analyzed using an analysis of covariance model with terms for study, treatment group, baseline anxiety subgroup (low versus high), interaction of treatment group by baseline anxiety subgroup, and baseline MADRS total score. Binary end points (MADRS response and remission rates) were analyzed using logistic regression models with terms for study, treatment group, baseline anxiety subgroup, treatment group by baseline anxiety subgroup interaction, and baseline MADRS total score.

Table 1 Studies included in the pooled analysis

Study number	N	Treatment arms	Duration	Study design
0600B-208 (Cunningham, 1997)	293	Placebo Venlafaxine extended release 75 or 150 mg/day Venlafaxine immediate release 75 or 150 mg/day	12 weeks	Flexible-dose, double-blind, placebo-controlled study in adult outpatients with major depression
0600B-209 (Thase, 1997)	197	Placebo Venlafaxine extended release 75–225 mg/day	8 weeks	Flexible-dose, double-blind, placebo-controlled study in adult outpatients with major depression
0600B-367 (Salinas for the Venlafaxine XR 367 Study Group, 1997)	329	Placebo Venlafaxine extended release 75 mg/day Venlafaxine extended release 150 mg/day Paroxetine 20 mg/day	8 weeks	Fixed-dose, double-blind, placebo-controlled study in adult outpatients with MDD
0600B1-211 (Rudolph and Feiger, 1999)	301	Placebo Venlafaxine extended release 75–225 mg/day Fluoxetine 20–60 mg/day	8 weeks	Flexible-dose, double-blind, placebo-controlled study in adult outpatients with MDD
0600B1-384[a]	425	Placebo Venlafaxine extended release 150–375 mg/day Imipramine 50–200 mg/day	6 weeks	Double-blind, placebo-controlled comparative efficacy study of the time of onset of antidepressant response in patients with severe MDD
0600B1-402[b]	688	Placebo Venlafaxine extended release 75–300 mg/day Sertraline 50–200 mg/day	10 weeks	Double-blind, placebo-controlled comparative efficacy study of remission in outpatients with MDD
0600B1-414[c]	697	Placebo Venlafaxine extended release 75–300 mg/day Sertraline 50–200 mg/day	10 weeks	Double-blind, placebo-controlled comparative efficacy study of remission in outpatients with MDD
B2411263 (Higuchi et al, 2016)	537	Placebo Venlafaxine extended release 75 mg/day Venlafaxine extended release 75–225 mg/day	8 weeks	Randomized, double-blind, placebo-controlled, efficacy and safety study in adult outpatients with MDD

N indicates the number of patients who received at least one dose of study medication in each study in the FAS.

FAS, full analysis set; MDD, major depressive disorder.

[a]Unpublished report – Wyeth-Ayerst USA. A double-blind, placebo-controlled, comparative study of an extended release formulation of venlafaxine and imipramine on the time of onset of antidepressant response in patients with severe major depression: Final report (Protocol 600B1-384-US/EU/CA). 12-9-2002.

[b]Unpublished report – Wyeth Research, Philadelphia. A double-blind, placebo-controlled, comparative efficacy study of venlafaxine ER and sertraline in producing remission in outpatients with major depressive disorder: Final report (Protocol 0600B1-402-US/CA). 28-5-2003.

[c]Unpublished report – Wyeth Research, Philadelphia. Final report: a double-blind, placebo-controlled, comparative efficacy study of venlafaxine ER and sertraline in producing remission in outpatients with major depressive disorder (Protocol 0600B1-414-US). 26-6-2009.

Table 2 Baseline demographics and clinical characteristics by treatment and baseline anxiety subgroup,[a] full analysis set

