A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder

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The efficacy, safety, and tolerability of desvenlafaxine (administered as desvenlafaxine succinate) were evaluated in two similarly designed, phase 3, randomized, double-blind, placebo-controlled, venlafaxine-extended-release-referenced, flexible-dose studies of outpatients with a primary diagnosis of major depressive disorder. Owing to a high placebo response, the individual studies were underpowered. Therefore, a post-hoc pooled analysis was performed (desvenlafaxine and placebo data were pooled; venlafaxine extended release data were not, owing to different flexible-dose regimens in the two studies). The primary outcome measure was the change from baseline on the 17-item Hamilton Rating Scale for Depression; the Clinical Global Impressions-Improvement item score was a secondary outcome. Analysis of the pooled data (using a mixed-effect model for repeated measures) revealed that after 8 weeks of treatment, desvenlafaxine was significantly better than placebo on 17-item Hamilton Rating Scale for Depression [−14.21 vs. −11.87 for desvenlafaxine and placebo, respectively; magnitude of effect = −2.34 ($P<0.001$)] and Clinical Global Impressions-Improvement item scores [1.95 vs. 2.32 for desvenlafaxine and placebo, respectively; magnitude of effect = −0.37 ($P<0.001$)]. Adverse events were comparable to those found with other drugs sharing a similar mechanism of action. These data support the efficacy, safety, and tolerability of desvenlafaxine in the treatment of major depressive disorder. *Int Clin Psychopharmacol* **23:188–197**

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Introduction

Depression, a common mental disorder, is a major cause of disability throughout the world, and a serious public health concern. Worldwide, more than 150 million people suffer from depression, and nearly 1 million commit suicide every year (World Health Organization, 2001). Even with treatment, a large percentage of patients, who receive currently available therapies, recover only partially, often with continued functional impairment owing to residual symptoms, underscoring the importance of and need for novel antidepressants (Steffens *et al.*, 1997; Thase *et al.*, 2001; Faravelli *et al.*, 2003; Segal *et al.*, 2003; Nelson *et al.*, 2004).

Desvenlafaxine (administered as desvenlafaxine succinate) is the major active metabolite of venlafaxine. Desvenlafaxine is an antidepressant that has been approved by the US Food and Drug Administration for the treatment of major depressive disorder (MDD). Desvenlafaxine is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants (with the exception of venlafaxine) and is classified as a dual-acting serotonin and norepinephrine reuptake inhibitor (SNRI) because preclinical studies have demonstrated that it inhibits the neuronal uptake of both serotonin and norepinephrine and, to a lesser degree, dopamine reuptake (Muth *et al.*, 1991; Clement *et al.*, 1998). It does not have any monoamine oxidase inhibitory activity, and shows virtually no affinity for rat brain muscarinic, cholinergic, H_1-histaminergic, or α_1-adrenergic receptors (Deecher *et al.*, 2006).

Desvenlafaxine has been examined in a series of preclinical in-vivo and in-vitro tests and has been found to be active in multiple models used to predict antidepressant activity (Alfinito *et al.*, 2006). Results of two phase 3 clinical trials showed that desvenlafaxine had significantly better efficacy compared with placebo based on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$) (Hamilton, 1960), the Clinical Global Impressions-Improvement Scale (CGI-I) (Guy, 1976), and the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) scores (Montgomery and Åsberg, 1979; DeMartinis *et al.*, 2007; Septien-Velez *et al.*, 2007).

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The two phase 3 studies discussed herein, which compared the antidepressant efficacy of desvenlafaxine and placebo in MDD, are the only studies that included venlafaxine extended release (ER) as a reference treatment. In retrospect, these studies were underpowered, largely owing to the high placebo response rate observed in both the studies. Therefore, to examine the efficacy of desvenlafaxine in an adequately powered analysis, the data from both of these studies were pooled *post hoc*. The results of the pooled analysis and the primary results of the individual studies are presented in this article.

Methods

Two similar studies were performed, one in Europe (EU) and one in the United States (US). Each was a double-blind, multisite, placebo-controlled, parallel-group, venlafaxine ER-referenced, flexible-dose trial designed to compare the antidepressant efficacy, safety, and tolerability of desvenlafaxine with placebo. The use of placebo was necessary to provide reliable scientific evidence of efficacy.

The studies were approved by an independent ethics committee or Institutional Review Board and were consistent with Principles of Good Clinical Practice and applicable regulatory requirements in each participating country. All participants provided written informed consent before enrollment.

Selection of study population

Men and women, outpatients 18–75 years of age with a primary diagnosis of MDD, based on a psychiatric interview using the 'Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition' (American Psychiatric Association, 1994) criteria, single or recurrent episode, without psychotic features, were eligible for study participation. At baseline and screening, patients were also required to have a minimum HAM-D_{17} score of 22 and score at least 2 on item one (depressed mood) of HAM-D_{17}, a Clinical Global Impressions-Severity (CGI-S) Scale (Guy, 1976) score of at least 4, and a Raskin Depression Scale (Raskin *et al.*, 1969) score greater than the Covi Anxiety Scale (Lipman, 1982) score.

The screening evaluation included a medical history and a psychiatric history. The modified Mini International Neuropsychiatric Interview was used as a secondary confirmation of the primary diagnosis of MDD and any comorbid psychiatric disorders that may have been present. Patients with comorbid substance use disorders were excluded; however, patients with comorbid generalized anxiety disorder, panic disorder, or social anxiety disorder were allowed to participate as long as MDD was the primary diagnosis. Patients at high risk for suicidal behaviors were excluded.

Dosing schedule

Following the screening period (6–14 days), eligible patients were randomly assigned to one of the treatment groups (desvenlafaxine, venlafaxine ER, or placebo) and received up to 8 weeks of treatment. Patients randomized to desvenlafaxine were treated with an initial target dose of 200 mg/day. Patients in the EU study were started on the initial target dose on day 1, whereas those in the US study received 4 days of 100 mg/day before reaching the target dose. Each study had an optional increase to 400 mg/day after day 28 or decrease back to 200 mg/day at any time, based on the investigator's judgment. At the end of the study, the patients underwent a taper period based on their final dose.

