

A Randomised Study Comparing Escitalopram with Venlafaxine XR in Primary Care Patients with Major Depressive Disorder

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Key Words

Escitalopram, depression · Major depressive disorder, drug responsiveness · Venlafaxine XR, depression

Abstract

This 8-week, randomised, double-blind study compared the efficacy and tolerability of escitalopram to that of venlafaxine XR in primary care patients with major depressive disorder. The efficacy of escitalopram (10–20 mg; n = 148) was similar to venlafaxine XR (75–150 mg; n = 145), based on mean change from baseline to week 8 in Montgomery and Åsberg Depression Rating Scale total score. In ad hoc analyses, escitalopram-treated patients achieved sustained remission significantly faster than did venlafaxine-treated patients. More venlafaxine-treated patients had nausea, constipation, and increased sweating ($p < 0.05$). When treatment was completed after 8 weeks, significantly more venlafaxine-treated patients had discontinuation symptoms ($p < 0.01$). Thus escitalopram treatment was similar to venlafaxine treatment with respect to efficacy and was better tolerated by patients in primary care.

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Introduction

Depression is a serious illness associated with considerable morbidity, risk of suicide, and disability [1–3]. Despite the availability of a number of antidepressants for the treatment of major depressive disorder (MDD), poor adherence to treatment often leads to a less than optimal treatment outcome in general practice. Nearly one third of patients discontinue antidepressant treatment during the first month of treatment [4, 5]. Early improvement in depressive symptoms as well as a low incidence of side effects provides positive feedback to the patient and results in greater compliance with treatment and a better chance of achieving remission [4, 6].

The selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants in the treatment of MDD in primary care [7]. However, it has been suggested that treatment with venlafaxine, a serotonin and noradrenaline reuptake inhibitor, results in a higher remission rate than SSRIs in the treatment of MDD [8].

Escitalopram is the most selective SSRI [9] and offers some advantages over citalopram in terms of efficacy in the treatment of MDD in controlled clinical trials [10–12]. It is therefore important to investigate the efficacy and safety of the most selective SSRI compared to venlafaxine. As the extended release formulation of venlafa-

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xine (XR) has been found to be superior to the immediate release formulation [13], it was judged more appropriate to compare escitalopram with venlafaxine XR.

The present comparison between escitalopram and venlafaxine XR was performed in primary care. The commonly used and recommended dose for venlafaxine in this setting is 75–150 mg, with the majority of patients receiving 75–100 mg. The doses of escitalopram and venlafaxine, chosen in accordance with their respective recommendations, were 10–20 mg/day [11, 14] and 75–150 mg/day, respectively [13, 15].

The aim of this study was to compare efficacy and tolerability parameters of 8 weeks' treatment with 10–20 mg/day escitalopram with that of 75–150 mg/day venlafaxine XR in primary care patients with MDD.

Methods

Patients

This study was conducted in 44 sites in 8 European countries, in accordance with the Declaration of Helsinki and the ICH guideline for good clinical practice [16]. The study protocol and protocol amendments were approved by the relevant local ethics committees, and all patients were required to provide written informed consent before entering the study.

Eligible patients were patients in primary care, 18–85 years of age, with a DSM-IV [17] diagnosis of MDD and a minimum score of 18 on the Montgomery and Åsberg Depression Rating Scale (MADRS) [18]. Patients were excluded if they met any of the following criteria: history of mania or any bipolar disorder, schizophrenia or any psychotic disorder, or were currently suffering from obsessive-compulsive disorder, eating disorders, mental retardation, any pervasive development disorder, or cognitive disorder (DSM-IV criteria); MADRS score ≥ 5 on item 10 (suicidal thoughts); alcohol or drug abuse problems within the previous 12 months; or had had treatment with antipsychotics, antidepressants, psychotropics (except zolpidem or stable low doses of benzodiazepines for insomnia), serotonin receptor agonists, lithium, carbamazepine, valproate, or valpromide; electroconvulsive treatment; treatment with behaviour therapy or psychotherapy; or if they were pregnant or breast feeding. Medications thought likely to interfere with the study were excluded.