Characteristic	Venlafaxine extended release		Placebo	
	Low anxiety (n = 1093)	High anxiety (n = 480)	Low anxiety (n = 560)	High anxiety (n = 271)
Age, years				
Mean (SD)	40.7 (12.45)	41.4 (12.69)	40.2 (11.58)	42.0 (12.71)
Sex, n (%)				
Female	649 (59)	298 (62)	342 (61)	167 (62)
Male	444 (41)	182 (38)	218 (39)	104 (38)
Duration of current depressive episode (weeks)				
Mean (SD)	75.3 (163.18)	49.0 (119.40)	98.4 (199.78)	81.1 (199.21)
CGI-Severity, n (%)				
Mildly ill	11 (1.0)	7 (1.5)	4 (0.7)	3 (1.1)
Moderately ill	722 (66.1)	177 (36.9)	396 (70.7)	109 (40.2)
Markedly ill	289 (26.4)	222 (46.3)	133 (23.8)	109 (40.2)
Severely ill	68 (6.2)	70 (14.6)	27 (4.8)	47 (17.3)
Among the most extremely ill patients	0	2 (0.4)	0	0
HAM-D$_{17}$ total score at baseline				
Mean (SD)	22.1 (3.35)	25.2 (3.89)	21.8 (3.19)	24.9 (3.90)
MADRS total score at baseline				
Mean (SD)	29.5 (5.34)	32.2 (5.90)	29.0 (5.25)	31.8 (5.93)

CGI, Clinical Global Impressions; HAM-D$_{17}$, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale.

[a]Subgroups based on HAM-D item 10 score: low anxiety, <3; high anxiety, ≥3.

All analyses based on HAM-D item 10 and 11 subgroups were repeated using a cutoff of 2. Only results for subgroups based on less than 3 and at least 3 were reported, as results using the different threshold values were similar.

Results

The FAS included 2405 patients; 1573 patients were treated with venlafaxine extended release and 832 were treated with placebo. The majority of patients were white (69.1%) and

female (60.5%). At baseline, patients had a median age of 40.0 years (range: 18–85 years) and their severity of depression was generally moderate to severe (Table 2). Mean daily venlafaxine extended release dose was 143.5 mg/day (median: 143.9 mg/day; range: 37.5–471.7 mg/day).

HAM-D item 10 subgroup analysis

The distribution of HAM-D item 10, psychic anxiety scores at baseline is shown in Fig. 1. A total of 751/2405
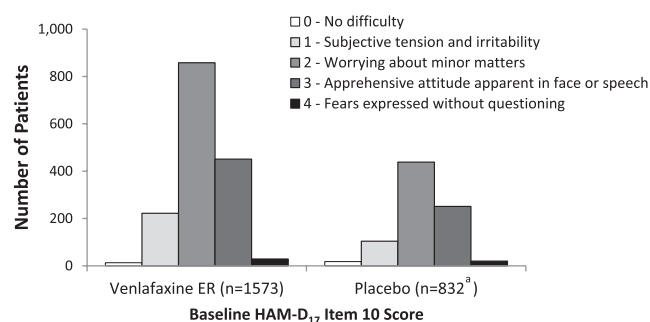
Distribution of HAM-D item 10 scores at baseline. [a]One patient assigned to placebo had missing HAM-D item score at baseline. HAM-D$_{17}$, 17-item Hamilton Rating Scale for Depression.

Change from baseline to final visit in MADRS total score, HAM-D item 10 anxiety subgroups. Low baseline anxiety, HAM-D item 10 score < 3; high baseline anxiety, HAM-D item 10 score ≥ 3. HAM-D$_{17}$, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; SE, standard error.

(31.2%) patients had a baseline HAM-D item 10 anxiety score greater than three and were included in the high baseline anxiety subgroup. Baseline mean MADRS total scores were 29.4 (venlafaxine extended release) and 28.9 (placebo) for patients in the low baseline anxiety subgroup and 32.0 (venlafaxine extended release) and 31.7 (placebo) for those with high baseline anxiety symptoms.

A statistically significant effect of interaction between baseline anxiety subgroup and treatment was observed (P = 0.0152). Venlafaxine extended release showed a significantly greater improvement from baseline in MADRS total score at final visit compared with placebo for both low and high baseline anxiety subgroups (both P < 0.0001; Fig. 2) based on HAM-D item 10 score. Among patients treated with venlafaxine extended release, those with high baseline anxiety (HAM-D item 10 scores ≥ 3) had greater improvement from baseline in MADRS total score at final visit (adjusted mean change [standard error], –16.98 [0.51]) compared with the low baseline anxiety subgroup (–15.76 [0.35]; P = 0.0440). However, no significant difference was found between baseline anxiety subgroups in improvement with placebo treatment (low, –11.87 [0.46]; high, –10.71 [0.65]).