Venlafaxine ER was used as an active control. In the EU study, patients assigned to venlafaxine ER received 75 mg/day for 28 days, with an optional increase to 150 mg/day after day 28, based on the investigator's judgment. In the US study, patients received a daily dose of 75 mg/day for 4 days. This dose was increased to 150 mg/day on day 5, and there was an optional increase to 225 mg/day after day 28. At the end of the study period, the patients underwent a taper period based on their final dose.

Efficacy, safety, and tolerability evaluations

The primary efficacy measure was the HAM-D_{17} total score, ascertained at each visit. Secondary efficacy measures included the CGI-I score, the response rate as measured by a 50% or greater decrease in the score on the HAM-D_{17}, the percentage of patients in remission (HAM-D_{17} scores of 7 or less), MADRS total score, CGI-S score, the Visual Analog Scale-Pain Intensity (VAS-PI) (DeLoach *et al.*, 1998) overall pain and subscale scores, HAM-D_6 [Bech version (Bech *et al.*, 1975)] total score, Covi Anxiety Scale total score, and response rates on the CGI-I (score = 1 or 2).

Safety and tolerability were determined using the following assessments: monitoring of adverse events (AEs), discontinuation because of AEs, physical examination, standard 12-lead electrocardiogram, vital signs (weight, pulse, and blood pressure), and laboratory determinations (hematology, blood chemistry, and urinalysis).

Statistical methods

The study designs of the US and EU studies were similar with respect to duration of treatment, desvenlafaxine daily dose, and efficacy measures; the dosing schedules of venlafaxine ER were different. In both the studies, desvenlafaxine was dosed from 200 to 400 mg/day, whereas the venlafaxine ER dosing was 75–150 mg/day in the EU study and 150–225 mg/day in the US study. The flexible dosing schedule of desvenlafaxine and placebo data allowed for pooling. However, the venlafax-

ine ER dosing schedule was lower in the EU study (75–150 mg/day) than in the US study (150–225 mg/day). Therefore, the venlafaxine ER data were not pooled and are presented as two groups, allowing for a four-arm, pooled analysis. As each study was designed to compare desvenlafaxine with placebo, the differences in the dosing of the active control did not affect the data analysis of the efficacy of desvenlafaxine.

All efficacy analyses were based on the intent-to-treat (ITT) population, or efficacy population, which consisted of all randomized patients who had a baseline primary evaluation, who took at least one dose of study drug, and who had at least one primary efficacy evaluation after the first dose of the study drug. Safety and tolerability analyses were based on the safety and tolerability population, which included all randomized patients who had taken at least one dose of the study drug.

Pooled analysis

Longitudinal changes from baseline on pooled data for the primary efficacy measure (HAM-D_{17} total) and the secondary measures (CGI-I, CGI-S, MADRS, HAM-D_6 total, Covi Anxiety Scale, and VAS-PI) were analyzed using a mixed-effect model for repeated measures (MMRM) analysis. For the MMRM analysis, the change from baseline on the respective scale (except for CGI-I) was analyzed as the outcome variable. An autoregressive first order [AR(1)] correlation structure was used to model the within correlation, with treatment groups, weeks, and the treatment-group-by-week interaction as fixed factors, center as a random factor, and baseline as a covariate. For the CGI-I, the score on the CGI-I Scale was used as the outcome. Changes from baseline to end point for secondary outcomes were also analyzed with an analysis of covariance (ANCOVA) with terms of treatment and study (protocol) as factors and the baseline score as a covariate; last-observation-carried-forward (LOCF) and observed cases (OC) data were analyzed. A logistic regression model was used for binary outcome variables (response and remission measured by the HAM-D_{17} and CGI-I). Treatment effects were tested at a two-sided significance level of 0.05.

Analysis of individual studies

In the individual studies the primary efficacy measure, HAM-D_{17} total score, was evaluated using ANCOVA on changes from baseline with the treatment arm and site as the factors and baseline scores as the covariate. LOCF (primary analysis) and OC analyses were both performed. The CGI-I score was analyzed by using analysis of variance (ANOVA) with the treatment arm and site as the factors. Response and remission rates on the HAM-D_{17} were analyzed with the logistic regression model, with treatment and site as the factors and baseline score as a covariate.

Study patients

Disposition

A total of 738 patients were randomly assigned to treatment (250 to placebo, 239 to desvenlafaxine, 128 to venlafaxine ER 75–150 mg/day, and 121 to venlafaxine ER 150–225 mg/day). Eighteen patients had no data after baseline and were not included in the safety population. The remaining 720 patients, who completed the prestudy period and took the randomly assigned study drug under double-blind conditions, were included in the safety analyses. Seven patients of the safety population did not meet criteria for the ITT population, which included 713 patients (226 desvenlafaxine, 127 venlafaxine ER 75–150 mg/day, 115 venlafaxine ER 150–225 mg/day, and 245 placebo). There were 574 completers (166 desvenlafaxine, 108 venlafaxine ER 75–150 mg/day, 90 venlafaxine ER 150–225 mg/day, and 210 placebo).

Demographic and other baseline characteristics

Demographic and baseline clinical characteristics of the pooled ITT population were generally similar (Table 1). Reflecting the geographic differences between the two pooled studies, minor differences in demographic characteristics were seen among the patients. Individuals in the EU study had a lower mean weight than those in the US study, and a greater percentage of patients were non-Hispanic whites. As the magnitude of these differences was small, they did not interfere with the use of the pooled analysis. Mean baseline severity on the HAM-D_{17} ranged from 25.1 to 25.8 and did not show statistically significant differences between groups.

