Differential effects of venlafaxine compared to selective serotonin reuptake inhibitors (SSRIs) in the treatment of MDD according to baseline severity – A Meta-Analysis

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Abstract

Objectives: Prior meta-analyses have suggested superior efficacy of venlafaxine compared to SSRIs. In this meta-analysis we compared the efficacy of venlafaxine and SSRIs in patients with MDD classified according to baseline severity

Methods: Data from 31 venlafaxine studies were pooled and remission rates defined as ≤ 7 on the HAM-D_{17} - score were analyzed. Subjects were divided into two groups based on their baseline HAM-D-17 total score ≥ 30 / < 30. Fisher's exact test was used to compare the treatment effects on the remission rates for each subgroup. All of the analyses were based on intent-to-treat patients, LOCF and completer analysis were performed using standardized measurements.

Results: 5836 patients with a baseline HAM-D_{17} < 30 could be identified. The LOCF analysis revealed, that the OR is 1.31 (95% CI 1.18, 1.46), p < 0.001 and the NNT is 16, whereas the completer analysis revealed, that the OR is 1.25 (95% CI 1.09, 1.43), p = 0.001 and the NNT is 16. Remission data for 656 patients with a baseline HAM-D_{17} > 30 were available. The LOCF analysis revealed, that the OR is 1.55 (95% CI 1.10, 2.18), p = 0.015 and the NNT is 11, whereas the completer analysis revealed, that the OR is 1.93 (95% CI 1.25, 2.97), p = 0.003 and the NNT is 7.

Conclusion: This analysis demonstrates that venlafaxine is superior to SSRIs in both the mild/moderate and severe depression in achieving remission. However, the magnitude of superiority was higher in the subgroup of patients with a baseline HAM-D_{17} ≥ 30 suggesting a pronounced clinical benefit for the treatment of severely depressed patients.

Introduction

Results of pooled analysis of relevant clinical trials suggest, that Venlafaxine is associated with higher remission rates than SSRIs. A recent meta-analysis (Nemeroff et al. 2008) showed a difference in remission rates of 6% in favor of venlafaxine suggesting a modest clinical advantage compared to SSRIs. Little data are available which analyse the clinical outcome based on the baseline severity of the disease. Due to generic competition by several classes of antidepressants (e.g. SSRIs) and national/international guidelines venlafaxine is widely used as second or third line therapy. Results of studies in treatment resistant depression demonstrated the efficacy of venlafaxine in depressed patients after failure of SSRIs (Baldomero et al. 2005, Thase et al. 2006).

The purpose of this meta-analysis was to extend the findings of a previous meta-analysis (Nemeroff et al. 2008) comparing the efficacy of venlafaxine and SSRIs in patients with MDD classified according to baseline severity. Similarly to the previous report this analysis was performed on an all-inclusive set of Wyeth-sponsored studies, for which individual patient data were available.

Methods

The data of the recent meta-analysis (Nemeroff et al. 2008) were used for the subanalysis shown here. Individual patient data were obtained from all studies completed by Wyeth Pharmaceuticals comparing venlafaxine and an SSRI in the treatment of major depressive disease (ca. January 2007). 31 from the reported 34 randomized controlled double-blind trials could be used for this analysis, showing. Further details concerning individual study characteristics like inclusion or exclusion criteria or detailed description of design are described by Nemeroff et al. 2008.

Twenty studies used venlafaxine immediate release (IR) and 11 studies used venlafaxine extended release (ER). The SSRI comparators were fluoxetine (18 studies), paroxetine (8 studies), sertraline (3 studies), citalopram (1 study) and fluvoxamine (1 study). Nine studies also included a placebo control group. Only Venlafaxine and SSRI (as a group) patients were included for the purpose of this analysis.

All analyses were based on the pooled data of the intent to treat (ITT) population. The ITT population included all randomized subjects who had a baseline HAM-D_{17} evaluation, received at least one dose of study medication and had at least one on-therapy assessment of HAM-D_{17}.