The test of interaction between treatment and baseline anxiety for MADRS response yielded a P value of 0.0616. Significantly, higher rates of MADRS response were observed at final visit for venlafaxine extended release versus placebo in both low and high baseline anxiety subgroups (low anxiety, 58.9% versus 40.5%; high anxiety, 64.2% versus 36.9%; both P < 0.0001; Fig. 3a). The adjusted odds ratio (OR) of MADRS response between venlafaxine extended release versus placebo was 2.02 (95% confidence interval [CI]: 1.61, 2.52) for the low anxiety subgroup and 2.94 (95% CI 2.11, 4.09) for the high anxiety subgroup. For patients receiving venlafaxine extended release, the probability of achieving MADRS response was significantly greater for patients with high baseline anxiety versus low baseline anxiety (OR: 1.31
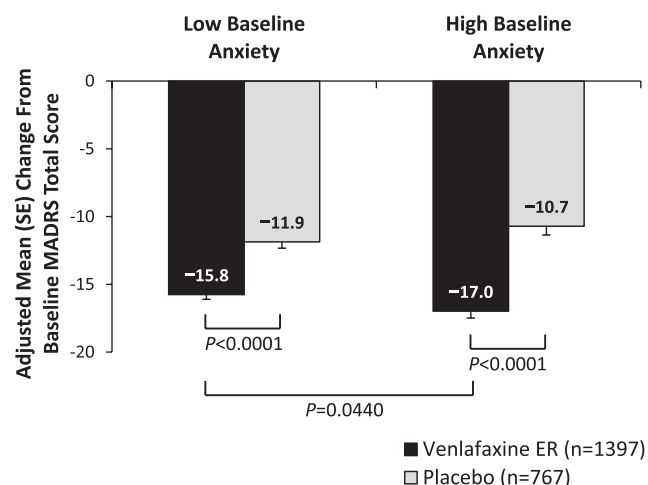
[95% CI: 1.02, 1.68]; P = 0.0318). Among those receiving placebo, MADRS response rates, however, were not found to be significantly different for low versus high anxiety subgroups (OR: 0.90 [95% CI: 0.65, 1.24]).

The effect of interaction between treatment and baseline anxiety was not statistically significant in the analysis of MADRS remission (P = 0.2865), allowing for an interpretation of the overall effects of treatment group and baseline anxiety subgroup. Overall, significantly higher proportions of patients treated with venlafaxine extended release versus placebo achieved MADRS remission at final visit (P < 0.0001; low baseline anxiety subgroup: 45.8 versus 28.3%, OR: 2.19 [95% CI: 1.72, 2.78]; high baseline anxiety subgroup: 48.7 versus 26.2%, OR: 2.76 [95% CI: 1.93, 3.93]; Fig. 3b). Rates of remission were numerically higher for patients with high versus low baseline anxiety treated with venlafaxine extended release, but the odds of achieving remission did not differ significantly between baseline anxiety groups treated with either venlafaxine extended release (OR: 1.27 [0.99, 1.63]) or placebo (OR: 1.01 [0.71, 1.44]).

HAM-D anxiety/somatization factor and HAM-D item 11 subgroup analyses

A greater proportion of patients (1554/2405 [64.6%]) were defined as having high baseline anxiety based on HAM-D anxiety/somatization factor score (≥7) compared with the HAM-D item 10 score definition. A total of 263/2405 (10.9%) patients were categorized as having high baseline somatic anxiety using a baseline HAM-D item 11 score cutoff of three or greater.