Study Design

After a 1-week run-in period with no treatment, patients were randomised to 8 weeks of double-blind treatment with escitalopram (10–20 mg/day) or venlafaxine XR (75–150 mg/day). The initial dose was 10 mg escitalopram or 75 mg venlafaxine XR per day. At week 2 or 4, the dose could be increased to 20 mg/day for escitalopram or 150 mg/day for venlafaxine XR at the investigator's discretion if the patient's response was unsatisfactory. This is in line with the dose recommendations for both products. Patients who completed 8 weeks of treatment entered a 1-week run-out period (week 9). Patients on higher-dose treatment, corresponding to 20 mg escitalopram or 150 mg venlafaxine XR per day, were down-tapered to 10 mg escitalopram or 75 mg venlafaxine XR per day, respectively,

for the first 4 days and placebo for the last 3 days. Patients on lower-dose treatment received placebo for all 7 days of the run-out period in both groups.

Assessments

The primary efficacy assessment was the MADRS total score. The ratings were conducted by the same person at each visit, whenever possible. Only persons experienced with MADRS rating and trained as raters during a co-rating session were allowed to rate patients on the MADRS. Additional efficacy parameters were the 17-item Hamilton Depression Rating Scale (HAM-D₁₇) [19, 20] and response and remission rates.

Safety and tolerability were evaluated on the basis of adverse events, electrocardiograms (ECGs), vital signs, weight, and laboratory tests. The 43-item Discontinuation Emergent Signs and Symptoms (DESS) checklist [21] was assessed at week 8 and at the end of the 1-week run-out period (week 9), after the general open questioning used for capturing adverse events.

Statistical Analysis

Efficacy analyses were conducted on the intention-to-treat (ITT) population, which included all randomised patients who took at least 1 dose of double-blind study medication and who had at least 1 valid post-baseline assessment of the MADRS total score. The primary efficacy endpoint was defined as the change from baseline to week 8 in the MADRS total score, using the principle of last observation carried forward (LOCF). The primary analysis was based on a general linear model for analysis of covariance (ANCOVA) with factors for treatment and centre, and with baseline MADRS total score as a covariate. The non-inferiority test of escitalopram versus venlafaxine XR was performed at a 5% level of significance using a 90% confidence interval of the estimated differences between escitalopram and venlafaxine XR. The sample size of approximately 300 patients was similar to that of previous controlled comparative studies [10–12] and permitted detecting if the mean change from baseline in the MADRS total score at week 8 would differ by more than 3 points between escitalopram and venlafaxine.

Response was defined as a $\geq 50\%$ decrease in the MADRS total score from baseline and remission was defined as a MADRS total score ≤ 12 [22, 23]. Parametric survival analysis was used to investigate time to sustained remission and response (which required that remission/response was maintained at the following visit) for the ITT population using nominal visits, including factors for centre and treatment.

For the logistic regression analysis of the ITT population, sustained remitters/responders are patients who go into remission/response and stay in remission/response until week 8 [24], allowing only minor fluctuations in the MADRS total score at intermediate visits. Thus, patients who withdrew were not considered sustained remitters/responders.

Safety analyses were conducted on the all-patients-treated set, which included all randomised patients who took at least one dose of double-blind study medication. Treatment-emergent adverse events (TEAEs) were defined as new events reported during treatment or baseline events that worsened during treatment. A reported DESS item was defined as a new symptom or an already existing, but worsened symptom. Mean DESS scores at weeks 8 and 9 were analysed by ANCOVA with factors for treatment and centre. The DESS score at week 8 was included as a covariate in the analysis at week 9.

Results

Patient Population

A total of 293 patients entered the double-blind period (148 patients were randomised to escitalopram and 145 to venlafaxine XR; table 1). Of these, 2 patients in each treatment group never received double-blind treatment and 1 patient had no post-baseline assessment. The ITT population thus comprised 146 patients in the escitalopram group and 142 patients in the venlafaxine group. A total of 249 patients completed the study. There were no clinically relevant differences at baseline between the two treatment groups on the basis of demography or disease severity. At baseline, 57.5% of patients in the escitalopram group and 54.2% of patients in the venlafaxine group were moderately ill (MADRS total score between 18 and 29, extremes included).

Mean Daily Dose

A total of 22% of the patients in the escitalopram group and 24% of the patients in the venlafaxine group had their dose of antidepressant increased. The mean daily dose at week 8 was 12.1 mg for escitalopram and 95.2 mg for venlafaxine XR. The proportions of patients who took concomitant medication, including zolpidem (escitalopram 5.5%; venlafaxine XR 4.9%) were similar for both groups.