Primary endpoint was the remission rate after 8 weeks of treatment, a remission defined as a HAM-D_{17} ≤ 7. For the observed cases analysis (OC) data were included of patients completing at least 8 weeks and showing values for that time point. LOCF analysis was carried out by carrying forward the last observed value in case of missing data at week 8.

Subjects were divided into two subgroups based on their baseline HAM-D_{17} total score. Patients with HAM-D17 ≥ 30 were considered as severely depressed and patients with HAM-D_{17} < 30 were considered as mildly to moderately depressed patients.

Fisher's exact test was used to compare treatment effects between venlafaxine and SSRI on the remission rates for each subgroup. No multiple comparison adjustment was made. For all studies included, a combined total effect size was computed as a raw odds ratio with 95 % confidence interval. NNTs (numbers needed to treat) were calculated to estimate clinical significance of differences.

Results

The 6592 patients of the ITT population (intent to treat) were divided into two subgroups following severity of depression at baseline before treatment, 5836 (venlafaxine: n=2925; SSRI: n=2911) patients with mild to moderate depression (baseline HAM-D_{17} < 30) and 656 (venlafaxine: n=349; SSRI: n=307) patients with severe depression (baseline HAM-D_{17} ≥ 30). Remission rates of venlafaxine were significantly superior to those of SSRI treated patients as a group in both severity groups (Figure 1). In OC analysis remission rates with venlafaxine and SSRIs were generally higher for patients with mild to moderate depression (50.0 % vs. 44.5 %) than for patients with severe depression (42.2 % vs. 27.6 %). The difference between treatment groups was more pronounced in severely depressed patients (14.8 %) than in patients with mild to moderate depression (5.5 %). Results of LOCF analysis were very similar (Figure 1).

Comparison of groups was characterized with further statistics (table 1). For patients with mild to moderate depression: in LOCF analysis, odds ratio (OR) was 1.31 (95% confidence interval CI 1.18 – 1.46), p < 0.001 and a number needed to treat (NNT) of 16 was calculated. OC analysis showed an OR of 1.25 (95 % CI 1.09 – 1.43), p = 0.001 and an NNT also of 16. For patients with severe depression LOCF analysis revealed an OR of 1.55 (95 % CI 1.10 – 2.18), p = 0.015 and an NNT of 11. OC analysis showed an OR of 1.93 (95 % CI 1.25 – 2.97), p = 0.003 and NNT was 7. Odds ratios generally favoured therapy with venlafaxine compared to SSRI treatment as a group. For patients with severe depression smaller NNTs could be reached than for patients with mild to moderate depression.

Figure 1: Comparison of remission rates in the treatment with venlafaxine vs. SSRIs in patients with mild / moderate depression (HAM-D_{17} < 30) or with severe depression (HAM-D_{17} ≥ 30). OC: observed cases, LOCF: last observation carried forward, Diff.: Difference, HAM-D_{17}: 17 items Hamilton depression scale