Fig. 3
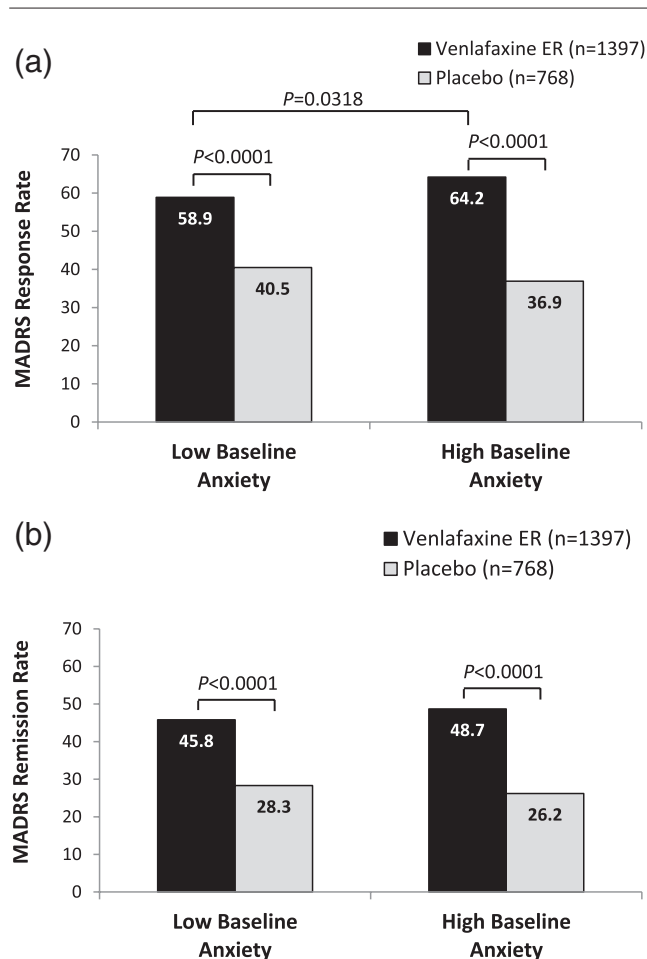
MADRS response (a) and remission (b) rates at final visit, HAM-D item 10 anxiety subgroups. Low baseline anxiety, HAM-D item 10 score < 3; high baseline anxiety, HAM-D item 10 score ≥ 3. (a) MADRS response. Response was defined as reduction from baseline of ≥50% in MADRS total score. (b) MADRS remission. Remission was defined as MADRS total score ≤ 10. ER, extended release; HAM-D$_{17}$, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale.

Venlafaxine extended release was associated with significantly greater improvement from baseline in MADRS total score and significantly higher rates of response and remission compared with placebo for low and high baseline anxiety subgroups based on either baseline HAM-D anxiety/somatization factor score or baseline HAM-D somatic anxiety (item 11) score (all $P \leq 0.0087$; Table 3). When baseline anxiety subgroups were defined based on HAM-D anxiety/somatization factor score, the probability of achieving MADRS remission was significantly lower for patients with high baseline anxiety compared with those with low baseline anxiety among patients receiving venlafaxine extended release (OR: 0.73 [95% CI: 0.58, 0.93]; $P = 0.0096$), but not among patients in the placebo group. No other significant differences between low and high anxiety subgroups were observed using either definition.

The tests for interactions between treatment and anxiety subgroup based on either definition (HAM-D anxiety/somatization factor score or HAM-D item 11) were not significant for any efficacy measure (Table 3).

Discussion

In this pooled, post hoc analysis of data from eight short-term, placebo-controlled clinical trials, treatment with venlafaxine extended release (75–375 mg/day) significantly reduced symptoms of depression in MDD patients regardless of the level of anxiety at baseline. A significant treatment effect on MADRS total score was observed in both low and high anxiety subgroups based on psychic anxiety symptoms (HAM-D item 10 score < or ≥3) at baseline. Odds of achieving response or remission were significantly higher for patients treated with venlafaxine extended release versus placebo, for low and high psychic anxiety subgroups. Among patients treated with venlafaxine extended release – but not placebo – patients with high baseline anxiety based on HAM-D item 10 score had significantly greater improvement from baseline in MADRS total score at final visit. That finding was supported by the significantly greater probability of achieving MADRS response compared with the low baseline anxiety subgroup; the effect of baseline anxiety on remission rates in venlafaxine extended release-treated patients approached significance.