Results

Efficacy evaluations

Pooled analysis

In the pooled analyses using MMRM, a significant difference in HAM-D_{17} total scores between desvenlafaxine and placebo was observed at week 3 and was maintained throughout the treatment period (Fig. 1, Table 2). By the week 8 evaluation, the change from baseline in the HAM-D_{17} total score was -14.21 for desvenlafaxine versus -11.87 for placebo (magnitude of effect = -2.34; $P < 0.001$) (Fig. 2a). Both venlafaxine ER groups were significantly different from placebo at the week 8 evaluation (75–150 mg/day: -14.26, $P = 0.001$; 150–225 mg/day: -14.56, $P < 0.001$); the venlafaxine ER 75–150 mg/day group showed significant separation from placebo beginning at week 6, whereas the 150–225 mg/day dose of venlafaxine ER showed more rapid efficacy beginning at week 2 (Fig. 1).

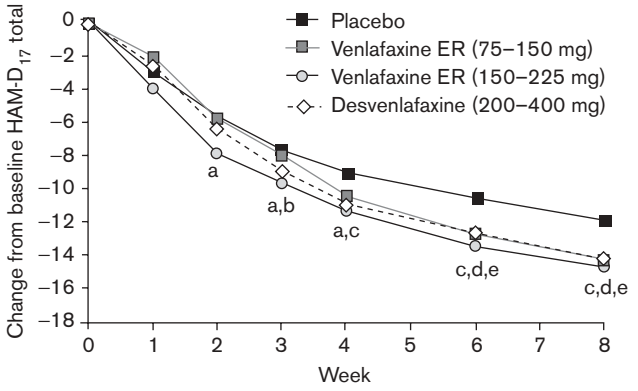
Statistically significant differences in CGI-I scores between desvenlafaxine and placebo were observed at week 8 (2.0 vs. 2.3; $P < 0.001$; MMRM analysis) (Fig. 2b); significant separation from placebo was also observed at weeks 3 (2.6 vs. 2.8; $P = 0.014$), 4 (2.3 vs. 2.7; $P < 0.001$), and 6 (2.1 vs. 2.4; $P < 0.001$). Both doses of venlafaxine

Table 1 Demographic and baseline characteristics: ITT pooled population

Characteristics	Placebo $n=245$	DVS 200–400 mg $n=226$	VEN ER 75–150 mg $n=127$	VEN ER 150–225 mg $n=115$
Age, mean (SD), years	42 (12)	43 (12)	46 (12)	42 (12)
Female, *n* (%)	160 (65)	153 (68)	92 (72)	80 (70)
Ethnicity/race, *n* (%)				
Non-Hispanic white	202 (82)	202 (89)	125 (98)	89 (77)
Weight, mean (SD), kg	80 (20)	77 (21)	72 (15)	83 (22)
Baseline HAM-D_{17}, total, mean (SD)	25.5 (2.8)	25.4 (2.9)	25.8 (3.0)	25.1 (2.4)
Baseline CGI-S, mean (SD)	4.6 (0.6)	4.6 (0.6)	4.8 (0.6)	4.3 (0.5)

CGI-S, Clinical Global Impressions-Severity; DVS, desvenlafaxine; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; VEN ER, venlafaxine extended release.

Fig. 1



Mean change from baseline of HAM-D_{17} total score over time, MMRM: pooled and individual populations (desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing). Mean doses: study 309: 302 mg desvenlafaxine; 118 mg venlafaxine ER Study 317: 336 mg desvenlafaxine; 206 mg venlafaxine ER. [a]$P<0{,}01$ venlafaxine ER 150–225 mg versus placebo; [b]$P<0{,}05$ desvenlafaxine versus placebo; [c]$P<0.001$ desvenlafaxine versus placebo; [d]$P<0{,}01$ venlafaxine ER 75–150 mg versus placebo; [e]$P<0.001$ venlafaxine ER 150–225 mg versus placebo. ER, extended release; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; MMRM, mixed-effect model for repeated measures.

Table 2 Change in HAM-D_{17} total score over time (MMRM), ITT pooled population[a]

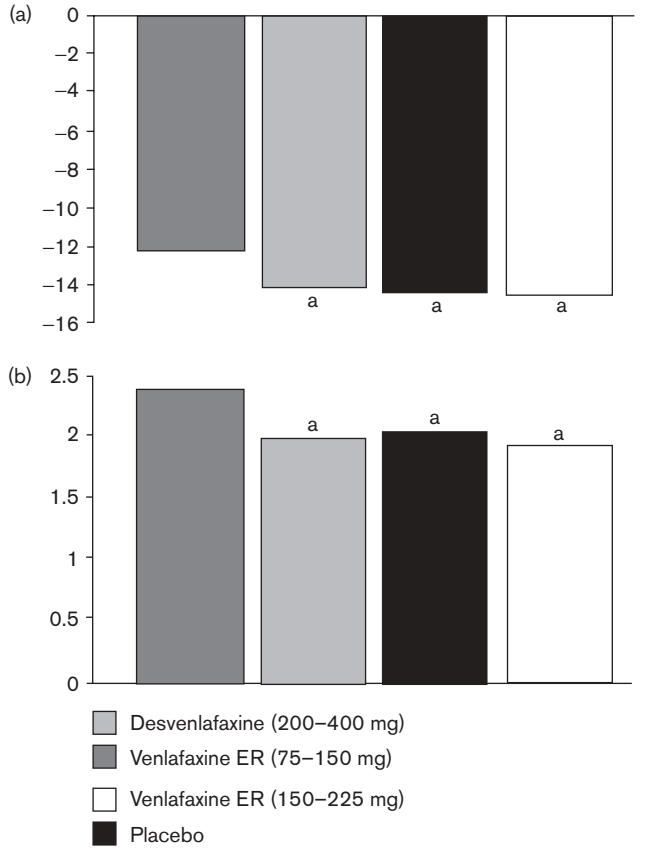
Treatment	Adjusted mean change from baseline (SE)	Adjusted mean difference versus placebo (SE)	*P* value versus placebo
Week 1			
Placebo	−3.00 (0.39)		
DVS 200–400 mg	−2.62 (0.40)	0.38 (0.55)	0.484
VEN ER 75–150 mg	−2.03 (0.56)	0.98 (0.68)	0.152
VEN ER 150–225 mg	−3.97 (0.61)	−0.97 (0.70)	0.168
Week 2			
Placebo	−5.73 (0.39)		
DVS 200–400 mg	−6.39 (0.41)	−0.66 (0.56)	0.235
VEN ER 75–150 mg	−5.75 (0.57)	−0.02 (0.69)	0.976
VEN ER 150–225 mg	−7.88 (0.61)	−2.16 (0.71)	0.002
Week 3			
Placebo	−7.68 (0.39)		
DVS 200–400 mg	−8.98 (0.42)	−1.30 (0.56)	0.022
VEN ER 75–150 mg	−7.97 (0.58)	−0.29 (0.69)	0.680
VEN ER 150–225 mg	−9.56 (0.62)	−1.88 (0.72)	0.009
Week 4			
Placebo	−9.06 (0.39)		
DVS 200–400 mg	−10.95 (0.43)	−1.89 (0.57)	<0.001
VEN ER 75–150 mg	−10.36 (0.58)	−1.30 (0.70)	0.063
VEN ER 150–225 mg	−11.36 (0.63)	−2.30 (0.73)	0.002
Week 6			
Placebo	−10.52 (0.40)		
DVS 200–400 mg	−12.74 (0.45)	−2.22 (0.59)	<0.001
VEN ER 75–150 mg	−12.70 (0.59)	−2.18 (0.72)	0.002
VEN ER 150–225 mg	−13.40 (0.66)	−2.88 (0.76)	<0.001
Week 8			
Placebo	−11.87 (0.42)		
DVS 200–400 mg	−14.21 (0.46)	−2.34 (0.61)	<0.001
VEN ER 75–150 mg	−14.26 (0.60)	−2.40 (0.73)	0.001
VEN ER 150–225 mg	−14.56 (0.67)	−2.69 (0.77)	<0.001