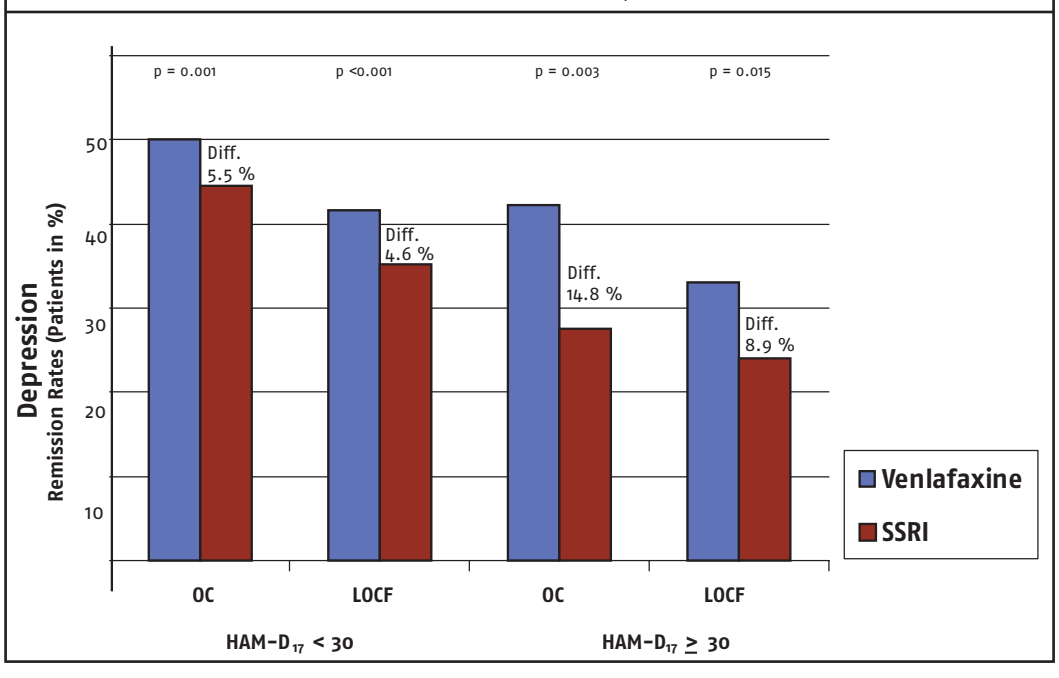

Table 1: Comparison of remission rates in the treatment with venlafaxine vs. SSRIs in patients with mild / moderate depression (HAM-D_{17} < 30) or with severe depression (HAM-D_{17} ≥ 30). OC: observed cases, LOCF: last observation carried forward, CI: confidence interval, HAM-D_{17}: 17 items Hamilton depression scale, NNT: number needed to treat.

Severity of Depression	Population	Group	Remission (%)	Difference (%)	p value	Odds Ratio (95 % CI)	NNT
Baseline HAMD 17 < 30	OC	Venlafaxine	50.0%	5.5%	0.001	1.25 (1.09-1.43)	16
		SSRI	44.5%				
	LOCF	Venlafaxine	41.6%	6.4%	< 0.001	1.31 (1.18-1.46)	16
		SSRI	35.2%				
Baseline HAMD 17 ≥ 30	OC	Venlafaxine	42.2%	14.8%	0.003	1.93 (1.25-2.97)	7
		SSRI	27.6%				
	LOCF	Venlafaxine	33.0%	8.9%	0.015	1,55 (1.10-2.18)	11
		SSRI	24.1%				

Conclusion

This analysis demonstrates that venlafaxine is superior to SSRIs as a class in both the mild/moderate and severe depression in achieving remission. However, the magnitude of superiority was higher in the subgroup of patients with a baseline HAM-D_{17} ≥ 30 suggesting a pronounced clinical benefit for the treatment of severely depressed patients.

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Treatment effects of venlafaxine on work activity compared to SSRIs in the treatment of MDD according to baseline severity

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Abstract

Objectives: In this meta-analysis we compared the effects of venlafaxine and SSRIs on work activity in major depressive disorder (MDD) patients classified according to baseline severity

Methods: Data from the work and activity item 7 of the $HAMD_{17}$ of 31 pooled studies comparing venlafaxine with SSRIs were used. Subjects were divided into two groups based on their baseline $HAMD_{17}$ total score ≥30/< 30.Score distributions and the proportions of patients achieving full work functionality were summarized for both LOCF and Completers at week 8. Fisher's exact test was used to compare the treatment effects.

Results: 5836 patients with a baseline $HAMD_{17}$ <30 were identified. The OR for all subjects achieving full work functionality is 1.22 (95%CI 1.08, 1.36), p<0.001 for LOCF and 1.19 (95%CI 1.04, 1.38), p=0.015 for completers. The OR for subjects with work impairment at baseline is 1.17 (95%CI 1.02, 1.35), p=0.029 for LOCF and 1.13 (95%CI 0.95, 1.35), p=0.18 for completers. 656 patients with a baseline $HAMD_{17}$ >30 were identified. The OR for all subjects achieving full work functionality is 1.80 (95%CI 1.24, 2.63), p=0.002 for LOCF and 1.64 (95%CI 1.05, 2.58), p=0.032 for completers. The OR for subjects with work impairment at baseline is 1.93 (95%CI 1.30, 2.87), p=0.001 for LOCF and 1.81 (95%CI 1.12, 2.92), p=0.017 for completers.