In both low and high somatic anxiety symptom subgroups, based on baseline HAM-D item 11 score, venlafaxine extended release treatment was associated with significantly higher rates of response and remission versus placebo. However, no effect of baseline somatic anxiety was observed. Differences between psychic and somatic symptoms of anxiety in response to treatment previously have been noted in the literature: several studies reported greater improvement in psychic symptoms than somatic anxiety symptoms with SSRI/SNRI treatment in GAD or MDD patients (Rocca *et al.*, 1997; Allgulander *et al.*, 2004a; Dahl *et al.*, 2005; Davidson *et al.*, 2008; Russell *et al.*, 2007; Bandelow *et al.*, 2007). It should be noted that those studies measured improvement in psychic versus somatic anxiety symptoms, but did not examine improvement in total depression score in patients with psychic versus somatic anxiety. The effectiveness of HAM-D approaches to identify patients with anxious depression has been recently examined. A kappa coefficient analysis demonstrated only a modest (but significant) concordance between HAM-D anxiety/somatization factor scores and DSM-5 anxious distress specifier criteria; HAM-D item 10 or 11 scores were not similarly assessed (Zimmerman *et al.*, 2018). Observed differences in outcomes in analyses based on different anxiety subgroup definitions do not necessarily indicate that one definition is more accurate or applicable than others, however. Rather, the current results suggest that definitions for high baseline anxiety based on psychic vs.

Table 3 Results based on alternate anxiety subgroup definitions, full analysis set

	Venlafaxine extended release (N = 1573)	Placebo (N = 832)	P value
HAM-D anxiety/somatization factor score[a] subgroups			
Change from baseline, MADRS total score (adj. mean [SE])			
HAM-D anxiety/somatization score < 7	−16.30 (0.49)	−11.94 (0.62)	<0.0001
HAM-D anxiety/somatization score ≥ 7	−16.06 (0.35)	−11.25 (0.46)	<0.0001
Low versus high baseline anxiety (adj. mean difference [95% CI]; P value)	0.24 (−0.92, 1.40); 0.6831	0.69 (−0.83, 2.21); 0.3729	
Treatment by baseline anxiety interaction			0.6376
MADRS response, %			
HAM-D anxiety/somatization score < 7	62	40	<0.0001
HAM-D anxiety/somatization score ≥ 7	60	39	<0.0001
High versus low baseline anxiety (adj. OR [95% CI]; P value)	0.88 (0.70, 1.12); 0.3034	0.89 (0.65, 1.21); 0.4610	
Treatment by baseline anxiety interaction			0.9681
MADRS remission, %			
HAM-D anxiety/somatization score < 7	51	28	<0.0001
HAM-D anxiety/somatization score ≥ 7	44	27	<0.0001
High versus low baseline anxiety (adj. OR [95% CI]; P value)	0.73 (0.58, 0.93); 0.0096	0.93 (0.66, 1.30); 0.6614	
Treatment by baseline anxiety interaction			0.2539
HAM-D item 11 score subgroups			
Change from baseline, MADRS total score (adj. mean [SE])			
HAM-D item 11 score < 3	−16.14 (0.31)	−11.67 (0.39)	<0.0001
HAM-D item 11 score ≥ 3	−16.15 (0.84)	−10.06 (1.14)	<0.0001
Low versus high baseline anxiety (adj. mean difference [95% CI]; P value)	−0.01 (−1.77, 1.75); 0.9899	1.61 (−0.76, 3.98); 0.1820	
Treatment by baseline anxiety interaction			0.2721
MADRS response, %			
HAM-D item 11 score < 3	60	40	<0.0001
HAM-D item 11 score ≥ 3	62	37	0.0017
High versus low baseline anxiety (adj. OR [95% CI]; P value)	1.04 (0.73, 1.50); 0.8136	0.94 (0.58, 1.53); 0.8119	
Treatment by baseline anxiety interaction			0.7358
MADRS remission, %			
HAM-D item 11 score < 3	46	27	<0.0001
HAM-D item 11 score ≥ 3	51	30	0.0087
High versus low baseline anxiety (adj. OR [95% CI]; P value)	1.24 (0.86, 1.78); 0.2415	1.32 (0.78, 2.23); 0.3065	
Treatment by baseline anxiety interaction			0.8538

CI, confidence interval; HAM-D$_{17}$, 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery–Åsberg Depression Rating Scale; OR, odds ratio; SE, standard error.
[a]HAM-D anxiety/somatization score is defined as a sum of HAM-D$_{17}$ items 10, 11, 12, 13, 15, and 17.

somatic symptoms capture different subsets of patients who may respond differentially to venlafaxine extended release treatment. Interestingly, in the current analysis of subgroups defined based on the HAM-D anxiety/somatization factor, which combines both psychic and somatic anxiety symptoms scores (Cleary and Guy, 1977), there was a statistically significant effect of baseline anxiety on likelihood of remission in venlafaxine extended release-treated patients, but no effect on improvement from baseline in MADRS total score or on MADRS response.

