Eur Arch Psychiatry Clin Neurosci (2009) 259:329–339
DOI 10.1007/s00406-009-0003-7

ORIGINAL PAPER

# Differential effects of venlafaxine in the treatment of major depressive disorder according to baseline severity

**Andreas B. Schmitt · Michael Bauer · Hans-Peter Volz · Hans-Jürgen Moeller · Qin Jiang · Philip T. Ninan · Peter-Andreas Loeschmann**

Received: 22 September 2008 / Accepted: 10 February 2009 / Published online: 3 March 2009
© Springer-Verlag 2009

**Abstract** In this meta-analysis, we compare the relative efficacy of venlafaxine to selective serotonin reuptake inhibitors (SSRIs) in patients with major depressive disorder classified according to baseline disease severity. Data from 31 double-blind randomised clinical trials comparing venlafaxine and SSRIs (intent-to-treat $n = 6{,}492$) were pooled. For this secondary analysis, patients were stratified into groups based on baseline HAM-$D_{17}$ total score ($\geq$30, $<$30, $\geq$25, and $<$25). Remission rates (HAM-$D_{17} < 8$) were analyzed for each subgroup using Fisher's exact test to compare treatment effects between venlafaxine and SSRIs; last observation carried forward (LOCF) and observed cases (OC) data were analyzed. The number needed to treat (NNT) to benefit was determined for each analysis. Statistically significant remission rate differences, favoring venlafaxine, were seen in LOCF and OC analyses for each subgroup. In patients with baseline HAM-$D_{17} < 25$ ($n = 3{,}928$) the differences were (LOCF) 7.3 [$P < 0.001$; NNT = 14] and (OC) 6.2 [$P = 0.003$; NNT = 16], and in patients with baseline HAM-$D_{17} \geq 25$ ($n = 2{,}564$) were (LOCF) 5.7 [$P = 0.002$; NNT = 17] and (OC) 6.7 [$P = 0.009$; NNT = 15]. In patients with baseline HAM-$D_{17} < 30$ ($n = 5{,}836$) the differences were (LOCF) 6.4 [$P < 0.001$; NNT = 16] and (OC) 5.5 [$P = 0.001$; NNT = 18], and in patients with baseline HAM-$D_{17} \geq 30$ ($n = 656$) were (LOCF) 8.9 [$P = 0.015$; NNT = 11] and (OC) 14.8 [$P = 0.003$; NNT = 7]. In conclusion, these analyses demonstrate that venlafaxine may be superior to SSRIs in achieving remission in both mild/moderate and severely depressed patients. The greater difference in remission rates among patients with baseline HAM-$D_{17} \geq 30$ suggests a more pronounced clinical benefit that may be achieved with venlafaxine in severely depressed patients.

**Keywords** Depression · Remission · SSRI · Meta-analysis

A. B. Schmitt (✉) · P.-A. Loeschmann
Department of Medical Affairs, Wyeth Pharma GmbH, Wienburgstraße 207, 48159 Münster, Germany
e-mail: schmitA2@wyeth.com

M. Bauer
Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Technical University Dresden, Fetscherstraße 74, 01307 Dresden, Germany

H.-P. Volz
Hospital for Psychiatry, Psychotherapy and Psychosomatic Medicine, Schloss Werneck, Balthasar-Neumann-Platz 1, 97740 Werneck, Germany

H.-J. Moeller
Department of Psychiatry, Ludwig-Maximilians-University, Nussbaumstrasse 7, 80336 Munich, Germany

Q. Jiang · P. T. Ninan
Wyeth Pharmaceuticals, Arcolaroad 500, 19426 Collegeville, PA, USA

## Introduction

Numerous studies and meta-analyses have demonstrated the safety, efficacy and tolerability of venlafaxine, a serotonin–norepinephrine reuptake inhibitor antidepressant [9]. Some evidence suggests that this dual mechanism of action is associated with greater efficacy as compared with selective serotonin reuptake inhibitors (SSRIs) [6, 34, 40, 51]. However, the clinical impact of these differences has been controversially discussed [24, 26, 34, 40, 41, 57]. In order to meet regulatory requirements the primary outcome measures of most trials are the differences in mean

depression rating scores, which are difficult to interpret clinically. Therefore, several meta-analyses have been conducted focusing on clinical relevant parameters such as response and remission rates. Results of pooled analyses of relevant clinical trials suggest that venlafaxine is associated with higher remission rates than SSRIs [6, 40, 51].

One of the recent meta-analysis showed a difference in remission rates of about 6% in favor of venlafaxine suggesting a modest clinical advantage over SSRIs [40]. However, even modest differences in antidepressant efficacy may have a significant clinical impact in particular for patients with severe depression. For various reasons including national/international guidelines [38] or generic price competition by several classes of antidepressants (e.g. SSRIs) venlafaxine is often reserved for the use as a second- or third-line therapy. In clinical practice, venlafaxine is widely prescribed for patients with severe depression, which may be more difficult to treat. This assumption is supported by data from large databases [33], non-interventional studies [29] and clinical trials in treatment resistant depression (including patients after failure of previous treatment, mainly SSRI therapy) [4, 45, 53]. However, for healthcare practitioners it is important to understand the relevant differences among available antidepressants for choosing therapeutic agents matching individual patient needs.

One relevant parameter is the severity of depression, thus differential effects of antidepressants particularly in severe depression have to be taken into consideration. Only a limited number of studies are available for any antidepressant which investigated the differential clinical outcome of patients with severe depression [3, 20, 25, 48]. One comparative study published recently demonstrated the superior efficacy of venlafaxine over citalopram only in severely depressed patients [28]. However, all previously published meta-analyses have not specifically examined whether baseline depression severity influences the relative efficacy of venlafaxine and SSRIs.

This meta-analysis was conducted to compare the efficacy of venlafaxine and SSRIs in patients with MDD, stratified according to severity of depression at baseline using two different cut offs on the Hamilton Depression Rating Scale (HDRS). This analysis was performed exclusively using clinical studies for which individual patient data were available.

## Methods

### Study selection

For this secondary meta-analysis, we analyzed data that have been used for a previous meta-analysis comparing the efficacy of venlafaxine and SSRIs [40]. Data are from all randomized, double-blind studies that included an active comparator, completed by Wyeth Pharmaceuticals, and included patients meeting the criteria for major depressive disorder as determined by the Diagnostic and Statistical Manual of Mental Disorders (either edition III-R or IV) or International Disease Classification-10 criteria. Further details have been described elsewhere [40]. All studies were conducted in accordance with GCP criteria and followed systematic data processes as outlined by Wyeth policy. An additional requirement for these analyses was that all individual patient data included evaluations utilizing the 17-item HDRS (i.e. HAM-$D_{17}$) Data from three studies used for the previous analysis [40] did not provided sufficient patient level information (e.g. not using the HAM-$D_{17}$) and were excluded. Table 1 summarizes the individual design of the 31 studies included in this analysis. The SSRI comparators were fluoxetine (18 studies), paroxetine (8 studies), sertraline (3 studies), citalopram (1 study), and fluvoxamine (1 study). Eight studies also included a placebo control group.