Conclusion: This analysis demonstrates that venlafaxine is superior to SSRIs in improving work functionality in both mild/moderate and even more pronounced in severe depression. These results emphasize the impact of the treatment with venlafaxine on patients returning to normal social life.

Introduction

The prevalence of major depression in working people (Eaton et al. 1990) causes a considerable work impairment (Kessler et al. 1997). Treatment with antidepressants can reduce depression symptom severity and restore occupational functioning (Finkelstein et al. 1996), defined as response or remission of depression and the concomitant work impairment. A recent meta-analysis (Nemeroff et al. 2008) showed a difference of remission rates in favour of the serotonin-norepinephrine reuptake inhibitor venlafaxine versus selective serotonin reuptake inhibitors (SSRIs) as a class. Several meta-analyses showed a 6 – 8 % difference in remission rates in favour of venlafaxine compared to SSRIs (Smith et al. 2002). However, the clinical relevance of these findings have been controversially discussed. Remission is associated with improved quality of life and work activity. Little data are available which investigate the impact of antidepressant therapy on work activity by randomized controlled trials. Therefore, this analysis used data from the Work and Activities item of the 17-item Hamilton Rating Scale for Depression (HAM-$DHAMD_{17}$) of the meta-analysis of Nemeroff et al. (2008) differentiating the effects in patients with mild or moderate depression and with severe depression.

Methods

The data of the recent meta-analysis (Nemeroff et al. 2008) were used for the subanalysis shown here. Individual patient data were obtained from all studies completed by Wyeth Pharmaceuticals comparing venlafaxine and an SSRI in the treatment of major depressive disease (ca. January 2007). 31 from the reported 34 randomized controlled double-blind trials were used for this analysis. Further details concerning individual study characteristics like inclusion or exclusion criteria or detailed description of design are described by Nemeroff et al. 2008.

Twenty studies used venlafaxine immediate release (IR) and 11 studies used venlafaxine extended release (ER). The SSRI comparators were fluoxetine (18 studies), paroxetine (8 studies), sertraline (3 studies), citalopram (1 study) and fluvoxamine (1 study). Nine studies also included a placebo control group. Only Venlafaxine and SSRI (as a group) patients were included for the purpose of this analysis.

All analyses were based on the pooled data of the intent to treat (ITT) population. The ITT population included all randomized subjects who had a baseline HAM-$DHAMD_{17}$ evaluation, received at least one dose of study medication and had at least one on-therapy assessment of HAM-D_{17}. For the observed cases analysis (OC) data were included of patients completing at least 8 weeks and showing values for that time point. LOCF analysis was carried out by carrying forward the last observed value in case of missing data at week 8.

Item 7 of HAM-D_{17} score at week 8 was used to rate the work activity. Patients with full work functionality showed an item 7 score of 0 and were defined as remitted concerning work activity.

Subjects were divided into two subgroups based on their baseline HAM-D_{17} total score: HAM-D_{17} ≥ 30 and HAM-D_{17} < 30. Data were analyzed for both subgroups within the total ITT population and within subjects having work impairment at baseline defined as an item 7 score of 1 or more.

Fisher's exact test was used to compare treatment effects between venlafaxine and SSRI on the remission rates for each subgroup. No multiple comparison adjustment was made. For all studies included, a combined total effect size was computed as a raw odds ratio with 95 % confidence interval.