DVS, desvenlafaxine; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; MMRM, mixed-effect model for repeated measures; SE, standard error; VEN ER, venlafaxine extended release.
[a]Desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing.

ER also were significantly different from placebo at week 8 (75–150 mg/day: 2.0, $P = 0.003$; 150–225 mg/day: 1.9, $P < 0.001$) (Fig. 2b). In the ANCOVA analysis, statistically significant differences were observed with desvenlafaxine on the week 8 OC analysis of HAM-D_{17} and CGI-I scores and for venlafaxine 150–225 mg/day on both the LOCF (final evaluation) and week 8 OC analyses of these outcomes (data not shown).

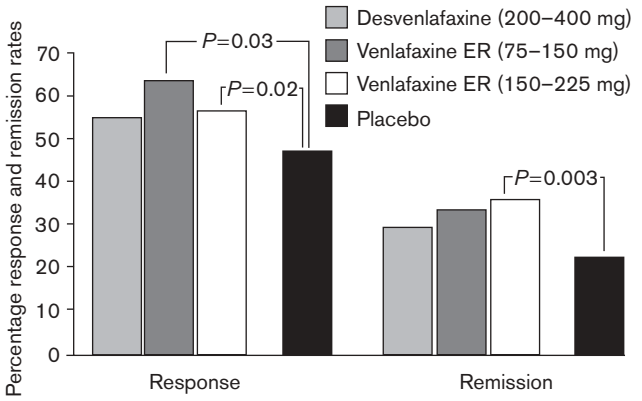
At the final evaluation, 55% of desvenlafaxine patients were HAM-D_{17} responders ($\geq 50\%$ reduction in HAM-D_{17} total score) compared with 47% of patients who had received placebo. Thirty percent of patients on desvenlafaxine achieved remission (HAM-D_{17} total score ≤ 7) compared with 23% of patients on placebo. The differences in HAM-D response and remission rates for desvenlafaxine versus placebo were not statistically significant; significant differences from placebo in response rates were observed for both venlafaxine ER dose groups (75–150 mg/day: 64%, $P = 0.033$; 150–225 mg/day: 57%, $P = 0.017$) and in remission rates for the 150–225 mg/day dose group (75–150 mg/day: 34%, $P = 0.133$; 150–225 mg/day: 36%, $P = 0.003$) (Fig. 3). CGI-I response rates were not significantly different for desvenlafaxine (62%) compared with placebo (56%); response rates were statistically significant for the venlafaxine ER 75–150 mg/day group (73%; $P = 0.039$) and 150–225 mg/day group (65%; $P = 0.011$) compared with placebo.

Fig. 2



(a) Efficacy results, MMRM, week 8 evaluation, HAM-D_{17}: pooled and individual populations (desvenlafaxine and placebo data represent pooled data from two studies: venlafaxine ER data were not pooled owing to differences in dosing). [a]$P<0.01$. (b) Efficacy results, MMRM, week 8 evaluation, CGI-I: pooled and individual populations (desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing). [a]$P<0.01$. CGI-I, Clinical Global Impressions-Improvement; ER, extended release; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; MMRM, mixed-effect model for repeated measures.

Fig. 3



HAM-D_{17} response and remission rates, final evaluation: pooled and individual populations (desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing). Response $\geq$ 50% reduction in HAM-D_{17} total score. Remission = HAM-D_{17} total score $\leq$ 7. ER, extended release; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression.