### Study population

Most of the trials used standard exclusion criteria such as the presence of a primary Axis I disorder other than depression, severe Axis II pathology (by investigator's discretion), history of any significant medical disorder, and a history of drug or alcohol abuse for at least 6 months before entering the study. Most studies excluded patients with a history of nonresponse to either venlafaxine or the particular comparator SSRI being studied. With the exception of one study that enrolled patients who had not responded to two antidepressant trials in the current depressive episode [42], all of the studies required that patients be off the antidepressants for at least 2 weeks before study participation.

For this analysis, subjects were assigned to groups based on their baseline HAM-$D_{17}$ total score with two approaches; ($\geq$30/<30 and $\geq$25/<25). Similar cut offs on rating scales have been used by retrospective and prospective studies [3, 20, 25, 28, 35, 48, 56]. HAM-$D_{17}$ baseline score $\geq$25 was used to define severe depression and the score of $\geq$30 was used to define very severe depression.

### Efficacy assessments

The primary efficacy outcome measure was remission, as defined by a final HAM-$D_{17}$ total score of $\leq$7. The intent-to-treat (ITT) population included all patients randomly assigned to treatment, who received at least one dose of study medication and had at least one on-therapy efficacy assessment performed. Week 8 was chosen a priori as the

**Table 1** Characteristics of individual studies

| Study | Authors | Drug treatment | Dose, mg/day[a] | | *N* (ITT) | Duration (weeks) | Practice setting | Baseline demographics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Range | Mean (SD) | | | | Age, mean (SD) | Female (%) | $HAM\text{-}D_{21}$, mean (SD) |
| S014[b] | Nemeroff and Thase [39] | Venlafaxine IR | 75–225 | 142 (64) | 96 | 6 | Out; psych | 40 (11) | 64 | 21 (3) |
| | | Fluoxetine | 20–60 | 41 (17) | 101 | | | 38 (12) | 70 | 21 (3) |
| S015[b] | Schatzberg and Roose [47] | Venlafaxine IR | 37.5–225 | 90 (53) | 94 | 8 | Out; psych | 71 (5) | 54 | 22 (3) |
| | | Fluoxetine | | 31 (13) | 99 | | | 71 (5) | 45 | 22 (3) |
| S016[b] | Cantillon and Daley [10] | Venlafaxine IR | 75–375 | 258 (108) | 91 | 6 | In; psych | 42 (13) | 51 | 27 (3) |
| | | Fluoxetine | 20–80 | 62 (21) | 99 | | | 38 (11) | 69 | 27 (4) |
| S102 | Data on file [58] | Venlafaxine ER | 75 | 75 (NA) | 28 | 8 | Out; psych | 47 (16) | 61 | 25 (5) |
| | | Fluoxetine | 20 | 20 (NA) | 26 | | | 47 (17) | 54 | 24 (5) |
| S211[b] | Rudolph and Feiger [44] | Venlafaxine ER | 75–225 | 147 (84) | 95 | 8 | Out; psych | 40 (11) | 73 | 23 (3) |
| | | Fluoxetine | 20–60 | 38 (22) | 103 | | | 40 (13) | 69 | 23 (3) |
| S332 | Data on file [58] | Venlafaxine IR | 75–225 | 162 (79) | 24 | 6 | Out; psych | 35 (9) | 71 | 22 (2) |
| | | Fluoxetine | 20–40 | 29 (10) | 23 | | | 39 (11) | 78 | 21 (2) |
| S340 | Clerc et al. [13] | Venlafaxine IR | 200 | 193 (30) | 33 | 6 | In; psych | 49 (17) | 70 | 28 (5) |
| | | Fluoxetine | 40 | 40 (0) | 34 | | | 54 (16) | 68 | 29 (4) |
| S348 | Dierick et al. [18] | Venlafaxine IR | 75–150 | 97 (43) | 145 | 8 | Out; psych | 44 (12) | 65 | 25 (4) |
| | | Fluoxetine | 20 | 19 (13) | 157 | | | 43 (13) | 65 | 25 (4) |
| S360[b] | Silverstone and Ravindran [49] | Venlafaxine ER | 75–225 | 120 (74) | 121 | 12 | Out; psych | 41 (12) | 64 | 25 (4) |
| | | Fluoxetine | 20–60 | 30 (20) | 115 | | | 43 (11) | 61 | 25 (4) |
| S372[b] | Rudolph et al. [43] | Venlafaxine IR | 75–375 | 236 (141) | 144 | 6 | Out; psych | 40 (9) | 63 | 22 (9) |
| | | Fluoxetine | 20–80 | 54 (29) | 146 | | | 38 (10) | 65 | 23 (10) |
| S624 | Tzanakaki et al. [55] | Venlafaxine IR | 75–225 | 200 (NA) | 54 | 6 | In; psych | 47 (11) | 74 | 26 (5) |
| | | Fluoxetine | 20–60 | 54 (NA) | 52 | | | 49 (10) | 83 | 26 (5) |
| S626 | Kornaat [27] | Venlafaxine IR | 75–225 | 143 (30) | 72 | 8 | Out; psych | 37 (11) | 63 | 20 (3) |
| | | Fluoxetine | 20–40 | 40 (16) | 73 | | | 38 (11) | 67 | 20 (3) |
| S635 | Tylee et al. [54] | Venlafaxine IR | 75 | 75 (NA) | 140 | 12 | Out; GP | 42 (14) | 64 | 23 (5) |
| | | Fluoxetine | 20 | 20 (NA) | 151 | | | 46 (14) | 74 | 23 (4) |
| S637 | De Nayer et al. [17] | Venlafaxine IR | 75–150 | 136 (31) | 64 | 12 | Out; psych | 41 (13) | 70 | 21 (3) |
| | | Fluoxetine | 20–40 | 37 (8) | 67 | | | 44 (13) | 64 | 22 (4) |
| S642 | Alves et al. [1] | Venlafaxine IR | 75–150 | 145 (18) | 37 | 12 | Out; GP | 46 (11) | 95 | 25 (4) |
| | | Fluoxetine | 20–40 | 39 (4) | 46 | | | 42 (12) | 91 | 24 (4) |
| S646 | Costa e Silva [15] | Venlafaxine IR | 75–150 | 85 (NA) | 196 | 8 | Out; psych | 40 (11) | 81 | 27 (5) |
| | | Fluoxetine | 20–40 | 33 (NA) | 185 | | | 40 (10) | 78 | 27 (5) |
| S654 | Stevens [52] | Venlafaxine IR | 75–150 | 88 (28) | 102 | 12 | Out; GP | 41 (11) | 68 | 22 (5) |
| | | Fluoxetine | 20–40 | 26 (10) | 114 | | | 40 (13) | 77 | 23 (5) |
| S98–81 | Mehtonen and Nordiska [31] | Venlafaxine ER | 75–150 | 117 (38) | 50 | 10 | Out; psych | 42 (11) | 68 | 22 (3) |
| | | Fluoxetine | 20–40 | 30 (10) | 50 | | | 42 (12) | 62 | 23 (3) |