Results

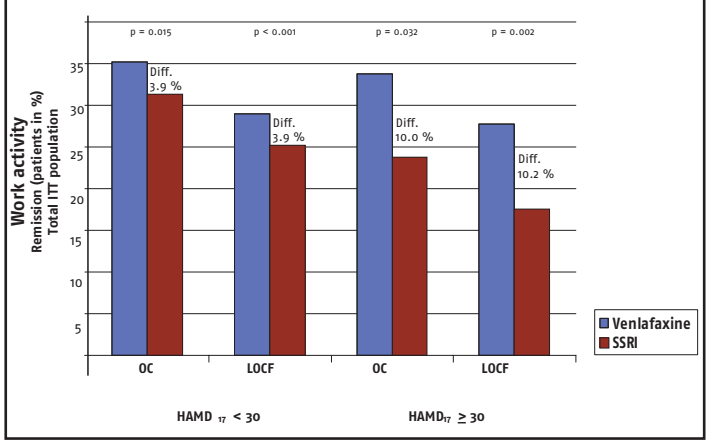
In this meta-analysis we compared the effects of venlafaxine and SSRIs on work activity in MDD patients classified according to baseline severity. The 6592 patients of the ITT population (intent to treat) were divided into two subgroups following severity of depression at baseline before treatment, 5836 (venlafaxine: n=2925; SSRI: n=2911) patients showing a baseline HAM-D_{17} < 30 and 656 (venlafaxine: n=349; SSRI: n=307) patients showing a baseline HAM-D_{17} ≥ 30. Remission was defined for item 7 of HAM-D_{17} (work and activity) by reaching a score of 0 (no impairment) at week 8.

Including all patients of the ITT population OC analysis resulted in the following remission rates for work activity for patients treated with venlafaxine and SSRIs respectively (figure 1): 35.2 % vs. 31.3 % for patients with mild to moderate depression (baseline HAM-D_{17} < 30) and 33.8 % vs. 23.8 % for patients with severe depression (baseline HAM-D_{17} ≥ 30). LOCF results were similar. All comparisons reached statistical significance. The difference in remission rates of venlafaxine and SSRIs were more pronounced for severely depressed patients (difference about 10 %) than for patients with mild to moderate depression (below 4 %).

Table 1:
Work activity (total ITT population)
OC: observed cases, LOCF: last observation carried forward, CI: confidence interval, HAM-D_{17}: 17 items Hamilton depression scale.

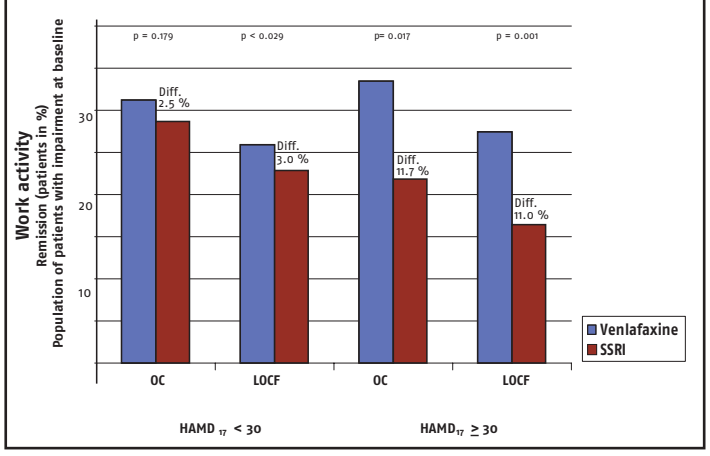
Severity of Depression	Population	Group	Remission (%)	Difference (%)	p value	Odds Ratio (95 % CI)
Baseline $HAMD_{17}$ < 30	OC	Venlafaxine	35.2%	3.9%	0.015	1.19 (1.04–1.38)
		SSRI	31.3%			
	LOCF	Venlafaxine	29.0%	3.8%	< 0.001	1.22 (1.08–1.36)
		SSRI	25.2%			
Baseline $HAMD_{17}$ ≥ 30	OC	Venlafaxine	33.8%	10.0%	0.032	1.64 (1.05–2.58)
		SSRI	23.8%			
	LOCF	Venlafaxine	27.8%	10.2%	0.002	1.80 (1.24–2.63)
		SSRI	17.6%			

Figure 1:
Work activity (total ITT population)
OC: observed cases, LOCF: last observation carried forward, Diff.: Difference, HAM-D_{17}: 17 items Hamilton depression scale.