Week 8 MMRM data for secondary efficacy measures are presented in Table 3. Desvenlafaxine was significantly superior to placebo on the majority of the secondary outcomes: MADRS ($P < 0.001$), CGI-S ($P < 0.001$), HAM-D_6 ($P < 0.001$), Covi Anxiety Scale ($P = 0.035$), VAS-PI overall pain ($P = 0.003$) and the back pain ($P < 0.001$), chest pain ($P = 0.037$), and arm, leg, or joint pain ($P = 0.027$) subscale scores. Venlafaxine ER 75–150 mg/day was superior to placebo on symptom improvement as measured by the MADRS ($P < 0.001$), CGI-S ($P < 0.001$), HAM-D_6 ($P = 0.002$), VAS-PI overall pain ($P < 0.001$) and back pain ($P = 0.029$), chest pain ($P = 0.023$), and arm, leg, or joint pain ($P < 0.001$) subscales. Venlafaxine ER 150–225 mg/day was better than placebo for MADRS ($P < 0.001$), CGI-S ($P < 0.001$), HAM-D_6 ($P < 0.001$), Covi Anxiety ($P = 0.015$), VAS-PI overall pain ($P = 0.004$), back pain ($P < 0.001$), and arm, leg, or joint pain ($P = 0.002$). Results of the ANCOVA analysis (LOCF final evaluation) reflected statistically significant differences from placebo on fewer outcomes, for all treatment groups (desvenlafaxine: HAM-D_6 and VAS-PI back pain; venlafaxine 75–150 mg/day: VAS-PI overall pain, back pain, and arm, leg, and joint pain; venlafaxine 150–225 mg/day: MADRS, CGI-S, HAM-D_6, and VAS-PI arm, leg, and joint pain); analysis of week 8 OC data showed the following statistically significant differences from placebo: desvenlafaxine (MADRS, CGI-S, HAM-D_6, Covi Anxiety, VAS-PI overall pain, back pain, and chest pain), venlafaxine 75–150 mg/day (VAS-PI overall pain and arm, leg, and joint pain), and venlafaxine 150–225 mg/day (MADRS, CGI-S, HAM-D_6, VAS-PI overall pain, back pain, and arm, leg, and joint pain).

Individual study results

Individual study results are presented in Tables 4 and 5. Owing to a high placebo effect, these individual studies were underpowered to show an effect of desvenlafaxine. As such, desvenlafaxine did not significantly separate from placebo on the primary analysis of either the HAM-D_{17} total score or CGI-I score (Table 4). Additionally, HAM-D_{17} response and remission rates were not significantly different for desvenlafaxine compared with placebo (Table 5). There were statistically significant differences in HAM-D_{17} and CGI-I scores between the venlafaxine and placebo groups in the US study only ($P = 0.005$ and $P = 0.011$, respectively). Response rates with venlafaxine ER were statistically significant in both studies ($P = 0.03$ and $P = 0.038$ in EU and US, respectively); remission rates were significant only in the US study ($P = 0.01$).

Table 3 Secondary efficacy endpoints, week 8 (MMRM analysis); pooled and individual populations[a]

Therapy group	*n*	Adjusted mean change from baseline	Adjusted mean difference versus placebo (95% CI)	*P* value
MADRS				
Placebo	186	−14.3		
DVS 200–400 mg	151	−18.27	4.0 (2.3, 5.7)	<0.001
VEN ER 75–150 mg	101	−17.82	3.5 (1.5, 5.5)	<0.001
VEN ER 150–225 mg	82	−18.81	4.5 (2.4, 6.6)	<0.001
CGI-S				
Placebo	186	−1.6		
DVS 200–400 mg	152	−2.04	0.4 (0.2, 0.6)	<0.001
VEN ER 75–150 mg	101	−2	0.4 (0.2, 0.6)	<0.001
VEN ER 150–225 mg	82	−2.09	0.5 (0.2, 0.7)	<0.001
HAM-D_6				
Placebo	186	−6.09		
DVS 200–400 mg	152	−7.83	1.7 (1.1, 2.4)	<0.001
VEN ER 75–150 mg	101	−7.36	1.3 (0.5, 2.1)	0.002
VEN ER 150–225 mg	82	−8.26	2.2 (1.3, 3.0)	<0.001
Covi				
Placebo	186	−1.45		
DVS 200–400 mg	151	−1.76	0.3 (0.0, 0.6)	0.035
VEN ER 75–150 mg	101	−1.69	0.2 (−0.1, 0.6)	0.167
VEN ER 150–225 mg	82	−1.9	0.4 (0.1, 0.8)	0.015
VAS-PI				
Stomach pain				
Placebo	186	−8.5		
DVS 200–400 mg	150	−10.14	1.6 (−2.1, 5.3)	0.384
VEN ER 75–150 mg	101	−11.04	2.5 (−1.8, 6.9)	0.256
VEN ER 150–225 mg	82	−10.04	1.5 (−3.1, 6.2)	0.516
Back pain				
Placebo	186	−9.31		
DVS 200–400 mg	150	−16.81	7.5 (3.4, 11.6)	<0.001
VEN ER 75–150 mg	101	−14.69	5.4 (0.6, 10.2)	0.029
VEN ER 150–225 mg	82	−19.18	9.9 (4.7, 15.0)	<0.001
Chest pain				
Placebo	186	−5.66		
DVS 200–400 mg	150	−9.02	3.4 (0.2, 6.5)	0.037
VEN ER 75–150 mg	101	−9.98	4.3 (0.6, 8.0)	0.023
VEN ER 150–225 mg	82	−6.83	1.2 (−2.8, 5.1)	0.562
Arm, leg, joint pain				
Placebo	186	−8.76		
DVS 200–400 mg	150	−13.18	4.4 (0.5, 8.3)	0.027
VEN ER 75–150 mg	101	−16.98	8.2 (3.5, 12.9)	<0.001
VEN ER 150–225 mg	82	−16.6	7.8 (2.9, 12.8)	0.002
Overall pain				
Placebo	186	−10.26		
DVS 200–400 mg	150	−15.9	5.6 (1.9, 9.4)	0.003
VEN ER 75–150 mg	101	−18.61	8.4 (3.9, 12.8)	<0.001
VEN ER 150–225 mg	82	−17.32	7.1 (2.3, 11.8)	0.004

CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; Covi, Covi Anxiety Scale; DVS, desvenlafaxine; HAM-D_6, 6-item Bech version of 17-item Hamilton Rating Scale for Depression; MADRS, Montgomery Åsberg Depression Rating Scale; MMRM, mixed-effect model for repeated measures; VAS-PI, Visual Analog Scale-Pain Intensity; VEN ER, venlafaxine extended release.
[a]Desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing.