**Table 1** continued

| Study | Authors | Drug treatment | Dose, mg/day[a] | | *N* (ITT) | Duration (weeks) | Practice setting | Baseline demographics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Range | Mean (SD) | | | | Age, mean (SD) | Female (%) | HAM-$D_{21}$, mean (SD) |
| S131 | Dufour et al. [19] | Venlafaxine ER | 75–150 | 97 (37) | 173 | 12 | Out; GP | 44 (14) | 70 | 24 (4) |
| | | Paroxetine | 20–40 | 27 (10) | 180 | | | 44 (14) | 76 | 24 (5) |
| S349 | Data on file [58] | Venlafaxine IR | 75–150 | 70 (32) | 76 | 8 | Out; psych | 39 (11) | 63 | 24 (5) |
| | | Paroxetine | 20–40 | 25 (9) | 80 | | | 39 (11) | 68 | 24 (5) |
| S367[b] | Salinas [46] | Venlafaxine | 75/150 | 73(12)/142(29) | 161 | 8 | Out; | 45 (12) | 67 | 25 (4) |
| | | ER Paroxetine | 20 | 18 (6) | 80 | | psych | 43 (12) | 55 | 24 (4) |
| S428 | Casabona et al. [11] | Venlafaxine ER | 75–150 | 84 (25) | 57 | 8 | Out; psych | 47 (12) | 74 | 25 (6) |
| | | Paroxetine | 20–40 | 26 (11) | 52 | | | 43 (12) | 83 | 25 (6) |
| S622 | Poirier and Boyer [42] | Venlafaxine IR | 75–300 | 269 (NA) | 60 | 4 | In/out; psych | 42 (9) | 73 | 25 (4) |
| | | Paroxetine | 20–40 | 36 (NA) | 62 | | | 44 (9) | 69 | 24 (4) |
| S632 | Data on file [58] | Venlafaxine IR | 75–150 | 103 (NA) | 40 | 8 | In; psych | 43 (11) | 48 | 22 (4) |
| | | Paroxetine | 20–40 | 28 (NA) | 45 | | | 42 (12) | 53 | 22 (4) |
| S643 | Ballús et al. [5] | Venlafaxine IR Paroxetine | 75–150 | 94 (NA) | 39 | 24 | Out: psych | 43 (12) | 87 | 21 (4) |
| | | | 20–40 | 25 (NA) | 43 | | | 45 (13) | 88 | 22 (5) |
| S670 | McPartlin et al. [30] | Venlafaxine ER | 75 | 75 (NA) | 167 | 12 | Out; GP | 45 (14) | 66 | 23 (4) |
| | | Paroxetine | 20 | 20 (NA) | 150 | | | 44 (14) | 67 | 23 (4) |
| S402[b] | Data on file [58] | Venlafaxine | 75–300 | 198 (89) | 287 | 10 | Out; | 39 (13) | 60 | 23 (3) |
| | | ER Sertraline | 50–200 | 132 (59) | 289 | | Psych | 40 (12) | 60 | 23 (3) |
| S414[b] | Data on file [58] | Venlafaxine ER | 75–300 | 212 (88) | 288 | | Out; psych | 42 (13) | 64 | 23 (3) |
| | | Sertraline | 50–200 | 130 (58) | 294 | 10 | | 41 (14) | 61 | 23 (3) |
| S631 | Mehtonen et al. [32] | Venlafaxine IR | 75–150 | 139 (36) | 70 | 8 | Out; psych | 44 (11) | 64 | 23 (3) |
| | | Sertraline | 50–100 | 97 (12) | 70 | | | 41 (11) | 66 | 23 (4) |
| S671 | Lenox-Smith | Venlafaxine ER | 75–300 | 180 (75) | 193 | 12 | Out; psych | 42 (11) | 68 | 26 (5) |
| | et al. [28] | Citalopram | 20–60 | 43 (15) | 198 | | | 44 (11) | 64 | 26 (5) |
| S347 | Hackett et al. [22] | Venlafaxine IR | 75–150 | 135 (33) | 77 | 6 | Out; psych | 44 (13) | 61 | 25 (4) |
| | | Fluvoxamine | 100–200 | 175 (54) | 34 | | | 40 (11) | 65 | 25 (4) |
| Total 31 | | Venlaxine | | | 3,274 | | | 43.3 | | 23.7 |
| | | SSRI | | | 3,218 | | | 43.3 | | 23.7 |

*ER* extended release, *IR* immediate release, *HAM-$D_{21}$* 21-item Hamilton Rating Scale for depression

*GP* general practice, *in* inpatient, *out* outpatient, *psych* psychiatric practice

*NA* not available

[a] Mean dose values and standard deviations could be calculated from individual patient dosage data for 23 studies. For the remaining studies, mean doses for the individual study were taken from the summary data provided in the study report or manuscript, and the corresponding standard deviations were listed as not available (NA)

[b] Placebo group was included

primary endpoint, as very few studies included data beyond 8 weeks.

### Statistical methods

Statistical tests for heterogeneity ($H^2$ and $I^2$ statistics) assessing the validity to combine groups of studies with similar, but not identical, designs were performed for the primary meta-analysis [40]. The primary analysis also addressed the issue of potential bias in study selection; a funnel plot analysis was included, which extended the primary data set by including all available (as of January 2007) studies in the public domain, regardless of sponsor, and by broadening the inclusion criteria to include studies that were open-label, provided that patients were randomized to the treatment groups [40].

Fisher's exact test (a statistical test that is used to compare categorical variables and is an appropriate alternative to the $\chi^2$ test when sample sizes are small) was used to compare the treatment effects on the remission rates at weeks 1, 2, 3, 4, 6 and 8 for each subgroup. The last observation carried forward (LOCF) method was used to account for missing observations; observed cases (OC) data were also analyzed. Remission rate differences were used as the efficacy measure; odds ratios (OR) with 95% confidence intervals (CIs) were calculated. The number needed to treat (NNT) to benefit [14], the effect size widely used in evidence-based medicine to correlate statistical results with clinical relevance, was also computed.