Premature Discontinuation

The incidence of withdrawals was low: 14.4% (21 patients) in the escitalopram group and 13.3% (19 patients) in the venlafaxine group. The proportions of patients who withdrew due to adverse events were 7.5% in the escitalopram group and 11.2% in the venlafaxine group. The adverse event with the highest incidence that led to withdrawal was nausea for both treatments. The proportions of patients who withdrew due to lack of efficacy were 4.1% in the escitalopram group and 2.1% in the venlafaxine group.

Efficacy

Change from Baseline in Depression Scores. Comparable efficacies of escitalopram and venlafaxine XR were achieved with respect to mean change from baseline in MADRS total score at week 8 (LOCF). The upper 90% confidence limit of 2.35 for the treatment difference at endpoint was within the specified 3 point margin. The mean MADRS total score (observed cases) decreased substantially over time for patients in both treatment groups (fig. 1; table 2). The same pattern was seen for the mean

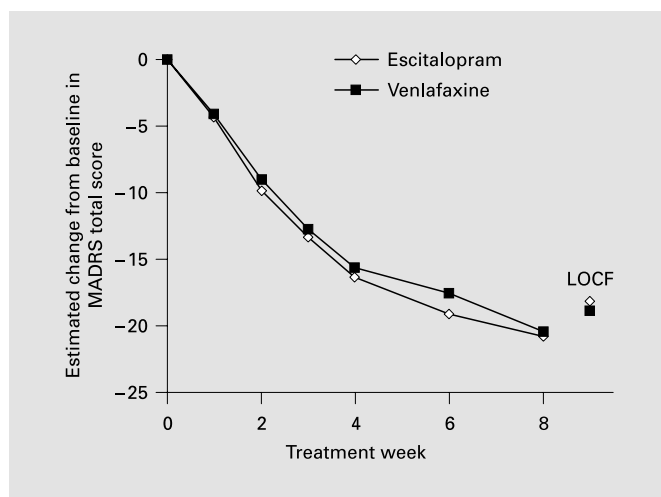


Fig. 1. Change from baseline in adjusted mean MADRS total scores (observed cases) for patients treated with escitalopram and venlafaxine XR. No statistically significant differences were obtained.

Table 1. Disposition, demographics, and mean baseline scores

	Escitalopram	Venlafaxine XR
<i>Disposition</i>		
Patients randomised	148	145
Patients treated	146	143
Patients completed	125 (86%)	124 (87%)
Patients withdrawn from study	21 (14%)	19 (13%)
Intention-to-treat	146	142
<i>Demographics</i>		
Sex		
Male	39 (27%)	42 (29%)
Female	107 (73%)	101 (71%)
Weight in kg, mean \pm SD	74 \pm 19	71 \pm 17
Age in years, mean \pm SD	49 \pm 15	47 \pm 14
<i>Baseline scores</i>		
MADRS total score, mean \pm SD	28.7 \pm 5.0	29.0 \pm 5.4
HAM-D ₁₇ total score, mean \pm SD	19.9 \pm 5.7	20.4 \pm 5.8

HAM-D₁₇ total score (table 2). In the model for the primary analysis, differences between centres were statistically significant ($p = 0.002$), but the treatment effect was not dependent on centre.

Response and Remission. There were approximately equal numbers of patients in both treatment groups who were responders or remitters at week 8 (table 3). Parametric survival analysis of time to sustained response (ITT $p < 0.01$) and sustained remission (ITT $p < 0.01$; fig. 2)

Table 2. Estimated mean change from baseline in MADRS and HAM-D₁₇ total scores

	MADRS (OC)				MADRS (LOCF)	
	escitalopram		venlafaxine XR		escitalopram	venlafaxine XR
	n	change	n	change	n = 146 change	n = 142 change
Week 1	144	-4.27	137	-4.05	-4.14	-3.84
Week 2	137	-9.88	133	-9.06	-8.84	-8.54
Week 3	136	-13.33	129	-12.76	-12.19	-11.80
Week 4	135	-16.37	129	-15.57	-14.91	-14.60
Week 6	128	-19.11	128	-17.50	-16.84	-16.43
Week 8	126	-20.74	125	-20.41	-18.16	-18.93