Although the EU study failed on the primary efficacy end point using ANCOVA (LOCF), significant differences were observed when alternative analytic methods were used; desvenlafaxine and venlafaxine ER were significantly better than placebo at week 8 for ANCOVA (OC data; $P < 0.001$ and $P = 0.027$, respectively) and MMRM ($P < 0.001$ and $P = 0.005$, respectively). In the US study, only venlafaxine ER separated from placebo, using both ANCOVA (LOCF and week 8 OC) and MMRM.

Pooled safety results

The most common treatment-emergent adverse events included nausea, somnolence, dry mouth, and sweating (Table 6). The type and frequency of treatment-emergent adverse events reported were similar to those reported with other SNRIs. In the desvenlafaxine group, there were increases in mean serum lipids, blood pressure, and pulse compared with placebo and decreases in mean weight. No deaths occurred in either study.

Discussion

The results of this analysis confirm and extend the results of the earlier phase 3 studies of desvenlafaxine (DeMartinis *et al.*, 2007; Liebowitz *et al.*, 2007; Septien-Velez *et al.*, 2007). The first of these studies ($n = 461$) showed a significant reduction in the HAM-D_{17} scores for the desvenlafaxine 100-mg ($P = 0.0038$) and 400-mg ($P = 0.0023$) dose groups versus the placebo group, and a trend toward significance ($P = 0.076$) in the 200-mg dose group. All desvenlafaxine dose groups showed significant improvement on the CGI-I Scale, a secondary efficacy measure, compared with placebo ($P < 0.05$) (DeMartinis *et al.*, 2007). In the second phase 3 trial ($n = 369$), the adjusted mean change from baseline in the HAM-D_{17} total score, the primary efficacy measure, was significantly greater for the desvenlafaxine 200-mg ($P = 0.002$) and 400-mg ($P = 0.008$) dose groups versus placebo (Septien-Velez *et al.*, 2007). A third, recently published study of desvenlafaxine ($n = 234$) that used a flexible-dose regimen – treatment was initiated at 100 mg/day for 14 days, after which the dose was increased to 200 mg/day, with an option to decrease the dose only if necessary for safety or tolerability – did not demonstrate a statistically significant difference between desvenlafaxine and placebo on the primary efficacy measure (difference in adjusted means = 1.0; $P = 0.277$), although significant differences were observed on some secondary measures (i.e. MADRS and VAS-PI overall pain, back pain, and arm, leg, or joint pain scales) (Liebowitz *et al.*, 2007).

Pooling of data from inconclusive placebo-controlled studies provides a useful method of establishing whether the treatment effect observed was significant, provided the studies are comparable. In this case, the design of the studies was similar, using the same duration and the same primary and secondary efficacy measures. The flexible dosage regime for desvenlafaxine was the same with the target treatment dose dependent on efficacy and tolerability, and this allowed for pooling of data on desvenlafaxine and placebo. By contrast, the dosage regime for venlafaxine ER was different in each study, with a low daily dose of 75–150 mg in the EU study and a higher daily dose of 150–225 mg in the US study; data from these treatment arms were not combined. The pooled analysis therefore allowed for valid conclusions for the efficacy of desvenlafaxine, but not for venlafaxine ER as a

Table 4 Efficacy results (LOCF), final evaluation: ITT individual studies

Efficacy variable	Therapy group	*n*	Adjusted mean change from baseline	Difference in adjusted means (95% CI) versus placebo	*P* value versus DVS	*P* value versus VEN ER
HAM-D_{17} total score (ANCOVA)	EU					
	Placebo	120	−12.5	–	0.381	0.171
	DVS 200–400 mg	116	−13.4	0.9 (−1.1, 2.8)		
	VEN ER 75–150 mg	127	−13.8	1.3 (−0.6, 3.2)		
	US					
	Placebo	125	−9.78	–	0.488	0.005
	DVS 200–400 mg	110	−10.5	0.7 (−1.3, 2.7)		
	VEN ER 150–225 mg	115	−12.6	2.9 (0.9, 4.9)		
CGI-I score (ANOVA)	EU					
	Placebo	120	2.3 (2.1, 2.5)	–	0.404	0.107
	DVS 200–400 mg	116	2.2 (1.9, 2.4)	0.1 (−0.2, 0.4)		
	VEN ER 75–150 mg	127	2.0 (1.8, 2.3)	0.2 (−0.1, 0.5)		
	US					
	Placebo	125	2.5 (2.3, 2.8)	–	0.604	0.011
	DVS 200–400 mg	110	2.5 (2.2, 2.7)	0.1 (−0.2, 0.4)		
	VEN ER 150–225 mg	115	2.1 (1.9, 2.4)	0.4 (0.1, 0.7)		

ANCOVA, analysis of covariance; ANOVA, analysis of variance; CGI-I, Clinical Global Impressions-Improvement; CI, confidence interval; DVS, desvenlafaxine; EU, Europe; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; ITT, intent to treat; LOCF, last observation carried forward; US, United States; VEN ER, venlafaxine extended release.

Table 5 HAM-D_{17} response and remission rates, final evaluation: individual studies

Efficacy variable	Therapy group	Proportion of responders (%)	OR (adjusted odds ratio 95% CI)	*P* value versus placebo
HAM-D_{17} response	EU			
	Placebo	60 (50)	–	–
	DVS 200–400 mg	69 (60)	1.507 (0.89, 2.55)	0.126
	VEN ER 75–100 mg	81 (64)	1.772 (1.06, 2.97)	0.03
	US			
	Placebo	55 (44)	–	–
	DVS 200–400 mg	55 (50)	1.248 (0.74, 2.11)	0.408
	VEN ER 150–225 mg	66 (57)	1.738 (1.03, 2.93)	0.038
HAM-D_{17} remission	EU			
	Placebo	30 (25)	–	–
	DVS 200–400 mg	39 (34)	1.549 (0.87, 2.76)	0.138
	VEN ER 75–100 mg	43 (34)	1.553 (0.88, 2.73)	0.127
	US			
	Placebo	26 (21)	–	–
	DVS 200–400 mg	29 (26)	1.331 (0.71, 2.48)	0.369
	VEN ER 150–225 mg	41 (36)	2.191 (1.21, 3.98)	0.01

CI, confidence interval; DVS, desvenlafaxine; EU, Europe; HAM-D_{17}, 17-item Hamilton Rating Scale for Depression; US, United States; VEN ER, venlafaxine extended release.