## Results

As described in the recent publication of Nemeroff et al. [40], tests for heterogeneity revealed no statistically significant differences, indicating that data from the individual studies could be combined. The funnel plot analysis revealed no evidence of statistically significant selection bias, suggesting that study sponsorship did not significantly influence outcomes [40].

Overall, 6,492 patients were included in the ITT analyses. There were 3,274 patients treated with venlafaxine and 3,218 treated with SSRIs. The mean age was 43.3 years (SD 11.8), the female to male ratio was approximately 2:1, and approximately 7% of the participants were inpatients (Table 1). All studies included patients with moderate to severe depression, with a mean pretreatment HAM-$D_{17}$ score of 23.7 (SD = 4.25) for both the venlafaxine and the SSRI groups. There were 3,928 patients with a baseline HAM-$D_{17}$ total score of <25 (venlafaxine: 1,954; SSRI: 1,974) and 2,564 patients with a baseline HAM-$D_{17}$ total score of ≥25 (venlafaxine: 1,320; SSRI: 1,244) (Table 2). There were 5,836 patients with a baseline HAM-$D_{17}$ total score of <30 (venlafaxine: 2,925; SSRI: 2,911) and 656 patients with a baseline HAM-$D_{17}$ total score of ≥30 (venlafaxine: 349; SSRI: 307) (Table 3).

### Efficacy analyses

Tables 2 and 3 show the details for every time point for which remission rates were available. Statistically significant differences in remission rates between venlafaxine and SSRIs were observed at week 2 for the groups of patients with a baseline HAM-$D_{17}$ total score of <25 or HAM-$D_{17}$ total score of <30, whereas for patients with a baseline HAM-$D_{17}$ total score of ≥25 or HAM-$D_{17}$ total score of ≥30 significant differences were not observed until week 6.

At week 8, the primary endpoint, remission rate differences were in favor of venlafaxine compared with SSRIs, regardless of baseline HAM-$D_{17}$ score (Figs. 1, 2). For the group of patients with a baseline HAM-$D_{17}$ score of <25 the LOCF analysis revealed a remission rate difference of 7.3 [OR 1.35 (95% CI: 1.19, 1.54), $P < 0.001$; NNT = 14]; the OC analysis revealed a remission rate difference of 6.2 [OR 1.28 (95% CI: 1.09, 1.51), $P = <0.003$; NNT = 16]. For the group of patients with a baseline HAM-$D_{17}$ score of ≥25 the LOCF analysis revealed a remission rate difference of 5.7 [OR 1.31 (95% CI: 1.10, 1.54), $P = 0.002$; NNT = 17]; the OC analysis revealed a remission rate difference of 6.7 [OR 1.32 (95% CI: 1.07, 1.63), $P = 0.009$; NNT = 15] (Table 2).

For the group of patients with a HAM-$D_{17}$ < 30 at baseline the LOCF analysis revealed a remission rate difference of 6.4 [OR 1.31 (95% CI: 1.18, 1.46), $P < 0.001$; NNT = 16]; the OC analysis revealed a remission rate difference of 5.5 [OR 1.25 (95% CI: 1.09, 1.43), $P = 0.001$; NNT = 18]. For the group of patients with a baseline HAM-$D_{17}$ ≥ 30 the LOCF analysis revealed a remission rate difference of 8.9 [OR 1.55 (95% CI: 1.10, 2.18), $P = 0.015$; NNT = 11]; the OC analysis revealed a remission rate difference of 14.8 [OR 1.93 (95% CI: 1.25, 2.97), $P = 0.003$; NNT = 7] (Table 3). Overall, remission rate differences were higher in more severely depressed patients with a baseline HAM-$D_{17}$ ≥ 30 resulting in the lower NNT values (Fig. 2).

## Discussion

This analysis of data from 31 double-blind RCTs comparing venlafaxine and SSRIs, including nearly 6,500 patients with MDD, extends the results of a large and comprehensive meta-analysis that demonstrated significantly greater rates of remission with venlafaxine compared with SSRIs as a class [6, 40, 51]. The findings of this analysis show further that the significant advantage of

**Table 2** Comparison of remission rates in the treatment with venlafaxine versus SSRIs in patients with mild/moderate depression (HAM-$D_{17}$ < 25) or with severe depression (HAM-$D_{17}$ ≥ 25)

| Severity of depression (baseline) | Time on therapy | Therapy group | #Remitters/ #patients (%) | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| HAM-$D_{17}$ < 25 | Week 1 | Venlafaxine | 53/1,776 (3.0) | 1.24 (0.82, 1.86) | 0.352 |
| Venlafaxine: $N = 1{,}954$ | | SSRI | 43/1,771 (2.4) | | |
| SSRI: $N = 1{,}974$ | Week 2 | Venlafaxine | 191/1,738 (11.0) | 1.44 (1.14, 1.81) | 0.002 |
| | | SSRI | 139/1,760 (7,9) | | |
| | Week 3 | Venlafaxine | 214/1,136 (18.8) | 1.29 (1.04, 1.60) | 0.024 |
| | | SSRI | 182/1,192 (15.3) | | |
| | Week 4 | Venlafaxine | 465/1,611 (28.9) | 1.31 (1.12, 1.54) | <0.001 |
| | | SSRI | 388/1,644 (23.6) | | |
| | Week 6 | Venlafaxine | 603/1,435 (42.0) | 1.31 (1.13, 1.52) | <0.001 |
| | | SSRI | 501/1,406 (35.6) | | |
| | Week 8 | Venlafaxine | 621/1,174 (52.9) | 1.28 (1.09, 1.51) | 0.003 |
| | | SSRI | 533/1,142 (46.7) | | |
| | Final on-therapy | Venlafaxine | 874/1,954 (44.7) | 1.35 (1.19, 1.54) | <0.001 |
| | | SSRI | 739/1,974 (37.4) | | |
| HAM-$D_{17}$ ≥ 25 | Week 1 | Venlafaxine | 16/1,228 (1.3) | 1.36 (0.63, 2.94) | 0.447 |
| Venlafaxine: $N = 1{,}320$ | | SSRI | 11/1,145 (1.0) | | |
| SSRI: $N = 1{,}244$ | Week 2 | Venlafaxine | 60/1,207 (5.0) | 0.93 (0.64, 1.33) | 0.709 |
| | | SSRI | 61/1,140 (5.4) | | |
| | Week 3 | Venlafaxine | 98/807 (12.1) | 1.22 (0.89, 1.67) | 0.231 |
| | | SSRI | 78/766 (10.2) | | |
| | Week 4 | Venlafaxine | 212/1,106 (19.2) | 1.07 (0.86, 1.34) | 0.543 |
| | | SSRI | 190/1,051 (18.1) | | |
| | Week 6 | Venlafaxine | 323/959 (33.7) | 1.50 (1.23, 1.83) | <0.001 |
| | | SSRI | 33/920 (25.3) | | |
| | Week 8 | Venlafaxine | 328/754 (43.5) | 1.32 (1.07, 1.63) | 0.009 |
| | | SSRI | 267/726 (36.8) | | |
| | Final on-therapy | Venlafaxine | 457/1,320 (34.6) | 1.31 (1.10, 1.54) | 0.002 |
| | | SSRI | 359/1,244 (28.9) | | |

Observed cases week 1–8 and LOCF final on-therapy

venlafaxine is observed in both the mild/moderate and severe depression at baseline. Moreover, the superiority of venlafaxine was more pronounced in patients with very severe depression.