	HAM-D ₁₇ (OC)				HAM-D ₁₇ (LOCF)	
	escitalopram		venlafaxine XR		escitalopram	venlafaxine XR
	n	change	n	change	n = 146 change	n = 142 change
Week 1	144	-3.00	137	-2.73	-2.90	-2.61
Week 2	137	-7.20	133	-6.22	-6.43	-5.88
Week 3	136	-9.86	129	-8.88	-8.98	-8.12
Week 4	135	-11.79	129	-10.91	-10.57	-10.04
Week 6	128	-13.45*	128	-11.95	-11.78	-11.14
Week 8	126	-14.38	125	-14.00	-12.52	-12.83

* $p < 0.05$ in favour of escitalopram.

showed that escitalopram-treated patients achieved sustained response and sustained remission faster than venlafaxine-treated patients.

For those patients who achieved response at week 8, the escitalopram group achieved sustained response 4.6 days faster ($p < 0.05$) than the venlafaxine group. For those patients who achieved remission, escitalopram-treated patients achieved sustained remission 6.6 days faster (ANCOVA, $p < 0.001$) than did venlafaxine-treated patients (fig. 3b).

A logistic regression analysis was used at each visit to investigate whether there was a significant difference in the proportion of sustained remitters. The proportion of patients (ITT) with sustained remission was greater in the escitalopram group than in the venlafaxine group, reaching statistical significance at weeks 2, 3, and 4 (fig. 3a).

Tolerability

TEAEs. A total of 67% of patients in the escitalopram group and 71% of the patients in the venlafaxine group reported TEAEs during the double-blind period (weeks 1–8). Venlafaxine-treated patients had a significantly higher incidence of nausea, constipation and increased sweating than did escitalopram-treated patients, whereas no TEAEs had a significantly higher incidence in escitalopram-treated patients (fig. 4).

DESS. At the end of the 1-week run-out period (week 9), a total of 23 symptoms were reported with an incidence $\geq 10\%$ in either treatment group: 5 symptoms in the escitalopram group and 23 symptoms in the venlafaxine group. Of these, a total of 11 symptoms occurred with a statistically significantly higher incidence in the venlafaxine group than in the escitalopram group (fig. 5). At week 8, the mean number of DESS was similar in the two treatment groups (1.2 in the escitalopram group vs. 1.5 in the venlafaxine group). At week 9, the mean number of DESS in the venlafaxine group (mean: 5.0) was significantly ($p < 0.001$) higher than that in the escitalopram group (mean: 2.4). Significantly more venlafaxine-treated patients than escitalopram-treated patients had a change in DESS score ≥ 4 from week 8 to week 9 ($p < 0.01$, Fisher's exact test).

Laboratory Tests, Vital Signs, and ECGs. There were no apparent trends within or between treatment groups with respect to laboratory values, ECGs, or weight (mean loss of 0.1 kg for escitalopram-treated patients vs. 0.4 kg for venlafaxine-treated patients). For vital signs, there was a statistically significantly higher increase in seated pulse rate from baseline to last assessment for venlafaxine-treated patients (2.4 bpm vs. 0.7 bpm for escitalopram-treated patients; $p = 0.04$).