Table 6 Most common TEAEs (≥ 5% and at least two times greater with DVS than with placebo): pooled and individual populations[a], *n* (%)

Adverse event	Placebo *n* = 245	DVS 200–400 mg *n* = 231	VEN ER 75–150 mg *n* = 127	VEN ER 150–225 mg *n* = 117
Nausea	30 (12)	87 (38)	27 (21)	34 (29)
Somnolence	16 (7)	31 (13)	12 (9)	22 (19)
Dry mouth	10 (4)	47 (20)	17 (13)	30 (26)
Sweating	10 (4)	45 (20)	12 (9)	21 (18)
Asthenia	10 (4)	21 (9)	10 (8)	7 (6)
Constipation	7 (3)	32 (14)	6 (5)	9 (8)
Abnormal vision	3 (1)	13 (6)	3 (2)	5 (4)
Anorexia	3 (1)	23 (10)	6 (5)	18 (15)
Vomiting	2 (1)	17 (7)	3 (2)	3 (3)
Tachycardia	2 (1)	13 (6)	0	5 (4)
Impotence[b]	1 (1)	7 (9)	2 (6)	4 (11)

DVS, desvenlafaxine; TEAEs, treatment-emergent adverse events; VEN ER, venlafaxine extended release.
[a]Desvenlafaxine and placebo data represent pooled data from two studies; venlafaxine ER data were not pooled owing to differences in dosing.
[b]Incidence based on the number of men: placebo = 85, desvenlafaxine = 75, and venlafaxine ER = 71.

whole. In the pooled analysis of the two underpowered studies described in this report, desvenlafaxine was effective compared with placebo on both primary and secondary efficacy measures. In particular, the efficacy of desvenlafaxine was reflected in the significant change in HAM-D_{17} and CGI-I scores compared with placebo. In addition, desvenlafaxine was associated with a significant improvement compared with placebo on the HAM-D_6 subscale, which assesses the core symptoms of depression, the MADRS, CGI-S, Covi Anxiety Scale, and three of four VAS-PI subscales as well as overall pain score.

The individual studies and pooled analysis were not designed or powered to directly compare desvenlafaxine and venlafaxine ER. However, it is interesting to note some differences in tolerability and on efficacy measures observed in this analysis. For example, the proportion of completers (from the safety population) in the desvenlafaxine group (72%) was somewhat lower than in either the venlafaxine ER group (75–150 mg/day: 85%; 150–225 mg/day: 77%) or the placebo group (86%). This larger number of dropouts in the desvenlafaxine group may reflect differences in tolerability; in particular, the rate of nausea was higher in the desvenlafaxine group (38%) than in either venlafaxine ER group (21 and 29% for the 75–150 mg/day and 150–225 mg/day dose ranges, respectively). This suggests that the higher dose range of desvenlafaxine used in these studies (i.e. 200–400 mg/day), although safe and effective, may not be tolerated as well as lower doses. Likewise, the lower dose range of venlafaxine ER had a lower discontinuation rate and may have been better tolerated than the higher dose range. Differences between desvenlafaxine and venlafaxine ER in the overall number and pattern of statistically significant findings on secondary efficacy measures were also observed in this pooled analysis. For example, although desvenlafaxine and both doses of venlafaxine ER were statistically significant in the analysis of HAM-D_{17} and CGI-I scores, such consistency was not observed in the responder analysis; rates of HAM-D_{17} response were not statistically significant with desvenlafaxine, but were so with both doses of venlafaxine ER. It is difficult to draw conclusions based on this data because the study was not designed to compare the two active compounds. Nevertheless, underlying differences in the effects of the two drugs cannot be ruled out.

The ANCOVA, using the LOCF method, which traditionally has been used as a primary analysis in registration studies in EU and the US, uses the last recorded data point to replace the missing points for a participant failing to complete the trial. This approach is believed to be the most conservative because it can reduce the apparent efficacy by assigning high scores for medications that are not well tolerated; however, recent comparisons of different methods have demonstrated that this approach might not be the best in all cases (Mallinckrodt *et al.*, 2004). The MMRM analysis is a type of likelihood-based, mixed-effects method in which missing points are estimated based on observed data. MMRM approaches are easy to implement, are more robust to the biases from missing data, and provide better control of type I and type II errors than LOCF ANOVA (Mallinckrodt *et al.*, 2004; Molenberghs *et al.*, 2004). The differences in results between analytic methods a clearly demonstrated by the lack of statistical separation in the EU and US studies, where in the pooled analyses, using MMRM, desvenlafaxine was significantly more effective than placebo as measured by the HAM-D_{17} and CGI-I, as well as MADRS, HAM-D_6, and CGI-S at week 8. The univariate repeated-measures ANOVA is still the most commonly used statistical analysis tool for repeated measures in depression trials because of its simplicity and familiarity. However, mixed-effects models, the use of which has substantially increased over the last 10 years, may have important advantages over traditional methods and may yield unbiased and more valid estimates (Gueorguieva and Krystal, 2004).

The high placebo response observed in the two studies discussed herein reflects the increasing placebo response observed in many studies over recent years. It has been estimated that the proportion of patients in studies, who respond to placebo, has risen by approximately 7% per decade (Walsh *et al.*, 2002). A high placebo response in a study makes it difficult, because of ceiling effects, to test for efficacy, as a larger number of patients would be required for a valid comparison. Unless the power calculations for the size of studies were constantly revised upward to account for this difficulty, it would be likely that the studies would be underpowered.