This information is relevant for health care practitioners, as it adds to the somewhat limited body of evidence regarding the relative efficacy of antidepressants in severe depression. Since severe depression is associated with increased suicides, physical illness and higher risk for a chronic course of the disease [36], the knowledge regarding the efficacy in patients with severe depression would enable the clinicians to select the most appropriate treatment for their patients. However, in prospective clinical trials mild/moderate and severe depression are usually not analyzed separately, which limits the body of evidence for the efficacy of any antidepressant especially in severe depression. Few randomized controlled trials have compared the relative efficacy of individual antidepressants or antidepressant classes in severe depression [3, 35]. The available evidence is derived largely from studies that compared tricyclic antidepressants (TCAs) with SSRIs [2]. These data suggest advantages in favor of individual TCAs such as clomipramine compared to various modern antidepressants, especially SSRIs [2, 16] and advantages of individual SSRIs such as paroxetine and fluoxetine when compared to various TCAs [37]. One prospective study showed superior efficacy of venlafaxine compared to fluoxetine in hospitalized patients [13] and one recent study demonstrated superior efficacy of venlafaxine when compared with citalopram in patients with severe depression who had not responded to previous antidepressant therapy [28].

In a recent meta-analysis, the drug-placebo differences of modern antidepressants in relation to the baseline severity using a meta-regression analysis was published

**Table 3** Comparison of remission rates in the treatment with venlafaxine versus SSRIs in patients with mild/moderate depression (HAM-$D_{17}$ < 30)

| Severity of depression (baseline) | Time on therapy | Therapy group | #Remitters/ # Patients (%) | Odds Ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| HAM-$D_{17}$ < 30 | Week 1 | Venlafaxine | 67/2,674 (2.5) | 1.23 (0.85, 1.76) | 0.312 |
| Venlafaxine $N = 2{,}925$ | | SSRI | 54/2,629 (2.1) | | |
| SSRI $N = 2{,}911$ | Week 2 | Venlafaxine | 241/2,628 (9.2) | 1.27 (1.04, 1.54) | 0.021 |
| | | SSRI | 193/2,614 (7.4) | | |
| | Week 3 | Venlafaxine | 287/1,748 (16.4) | 1.24 (1.03, 1.49) | 0.027 |
| | | SSRI | 243/1,774 (13.7) | | |
| | Week 4 | Venlafaxine | 629/2,425 (25.9) | 1.24 (1.09, 1.42) | 0.001 |
| | | SSRI | 543/2,432 (22.0) | | |
| | Week 6 | Venlafaxine | 844/2,140 (39.4) | 1.34 (1.18, 1.52) | <0.001 |
| | | SSRI | 687/2,100 (32.7) | | |
| | Week 8 | Venlafaxine | 865/1,730 (50.0) | 1.25 (1.09, 1.43) | 0.001 |
| | | SSRI | 750/1,687 (44.5) | | |
| | Final on-therapy | Venlafaxine | 1,216/2,925 (41.6) | 1.31 (1.18, 1.46) | <0.001 |
| | | SSRI | 1,024/2,911 (35.2) | | |
| HAM-$D_{17} \geq 30$ | Week 1 | Venlafaxine | 2/330 (0.6) | | 0.502 |
| Venlafaxine $N = 349$ | | SSRI | 0/287 (0.0) | | |
| SSRI $N = 307$ | Week 2 | Venlafaxine | 10/317 (3.2) | 1.30 (0.49, 3.46) | 0.632 |
| | | SSRI | 7/286 (2.4) | | |
| | Week 3 | Venlafaxine | 25/195 (12.8) | 1.44 (0.75, 2.77) | 0.326 |
| | | SSRI | 17/184 (9.2) | | |
| | Week 4 | Venlafaxine | 48/292 (16.4) | 0.98 (0.63, 1.53) | >0.999 |
| | | SSRI | 44/263 (16.7) | | |
| | Week 6 | Venlafaxine | 82/254 (32.3) | 1.82 (1.20, 2.75) | 0.005 |
| | | SSRI | 47/226 (20.8) | | |
| | Week 8 | Venlafaxine | 84/198 (42.4) | 1.93 (1.25, 2.97) | 0.003 |
| | | SSRI | 50/181 (27.6) | | |
| | Final on-therapy | Venlafaxine | 115/349 (33.0) | 1.55 (1.10, 2.18) | 0.015 |
| | | SSRI | 74/307 (24.1) | | |

Venlafaxine $N = 2{,}925$; SSRI $N = 2{,}911$ or with severe depression (HAM-$D_{17} \geq 30$)

Observed cases week 1–8 and LOCF final on-therapy

[26]. The authors conclude that modern antidepressants are associated with greater differences from placebo at higher levels of severity and those clinically meaningful effects of antidepressants may be limited to patients with more severe depression [26]. However, the study has a number of limitations including a selected subset data of the available evidence being included (a number of modern antidepressants and post registration trials were not included). One key weakness of the study is that only mean changes on depression rating scales were analyzed thereby ignoring the response and remission rates. Although changes in depression rating scales are frequently used as the primary efficacy measures in clinical trials, remission is widely regarded as the most clinically relevant outcome parameter [2, 7], as it is considered the ultimate treatment goal and is associated with a better long-term prognosis [2, 7]. In this context, the European regulatory body CHMP has recently emphasized that the mean change on a depression rating scale is an inadequate basis for the evaluation of clinical relevance of an antidepressant [21]. Therefore, systematic reviews should provide information at least for response and ideally remission rates.

In line with previous studies and meta-analyses, this analysis focused on differences in rates of remission. The difference of remission rates in favor of venlafaxine observed, here, were generally consistent across the subgroups analyzed and, as expected, consistent with the differences reported in the primary analysis [40]. However, the remission rate differences among the most severely depressed subgroup of patients (i.e. patients with baseline HAM-$D_{17}$ score $\geq$30) were greater (9% LOCF, 15% OC) compared with the other subgroups.