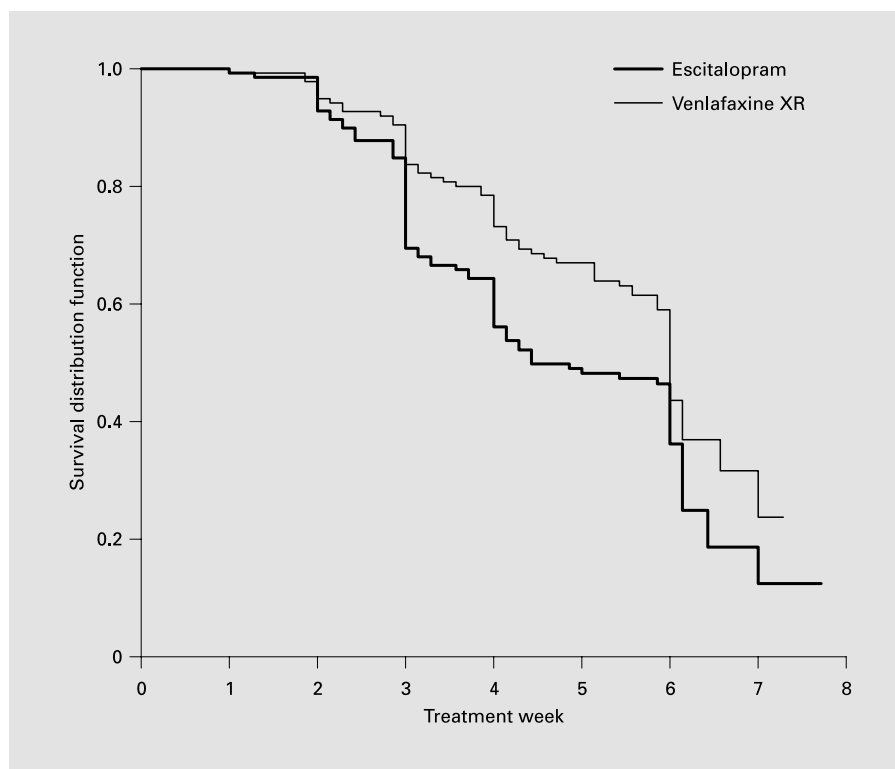


Fig. 2. Survival analysis. Time to sustained remission (ITT). Escitalopram-treated patients achieved sustained remission significantly faster than did venlafaxine-treated patients ($p < 0.01$).

Table 3. Responders, remitters and sustained responders/remitters

	Responders				Remitters			
	escitalopram n = 146		venlafaxine XR n = 142		escitalopram n = 146		venlafaxine XR n = 142	
	n	%	n	%	n	%	n	%
Week 1	4	2.8	4	2.9	3	2.1	1	0.7
Week 2	28	20.4	24	18.0	19	13.9	15	11.3
Week 3	57	41.9	51	39.5	49	36.0*	33	25.6
Week 4	82	60.7	72	55.8	72	53.3*	54	41.9
Week 6	104	81.3**	87	68.0	86	67.2	79	61.7
Week 8	110	87.3	108	86.4	99	78.6	93	74.4
Endpoint	113	77.4	113	79.6	102	69.9	99	69.7
	Sustained responders ^a				Sustained remitters ^a			
Week 1	3	2.05	2	1.41	3	2.05	1	0.7
Week 2	26	17.1	17	12.0	20	13.7*	8	5.63
Week 3	53	36.3	39	27.5	46	31.5**	27	19.0
Week 4	74	50.7	65	45.8	65	44.5**	44	31.0
Week 6	103	70.6*	84	59.2	86	58.9	74	52.1
Week 8	110	75.3	108	76.1	99	67.8	93	65.5

^a Sustained remitters/responders were defined as patients in remission/response that was maintained until week 8.

* $p < 0.05$; ** $p < 0.01$ in favour of escitalopram (logistic regression analysis including factors for treatment, centre, and baseline MADRS score).