The significantly greater effect of venlafaxine extended release in patients with high versus low baseline psychic anxiety reported here is in contrast with results of several previously published analyses, in which high levels of anxiety in MDD patients were associated with poor response to medication (Joliat et al., 2004; Fava et al., 2008; Wiethoff et al., 2010; Papakostas et al., 2012). Each of those analyses defined baseline anxiety subgroups using the HAM-D anxiety/somatization factor score. In contrast, in an analysis that used psychic anxiety symptoms to define baseline anxiety subgroups, duloxetine treatment significantly improved symptoms of depression in the high anxiety group (baseline HAM-D item 10 score ≥ 2) but not in the low anxiety group (Russell et al., 2007). Subgroups based on somatic anxiety symptoms were not examined. Other analyses showed no

difference in antidepressant efficacy outcome based on improvement in depression scale scores or remission rate in low versus high anxiety subgroups (Farabaugh et al., 2010; Nelson, 2010).

Clinical practice guidelines support the use of SSRIs or SNRIs as first-line antidepressant treatment of MDD with anxious symptoms (Schaffer et al., 2012). The Canadian Network for Mood and Anxiety Treatments guidelines recommend the use of an antidepressant with efficacy for GAD in MDD patients with anxious distress, including SSRIs and SNRIs (Kennedy et al., 2016). Several SSRIs/SNRIs in addition to venlafaxine extended release have demonstrated efficacy versus placebo for treating symptoms of depression in low and high baseline anxiety subgroups using the HAM-D anxiety/somatization factor score. Fluoxetine improved symptoms of depression, based on 21-item HAM-D total score, compared with placebo in both anxious and nonanxious depressed patients (Tollefson et al., 1994). Duloxetine had significantly greater efficacy for treating depression compared with placebo in both anxious and nonanxious patients, based on response, remission, and depression scale scores (Nelson, 2010). Desvenlafaxine treatment was associated with significantly greater improvement from baseline in HAM-D$_{17}$ total score, and significantly higher rates of HAM-D response and remission compared with placebo

in low and high anxiety groups (Kornstein *et al.*, 2014), although it has never formally been studied or approved for any anxiety indication.

Studies suggest that the majority of patients diagnosed with MDD have symptoms of anxiety or a comorbid anxiety disorder (Fava *et al.*, 2000; Zimmerman *et al.*, 2002a; Fava *et al.*, 2008; Wiethoff *et al.*, 2010; Gaspersz *et al.*, 2018). Clinicians are well aware of the need to address anxiety symptoms in depressed patients: severe anxiety in such patients may be associated with suicidality (Allgulander, 2000) and cardiovascular disease (Allgulander, 2016). Prospective studies of population samples and of patients with cardiovascular disease point to the emergence of anxiety driving other well-known risk factors such as sedentary lifestyle, tobacco smoking, and depression (Allgulander, 2016). Therefore, assessment for and effective treatment of anxiety in MDD is critical. The observed efficacy of venlafaxine extended release in MDD patients with either low or high levels of anxiety at baseline is not unexpected, as it is approved for the treatment of several anxiety disorders. Nonetheless, given the high comorbidity of major depression with anxiety symptoms, this is a reassuring result for clinicians treating patients with both depression and strong anxiety symptoms, and underscores that venlafaxine extended release is an effective therapeutic option for those patients. Furthermore, patients with GAD may present with depression in primary care settings where clinicians may be less likely to diagnose a primary anxiety disorder (Bandelow *et al.*, 2013; Roberge *et al.*, 2015). From a pragmatic point, the results of this analysis indicate that venlafaxine extended release can be valuable in patients with anxiety and depression treated in settings that cannot offer a qualified diagnostic procedure for the anxiety disorder. On the basis of the results of this meta-analysis, physicians can expect venlafaxine extended release to be effective in depressed patients in both primary and tertiary care settings with and without anxiety symptoms.