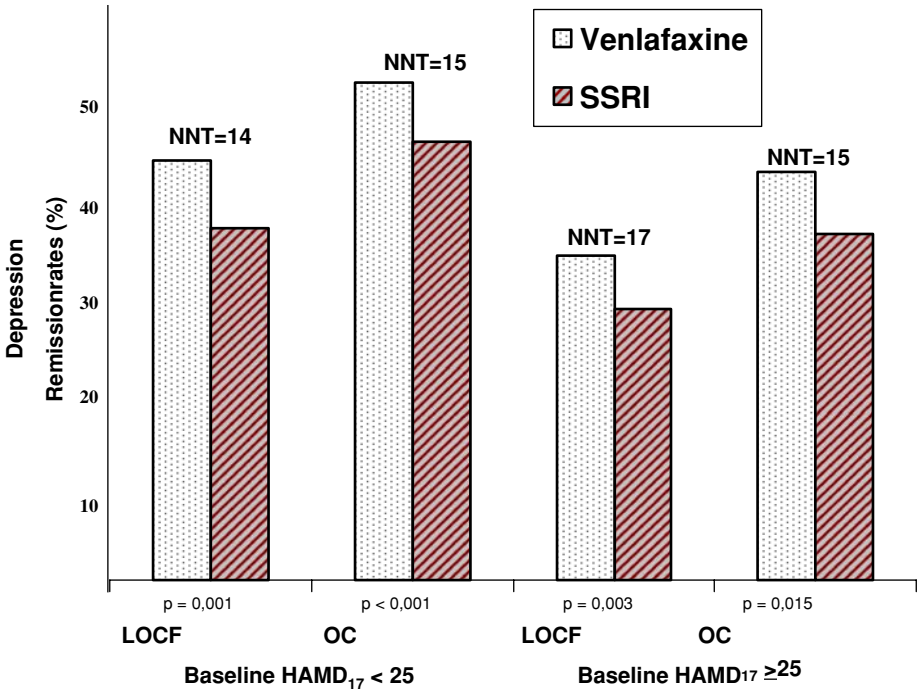


**Fig. 1** Comparison of remission rates in the treatment with venlafaxine versus SSRIs in patients with baseline HAM-$D_{17}$ score <25 or with baseline HAM-$D_{17}$ score ≥25. *LOCF* last observation carried forward, *OC* observed cases, *NNT* number needed to treat

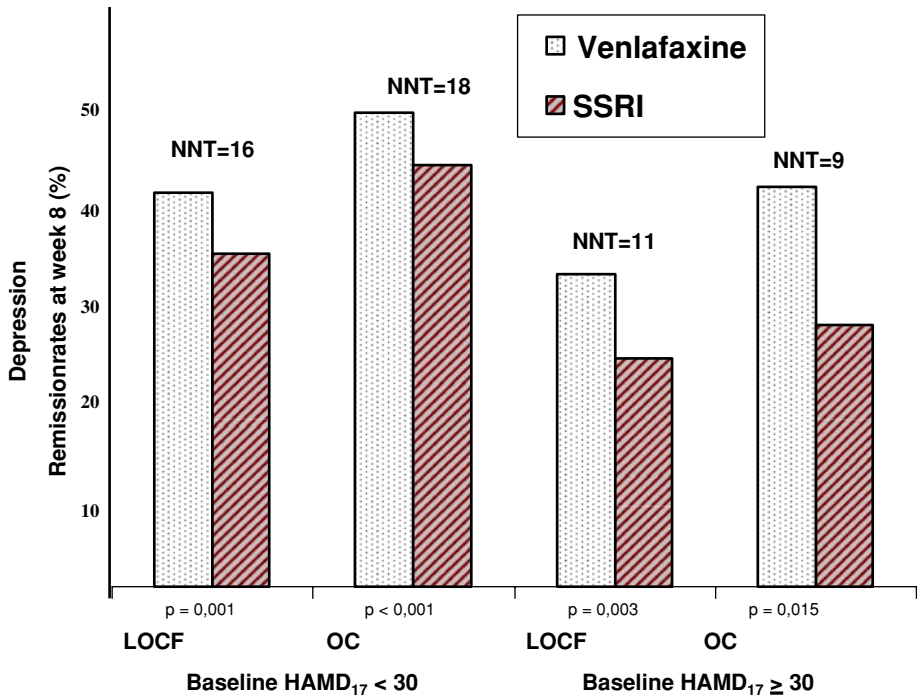


**Fig. 2** Comparison of remission rates in the treatment with venlafaxine versus SSRIs in patients with baseline HAM-$D_{17}$ score <30 or with baseline HAM-$D_{17}$ score ≥30. *LOCF* last observation carried forward, *OC* observed cases, *NNT* number needed to treat

The clinical relevance of remission rate differences of 6–8%, as observed in previous analyses has been questioned. Therefore, other methodological approaches such as the NNT, an epidemiological measure that indicates how many patients would require treatment with a product for one patient to reach a defined endpoint, are useful to evaluate the relative efficacy of one drug compared to placebo or an active comparator. In recent meta-analyses, which compared remission rates between venlafaxine and SSRIs, the NNT varied between 17 and 19 [6, 40]. Smaller differences shown by other meta-analyses are mainly due to the limited inclusion of available data, such as unpublished studies or not generally established exclusion criteria [57].

Since no generally accepted cut offs have been established to define the clinical relevance of treatment effects,

the NNTs have to be interpreted with caution [50]. In general, the NNTs should be interpreted in the context of the severity of the disease, the need for additional treatment options and the comparison versus placebo or an active comparator (i.e., in a comparison between two effective treatments the NNT will certainly be higher than a comparison between an effective treatment and placebo). Although a NNT of 10 (i.e. 10% difference in remission rates) has been suggested as being a possible cut off correlated with clinical superiority [12], NNTs of 20 and higher are considered acceptable for medical interventions such as stroke prevention [23].

Similar to previous meta-analyses, the results of this analysis detected NNTs ranging from 14 to 18 for patients with baseline HAM-$D_{17}$ scores of <24, ≥24 and <30 suggesting similar efficacy across these subgroups. One of the key finding of this analysis is that, in patients with very severe depression defined by the baseline HAM-$D_{17}$ score of ≥30 the NNT decreased to 11 (LOCF) and 7 (OC) reaching the threshold suggested by others [41] and reflecting a clinically relevant difference in the efficacy of venlafaxine compared with SSRIs in this subgroup of patients for whom remission of symptoms may be more difficult to achieve. This supports the current clinical practice, whereas venlafaxine is often used for the treatment of more severely affected patients bearing higher risks for relapse and treatment resistance [33].