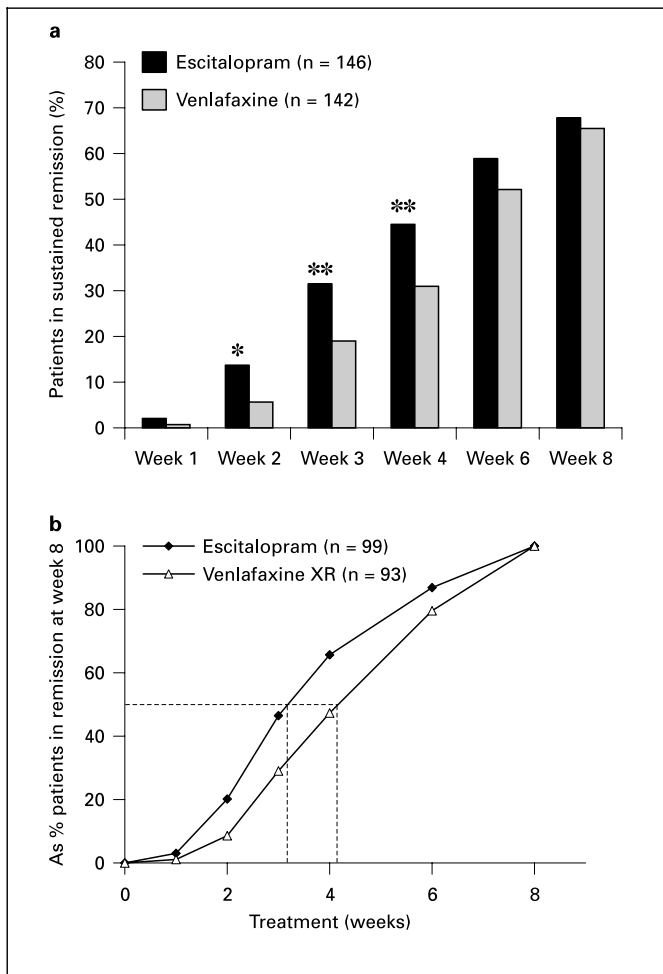


Fig. 3. **a** A larger proportion of escitalopram-treated patients achieved sustained remission at weeks 2–8 (ITT). * $p < 0.05$; ** $p < 0.01$ (logistic regression, including factors for treatment, centre, and baseline MADRS score). Sustained remission was defined as patients in remission (MADRS ≤ 12) that was maintained until week 8. **b** For those patients who achieved remission at week 8, escitalopram-treated patients ($n = 99$) achieved sustained remission 6.6 days faster (ANCOVA, $p < 0.001$) than did venlafaxine-treated patients ($n = 93$). The dotted lines indicate median time to achieve remission for each treatment group.

Discussion

This randomised, double-blind study comparing escitalopram to venlafaxine XR in the treatment of MDD showed clear treatment-related improvements in MADRS and HAM-D₁₇ scores in both treatment groups during the study. On the basis of the primary efficacy endpoint, the efficacy of escitalopram (10–20 mg) was similar to venlafaxine XR (75–150 mg) when used in primary care. This is in line with results seen in another study com-

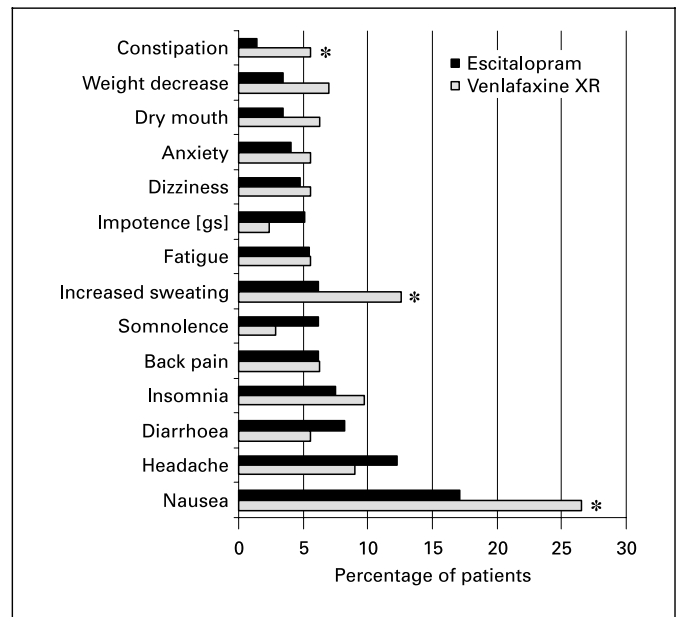


Fig. 4. TEAEs with an incidence $\geq 5\%$ in either treatment group (weeks 1–8). The incidence of nausea, increased sweating, and constipation was statistically significantly greater in the venlafaxine group than in the escitalopram group. * $p < 0.05$ (one-sided Fisher's exact test; H_0 : same incidences in the groups; H_1 : greater risk for venlafaxine-treated patients). gs = Gender specific.

paring escitalopram to venlafaxine XR in specialist settings, in which higher fixed doses were used for escitalopram (20 mg/day) and venlafaxine XR (225 mg/day); this study also showed comparable efficacy for escitalopram and venlafaxine treatment [25].

On the basis of a meta-analysis of the positive studies comparing venlafaxine to other SSRIs [8], it has been suggested that venlafaxine XR has higher remission rates in comparison to the SSRIs, mainly fluoxetine. This is not supported by the results of the present study with escitalopram. The 8-week remission rates of 69.9% (escitalopram) and 69.7% (venlafaxine) are higher than usually found. This result may, in part, reflect that placebo was not included in the present study. In previous studies with escitalopram that included a placebo arm, the remission rates were lower (e.g. 55% remission [14]). Higher remission rates are often seen in clinical studies including only active treatments, since the inclusion of a placebo arm can increase the readiness to withdraw patients from the study [26]. Thus the high completion rates in both treatment groups may contribute to the high remission rates reported.