Placebo response is a major issue in clinical trials for psychiatric disorders. The causes of a high placebo response in modern studies are many and varied and are the subject of controversy. It is often claimed that the increased number of assessment visits and increased nonspecific contact and support, which are part of current high contact trial practice, automatically increase the response rate to both placebo and active treatment and raise the placebo response rate to a level where it is often difficult to distinguish from active treatment. Similarly, the use of many assessment instruments and the careful collection of AEs have the consequence of increasing contact time with the treatment team, and this may need to be more carefully controlled. Evidence also exists that the placebo response is higher in patients with mild-to-moderate depression and lower in those with more severe depression; therefore, the inclusion of patients with more severe depression has been recommended as a means of controlling the placebo response (Fava *et al.*, 1997).

The treatment effect – the magnitude of change on the pivotal scale of an antidepressant compared with placebo – is also likely to be affected by the raised placebo response. The treatment effect of desvenlafaxine observed using an MMRM analysis is 2.3 points on the HAM-D_{17}, which compares well with the treatment effect of between 2 and 3 points that has been reported in positive placebo-controlled studies of the most recently licensed antidepressant, the SNRI duloxetine (Mallinckrodt *et al.*, 2004). The treatment effect of desvenlafaxine in this pooled analysis is also in line with that observed with the comparator venlafaxine ER, 75–150 mg/day (2.4) and 150–225 mg/day (2.7), in the individual studies. The effect size using a Cohen's *d* measure was 0.41 for desvenlafaxine, 0.41 for venlafaxine ER 75–150 mg/day, and 0.46 for venlafaxine ER 150–225 mg/day. The clinical relevance of the significant difference of the treatment effect observed with desvenlafaxine and venlafaxine ER is shown by the significant advantage compared with placebo measured on the CGI-S and CGI-I scores, which represent the view of the independent clinician who is making a clinical judgment of the individual patient under double-blind conditions.

Conclusion

Desvenlafaxine was generally safe and well tolerated in this population. Pooled analyses of the data with MMRM models demonstrate that desvenlafaxine was efficacious in the treatment of MDD, despite the fact that the underpowered individual studies failed to reach statistical significance.

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References

Alfinito PD, Huselton C, Chen X, Deecher DC (2006). Pharmacokinetic and pharmacodynamic profiles of the novel serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized Sprague-Dawley rats. *Brain Res* **1098**:71–78.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders (DSM-IV)*. 4th edition. Washington, DC: American Psychiatric Association.

Bech P, Gram LF, Dein E, Jacobsen O, Vitger J, Bolwig TG (1975). Quantitative rating of depressive states. *Acta Psychiatr Scand* **51**:161–170.

Clement EM, Odontiadis J, Franklin M (1998). Simultaneous measurement of venlafaxine and its major metabolite, oxydesmethylvenlafaxine, in human plasma by high-performance liquid chromatography with coulometric detection and utilisation of solid-phase extraction. *J Chromatogr B Biomed Sci Appl* **705**:303–308.

Deecher DC, Beyer CE, Johnston G, Bray J, Shah S, Abou-Gharbia M, *et al.* (2006). Desvenlafaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther* **318**:657–665.

DeLoach LJ, Higgins MS, Caplan AB, Stiff JL (1998). The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg* **86**:102–106.

DeMartinis NA, Yeung PP, Entsuah R, Manley AL (2007). A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* **68**: 677–688.

Faravelli C, Cosci F, Ciampelli M, Scarpato MA, Spiti R, Ricca V (2003). A self-controlled, naturalistic study of selective serotonin reuptake inhibitors versus tricyclic antidepressants. *Psychother Psychosom* **72**:95–101.

Fava M, Uebelacker LA, Alpert JE, Nierenberg AA, Pava JA, Rosenbaum JF (1997). Major depressive subtypes and treatment response. *Biol Psychiatry* **42**:568–576.

Gueorguieva R, Krystal JH (2004). Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry* **61**:310–317.

Guy W (1976). Clinical global impressions. Publication ADM 76–338. In: Guy W, editor. *ECDEU assessment manual for psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare. pp. 217–222.

Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**:56–62.

Liebowitz M, Yeung PP, Entsuah R (2007). A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* **68**:1663–1672.

Lipman RS (1982). Differentiating anxiety and depression in anxiety disorders: use of rating scales. *Psychopharmacol Bull* **18**:69–77.

Mallinckrodt CH, Kaiser CJ, Watkin JG, Molenberghs G, Carroll RJ (2004). The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. *Clin Trials* **1**:477–489.

Molenberghs G, Thijs H, Jansen I, Beunckens C, Kenward MG, Mallinckrodt C, *et al*. (2004). Analyzing incomplete longitudinal clinical trial data. *Biostatistics* **5**:445–464.

Montgomery SA, Asberg M (1979). A new depression scale designed to be sensitive to change. *Br J Psychiatry* **134**:382–389.

Muth EA, Moyer JA, Haskins JT, Andree TH, Husbands GEM (1991). Biochemical, neurophysiological, and behavioral effects of Wy-45,233 and other identified metabolites of the antidepressant venlafaxine. *Drug Dev Res* **23**:191–199.

Nelson JC, Mazure CM, Jatlow PI, Bowers MB Jr, Price LH (2004). Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry* **55**: 296–300.

Raskin A, Schulterbrandt J, Reatig N, McKeon JJ (1969). Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. *J Nerv Ment Dis* **148**:87–98.

Segal ZV, Pearson JL, Thase ME (2003). Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. *J Affect Disord* **77**:97–108.

Septien-Velez L, Pitrosky B, Padmanabhan SK, Germain J-M, Tourian KA (2007). A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* **22**:338–347.

Steffens DC, Krishnan KR, Helms MJ (1997). Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress Anxiety* **6**: 10–18.

Thase ME, Entsuah AR, Rudolph RL (2001). Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* **178**:234–241.

Walsh BT, Seidman SN, Sysko R, Gould M (2002). Placebo response in studies of major depression: variable, substantial, and growing. *J Am Med Assoc* **287**:1840–1847.

World Health Organization (2001). *The World Health Report: 2001–Mental Health: New Understanding, New Hope*. Geneva: World Health Organization.