One other important result of this study is that significant differences in remission rates could be detected as early as 2 weeks of treatment in patients with mild/moderate depression, whereas a significant difference could be detected after 6 weeks of treatment in patients with severe depression. This finding supports the clinical experience that patients with severe depression need more time to achieve remission, which should be taken into account for individual treatment regimens.

One limitation that must be considered when interpreting the findings presented here is the absence of a generally accepted definition of severe depression [36] except the categorical definition of ICD-10. Criteria to define severe depression may include the presence of melancholia or hospitalization, which have been acknowledged to be inadequate [36] or cut off scores on depression rating scales [3, 13, 20, 25, 28]. Moderate and severe depressions are regarded to be on a continuum and no currently used rating scale provides an inherent dividing cut off point [36]. Furthermore, the threshold chosen for any given study may reflect the severity of the sample studied rather than a general criterion to separate moderate and severe depression. Although cut off scores on depression scales may be regarded as an arbitrary, antidepressant studies have generally used cut offs of 25, 28 or 30 on the HDRS and 28 or 30 on the Montgomery-Åsberg Depression Rating Scale (MADRS) providing an useful information of the level of efficacy of some antidepressants in severe depression [3, 20, 25, 28, 35, 56].

The following additional limitations of this analysis have to be considered: first, the efficacy of venlafaxine was compared with SSRIs as a class. Although this is a widely accepted approach [6, 24, 40, 51, 57], individual SSRIs have distinct pharmacologic properties including different dose responses and may not be interchangeable. Therefore, the advantages of venlafaxine may differ when compared with individual SSRIs. Second, methodological aspects of the individual studies (e.g. population, study duration, dosing) should be considered. None of the individual studies were powered to demonstrate superiority in achieving remission. The limited use of the full dose-range of venlafaxine (mostly 150 mg/d instead of the maximum between 225 and 375 mg/d) or the use of the immediate-release (IR) formulation of venlafaxine (instead of the better tolerated sustained-release [SR]) and inappropriately rapid dose escalation [5, 8, 32] may rather have contributed to underestimate the possible maximum effect of venlafaxine [6]. However, the inclusion of 31 comparative trials including more than 6,500 patients which have been used for this analysis strengthen the plausibility of our results. Third, given the nature of the data, the LOCF and OC analyses would be complemented by the use of a repeated-measures analysis (e.g. MMRM). Finally, this is a secondary analysis. Therefore, these findings should not be considered as confirmatory. However, our findings suggest that future clinical trials should investigate antidepressant efficacy in subgroups of patients such as according to the severity of depression.

## Conclusion

To our knowledge, this is the first report addressing the impact of baseline severity for venlafaxine and finding superior remission rates in favor of venlafaxine compared to SSRIs in both mild/moderate and severe depression using two different cut offs on the HDRS. Overall, venlafaxine therapy was associated with a significant advantage in achieving remission compared with SSRIs regardless of the baseline depression severity. Importantly, the magnitude of the remission rate differences advantage was more prominent in patients with very severe depression. The results of this study contribute to a better understanding of the level of efficacy of venlafaxine in comparison with SSRIs for important subpopulations of patients which clinicians should take into account for appropriate treatment decisions.

## References


1. Alves C, Cachola I, Brandao J (1999) Efficacy and tolerability of venlafaxine and fluoxetine in outpatients with major depression. Prim Care Psychiatry 5:57–63
2. Anderson IM, Nutt DJ, Deakin JF (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. J Psychopharmacol 14:3–20
3. Angst J, Amrein R, Stabl M (1995) Moclobemide and tricyclic antidepressants in severe depression: meta-analysis and prospective studies. J Clin Psychopharmacol 15:16S–23S
4. Baldomero EB, Ubago JG, Cercos CL, Ruiloba JV, Calvo CG, Lopez RP (2005) Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. Depress Anxiety 22:68–76
5. Ballús C, Quiros G, De Flores T, De la Torre J, Palao D, Rojo L, Gutiérrez L, Riesgo Y (2000) The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder of dysthymia. Int Clin Psychopharmacol 15:43–48
6. Bauer M, Tharmanathan P, Volz H-P, Moeller H-J, Freemantle N (2009) The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: a meta-analysis. Eur Arch Psychiatry Clin Neurosci. doi: 10.1007/s00406-008-0849-0 [epub ahead of print]
7. Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, Moller HJ (2007) World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for biological treatment of unipolar depressive disorders in primary care. World J Biol Psychiatry 8:67–104
8. Bielski RJ, Ventura D, Chang CC (2004) A double-blind comparison of escitalopram and venlafaxine extended release in the treatment of major depressive disorder. J Clin Psychiatry 65:1190–1196
9. Blier P (2006) Dual serotonin and noradrenaline reuptake inhibitors: focus on their differences. Int J Psychiatry Clin Pract 10(suppl 2):22–32
10. Cantillon M, Daley M (2000) Further superiority of SNRI venlafaxine over SSRI fluoxetine in major depression and melancholia: a double-blind, placebo-controlled study of both response and remission (wellness). In: Poster. First annual meeting of the international forum on mood and anxiety disorders, Monte Carlo, Monaco
11. Casabona GM, Silenzi V, Guazzelli M (2002) A randomized, double-blind, comparison of venlafaxine ER and paroxetine in outpatients with moderate to severe major depression. Eur Neuropsychopharmacol 12(suppl 3), 208 (abstract)
12. Cipriani A, Barbui C, Brambilla P, Furukawa TA, Hotopf M, Geddes JR (2006) Are all antidepressants really the same? The case of fluoxetine: a systematic review. J Clin Psychiatry 67:850–864
13. Clerc GE, Ruimy P, Verdeau-Palles J (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. The Venlafaxine French Inpatient Study Group. Int Clin Psychopharmacol 9:139–143
14. Cook RJ, Sackett DL (1995) The number needed to treat: a clinically useful measure of treatment effect. BMJ 310:452–454
15. Costa e Silva J (1998) Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. J Clin Psychiatry 59:352–357
16. Danish University Antidepressant Group (1990) Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Danish University Antidepressant Group. J Affect Disord 18:289–299
17. Nayer De, Geerts S, Ruelens L, Schittecatte M, De Bleeker E, Van Eeckhoutte I, Evrard JL, Linkowski P, Fossion P, Leyman S, Mignon A (2002) Venlafaxine compared with fluoxetine in outpatients with depression and concomitant anxiety. Int J Neuropsychopharmacol 5:115–120
18. Dierick M, Ravizza L, Realini R, Martin A (1996) A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry 20:57–71
19. Dufour A, Van Hauteghem D, Slachmuylders P, Leyman S, Mignon A (2001) Clinical acceptability of venlafaxine extended release and paroxetine in outpatients treated for depression by general practitioners. Eur Neuropsychopharmacol 11(suppl 3), 224 (abstract)
20. Dunner DL, Lipschitz A, Pitts CD, Davies JT (2005) Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression: post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. Clin Ther 27:1901–1911
21. European Medicines Agency, EMEA, CHMP (2008) CHMP Assessment report on antidepressants
22. Hackett D, Salinas E, Desment A (1998) Efficacy and safety of venlafaxine versus fluvoxamine in outpatients with major depression. Eur Neuropsychopharmacol 8(suppl 3), 1.210 (abstract)
23. Hankey GJ, Warlow CP (1999) Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations. Lancet 354:1457–1463
24. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS (2005) Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med 143:415–426
25. Kasper S (1997) Efficacy of antidepressants in the treatment of severe depression: the place of mirtazapine. J Clin Psychopharmacol 17(suppl 1):19S–28S
26. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Medicine 5:e45
27. Kornaat H (1998) Randomized, double-blind comparison of venlafaxine and fluoxetine for moderately depressed outpatients. Int J Neuropsychopharmacol 3(suppl 1), PMK02021 (abstract)
28. Lenox-Smith AJ, Jiang Q (2008) Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. Int Clin Psychopharmacol 23:113–119
29. Linden M, Ludewig K, Munz T, Dierkes W (2003) Dosage finding and outcome of venlafaxine treatment in psychiatric outpatients and inpatients: results of a drug utilization observation study. Pharmacopsychiatry 36:197–205
30. McPartlin GM, Reynolds A, Anderson C, Casoy J (1998) A comparison of once-daily venlafaxine XR and paroxetine in depressed outpatients treated in general practice. Prim Care Psychiatry 4(3):127–132
31. Mehtonen O (2002) A double-blind, randomized study of the efficacy and safety of venlafaxine extended release (ER) versus fluoxetine in outpatients with major depression. Eur Neuropsychopharmacol 12(suppl 3), 253 (abstract)
32. Mehtonen OP, Sogaard J, Roponen P, Behnke K (2000) Randomized, double-blind comparison of venlafaxine and sertraline in outpatients with major depressive disorder. Venlafaxine 631 Study Group. J Clin Psychiatry 61:95–100
33. Mines D, Hill D, Yu H, Novelli L (2005) Prevalence of risk factors for suicide in patients prescribed venlafaxine, fluoxetine, and citalopram. Pharmacoepidemiol Drug Saf 14:367–372