While similar remission rates were found in the two treatment groups at the end of the study, it was of interest

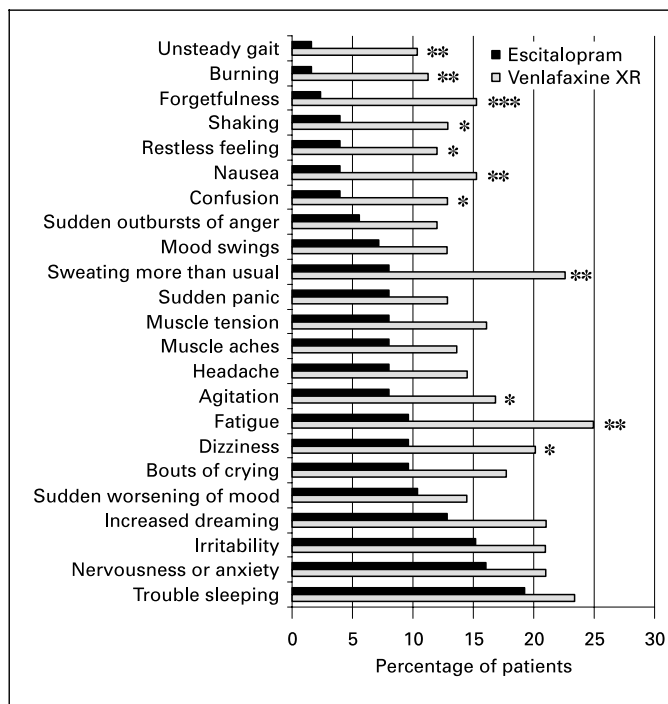


Fig. 5. DESS single items with an incidence $\geq 10\%$ at the end of the 1-week run-out period (week 9). The incidence of 11 symptoms was statistically significantly greater in the venlafaxine group than in the escitalopram group; no symptoms occurred with a greater incidence in the escitalopram group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (two-sided Fisher's exact test).

to see if these were achieved with similar speed during the treatment period. Therefore an analysis of the proportion of sustained remitters was performed. It was found that sustained remission was achieved almost 1 week faster with escitalopram ($p < 0.01$). This finding is of interest, as it may indicate reduced morbidity for some patients treated with escitalopram, although the overall outcome at week 8 was similar between the two drugs.

In the present study, only 22% of escitalopram-treated patients and 24% of venlafaxine-treated patients had their dose increased, as reflected in the mean daily doses at week 8. A recent drug utilisation observation study of 6,706 patients treated with venlafaxine by psychiatrists in routine care in Germany reported a dose increase in approximately 25% of outpatients [27]. The authors concluded that a dose of 75 mg/day was sufficient for the majority of cases, particularly outpatients, and that higher doses did not increase the response rate. Higher doses of venlafaxine were beneficial for inpatients with extremely severe depression. The dosing in primary care in the present study is therefore consistent with the conclusions of Linden et al. [27].

Escitalopram (10–20 mg/day) had a better tolerability profile than venlafaxine XR (75–150 mg/day). The blockade of noradrenaline reuptake by venlafaxine is probably a contributing factor. Systemic effects of venlafaxine on the cardiovascular system and salivary glands have previously been observed at single doses of 75 mg [28, 29]. In the present study, patients in the venlafaxine group had a statistically significantly greater mean increase in pulse rate. Furthermore, known noradrenergic effects, such as constipation and increased sweating [30], were observed in a significantly greater proportion of patients in the venlafaxine group than in the escitalopram group. Dry mouth was also reported with a higher incidence in the venlafaxine group.

Discontinuation symptoms represent a serious problem in clinical management. Several controlled studies have reported significant differences between antidepressants in discontinuation symptoms observed following treatment interruption, with fluoxetine and citalopram associated with the lowest level of discontinuation symptoms compared to paroxetine [21, 31, 32]. Venlafaxine has been associated with significant discontinuation symptoms and a down-tapering regimen is recommended [33]. In spite of down-tapering in the present study, significantly more discontinuation symptoms were observed in the venlafaxine group than in the escitalopram group.

In conclusion, this randomised, double-blind study comparing the SSRI escitalopram (10–20 mg/day) with the non-selective venlafaxine XR (75–150 mg/day) showed that the efficacy of escitalopram was similar to that of venlafaxine XR and that escitalopram had benefits with respect to tolerability in the treatment of primary care patients with MDD.

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