Although specific changes to treatment of MDD are not recommended for patients with anxious depression as a group (Schaffer *et al.*, 2012), the APA clinical practice guideline suggests that some patients with prominent anxiety may need adjunctive treatment with an anxiolytic or sedative-hypnotic medication (e.g. buspirone, benzodiazepines, or selective γ-aminobutyric acid agonists) (Gelenberg *et al.*, 2010). In the authors' experience, it may be beneficial to coprescribe an anxiolytic while titrating an effective antidepressant dose, usually for 2–4 weeks. While patients with depression often have periods when they are well, symptoms of GAD are chronic and thus may require maintenance therapy (Bandelow *et al.*, 2013; Roberge *et al.*, 2015). Indeed, treatment guidelines recommend maintenance therapy in MDD patients with factors associated with anxiety, including comorbid disorders and risk of suicide (Gelenberg *et al.*, 2010; Lam

et al., 2016). Anxiety Disorders Association of Canada guidelines cite benefits of maintenance therapy with SSRIs/SNRIs, whereas long-term treatment with benzodiazepines is not recommended (Katzman *et al.*, 2014).

Several limitations of the current analysis should be considered in the discussion of results. First, this was a post hoc analysis of data from clinical trials that were not designed to assess the effect of anxiety symptoms, and individual HAM-D items have not been validated as measures separate from their use in the scale. Few randomized controlled trials of venlafaxine extended release for MDD utilize in-depth assessments of anxiety such as the Hamilton Anxiety Rating Scale (Hamilton, 1959) (HAM-A); the HAM-A was administered in only one trial included in this analysis. Therefore, the HAM-D psychic anxiety item (item 10) was selected as an indicator of anxious symptoms for this analysis, with the somatic anxiety item (item 11) and the anxiety/somatization factor included for comparison. Definitions based on each of the three measures have been used in the published literature to characterize the severity of baseline anxiety symptoms (Nelson, 2010). An additional limitation of the analysis was that the eight pooled trials differed in their enrolled populations based on enrollment criteria and varied in aspects of their design, including the use of fixed versus flexible dosing, dosages assessed, and trial duration. Three of the studies in this analysis were flexible-dose trials that allowed venlafaxine extended release doses exceeding the recommended therapeutic dose range; however, the median daily venlafaxine extended release dose was 143.9 mg (mean: 143.5 mg). In each trial, generally healthy patients with few comorbidities were selected for enrollment; therefore, results may not generalize to a broader population of MDD patients (Zimmerman *et al.*, 2002b). Finally, it is important to note that the efficacy end points used in this analysis included depression measures only. Improvement in anxiety symptoms was not determined, and therefore, these results do not address the efficacy of venlafaxine extended release for treating anxiety symptoms in MDD patients.

Conclusion

The results of this meta-analysis of eight short-term, double-blind, placebo-controlled studies support the efficacy of venlafaxine extended release for the treatment of MDD in those patients with either low or high severity of anxiety symptoms at baseline. Patients with high baseline anxiety based on HAM-D item 10 score had significantly greater improvement from baseline in MADRS total score at final visit and a significantly greater probability of achieving MADRS response compared with the low baseline anxiety subgroup. All three end points assessed (change from baseline in MADRS total score, MADRS response, and MADRS remission rates) remained statistically significant for venlafaxine

extended release versus placebo when analyzed for the low or high anxiety subgroups.

Acknowledgements

Conflicts of interest

Gavin J. Lyndon is a full-time employee of Pfizer Ltd. and holds Pfizer stock and stock options. Rita Prieto is a full-time employee of Pfizer GEP SLU Spain and holds Pfizer stock and stock options. Dalia B. Wajsbrot is a full-time employee of Pfizer Inc and holds Pfizer stock and stock options. Christer Allgulander has no potential financial conflicts. In the last 36 months and in the near future, Borwin Bandelow will receive/has received speaker's honorarium from Hexal, Novartis, Janssen, Lilly, Lundbeck, and Pfizer, will serve or has served on an advisory board for Mundipharma, and will receive or has received publication honorarium from Servier.

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