34. Moeller HJ (2000) Are all antidepressants the same? J Clin Psychiatry 61(suppl 6):24–28
35. Montgomery S, Ferguson JM, Schwartz GE (2003) The antidepressant efficacy of reboxetine in patients with severe depression. J Clin Psychopharmacol 23:45–50
36. Montgomery SA, Lecrubier Y (1999) Is severe depression a separate indication? ECNP Consensus Meeting September 20, 1996, Amsterdam European College of Neuropsychopharmacology. Eur Neuropsychopharmacol 9:259–264
37. Montgomery SA, Rasmussen JG, Lyby K, Connor P, Tanghoj P (1992) Dose response relationship of citalopram 20 mg, citalopram 40 mg and placebo in the treatment of moderate and severe depression. Int Clin Psychopharmacol 6(suppl 5):65–70
38. National Collaborating Centre for Mental Health (2004) Depression: management of depression in primary and secondary care. National Clinical Practice Guideline Number 23
39. Nemeroff CB, Thase ME (2007) A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. J Psychiatr Res 41:351–359
40. Nemeroff CB, Entsuah R, Benattia I, Demitrack M, Sloan DM, Thase ME (2008) Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol Psychiatry 63:424–434
41. Papakostas GI, Fava M, Thase ME (2008) Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol Psychiatry 63:699–704
42. Poirier M-F, Boyer P (1999) Venlafaxine and paroxetine in treatment-resistant depression double-blind, randomised-comparison. Br J Psychiatry 174:12–16
43. Rudolph R, Aguiar L, Entsuah R, and Derivan A (1998) Early onset of antidepressant activity of venlafaxine compared with placebo and fluoxetine in outpatients in a double-blind study. Eur Neuropsychopharmacol 8(suppl 3), P. 1.027 (abstract)
44. Rudolph RL, Feiger AD (1999) A double-blind, randomized, placebo-controlled trial of once-daily venlafaxine extended release (XR) and fluoxetine for the treatment of depression. J Affect Disord 56:171–181
45. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, Shores-Wilson K, Niederehe G, Fava M (2006) Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N Engl J Med 354:1231–1242
46. Salinas E (1997) Once daily extended release (XR) venlafaxine versus paroxetine in outpatients with major depression. Biol Psychiatry 42(suppl 1), 244S (abstract)
47. Schatzberg A, Roose S (2006) A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. Am J Geriatr Psychiatry 14:361–370
48. Shelton RC, Prakash A, Mallinckrodt CH, Wohlreich MM, Raskin J, Robinson MJ, Detke MJ (2007) Patterns of depressive symptom response in duloxetine-treated outpatients with mild, moderate or more severe depression. Int J Clin Pract 61:1337–1348
49. Silverstone PH, Ravindran A (1999) Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. Venlafaxine XR 360 Study Group. J Clin Psychiatry 60:22–28
50. Smeeth L, Haines A, Ebrahim S (1999) Numbers needed to treat derived from meta-analyses—sometimes informative, usually misleading. BMJ 318:1548–1551
51. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I (2002) Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 180:396–404
52. Stevens I (1997) Comparison of the efficacy and safety of venlafaxine and fluoxetine in GP patients with moderate to severe depression. Biol Psychiatry 42 (suppl 1), 244S (abstract)
53. Thase ME, Shelton RC, Khan A (2006) Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. J Clin Psychopharmacol 26:250–258
54. Tylee A, Beaumont G, Bowden MW, Reynolds A (1997) A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. Prim Care Psychiatry 3(1):51–58
55. Tzanakaki M, Guazzelli M, Nimatoudis I, Zissis NP, Smeraldi E, Rizzo F (2000) Increased remission rates with venlafaxine compared with fluoxetine in hospitalized patients with major depression and melancholia. Int Clin Psychopharmacol 15:29–34
56. Versiani M, Moreno R, Ramakers-van Moorsel CJ, Schutte AJ (2005) Comparison of the effects of mirtazapine and fluoxetine in severely depressed patients. CNS Drugs 19:137–146
57. Weinmann S, Becker T, Koesters M (2008) Re-evaluation of the efficacy and tolerability of venlafaxine versus SSRI: meta-analysis. Psychopharmacology (Berl) 196:511–520
58. Wyeth Research (2008) Data on file. Collegeville, PA