Since remission of work activity was defined as a score of 0 in item 7 of HAM-D_{17}, further analyses were carried out with patients showing already at baseline impairment of work activity (item 7 > 0). This criterion was met for 4692 patients of the ITT population, 4084 (venlafaxine: n=2060; SSRI: n=2024) of them showing a baseline HAM-D_{17} < 30 and 608 (venlafaxine: n=321; SSRI: n=287) showing a baseline HAM-D_{17} ≥ 30. In this population remission rates (OC analysis) for venlafaxine or SSRI were 31.2 % vs. 28.7 % (not significant) in the mildly to moderately depressed group and 33.5 % vs. 21.8 % for the severely depressed group. Results of LOCF analysis showed the same tendency. In this population again, the difference of remission rates between therapy groups was more pronounced for the group with baseline HAM-D_{17} ≥ 30 (11.7 % / 11.0 %) than for the group with baseline HAM-D_{17} < 30 (2.5 % / 3.0 %), as shown in figure 2.

Figure 2:
Work activity (population with impairment in work activity at baseline)
OC: observed cases, LOCF: last observation carried forward, Diff.: Difference, HAM-D_{17}: 17 items Hamilton depression scale.



Comparison of groups was characterized with further statistics (table 1 and 2). Patients with mild or moderate depression: The odds ratio (OR) for remission of impairment of work activity in the total ITT population was 1.22 (95 % CI 1.08 – 1.36), p < 0.001 in LOCF analysis and 1.19 (95 % CI 1.04 - 1.38), p = 0.015 in OC analysis. With regard to the population of patients with impairment of work activity already at baseline, an OR of 1.17 (95 % CI 1.02 – 1.35), p = 0.029 was found in LOCF analysis and of 1.13 (95 % CI 0.95 – 1.35), p = 0.18 in OC analysis. Patients with severe depression: The odds OR for remission of impairment of work activity in the total ITT population was 1.80 (95 % CI 1.24 – 2.63), p = 0.002 in LOCF analysis and 1.64 (95 % CI 1.05 – 2.58), p = 0.032 in OC analysis. With regard to the population of patients with impairment of work activity already at baseline, an OR of 1.93 (95 % CI 1.30 – 2.87), p = 0.001 was found in LOCF analysis and of 1.81 (95 % CI 1.12 – 2.92), p = 0.017 in OC analysis.

Table 2:
Work activity (population with impairement in work activity at baseline)
OC: observed cases, LOCF: last observation carried forward, CI: confidence interval, HAM-D_{17}: 17 items Hamilton depression scale.

Severity of Depression	Population	Group	Remission (%)	Difference (%)	p value	Odds Ratio (95 % CI)
Baseline $HAMD_{17}$ < 30	OC	Venlafaxine	31.2%	2.5%	0.179	1.13 (0.95–1.35)
		SSRI	28.7%			
	LOCF	Venlafaxine	25.9%	3.0%	0.029	1.17 (1.02–1.35)
		SSRI	22.9%			
Baseline $HAMD_{17}$ ≥ 30	OC	Venlafaxine	33.5%	11.7%	0.017	1.81 (1.12–2.92)
		SSRI	21.8%			
	LOCF	Venlafaxine	27.4%	11.0%	0.001	1.93 (1.30–2.87)
		SSRI	16.4%			

Conclusion

Given the substantial work impairment associated with MDD, evaluating antidepressant treatment in terms of return to work functioning is important.

For this analysis it was possible to define a remission for the HAM-D_{17} item 7 (work and activities). A significant superiority could be demonstrated for venlafaxine vs. SSRIs for the remission rate concerning item 7. A smaller proportion of the investigated population started treatment without a baseline impairment in work and activities. Analysis only for patients with impairment in item 7 at baseline corroborated results of the total population. Superiority could be demonstrated for mild/moderate depression and for severe depression. There was a more pronounced difference of effects of venlafaxine versus SSRIs in the population with severe depression.

This analysis demonstrates that venlafaxine is superior to SSRIs as a class in improving work functionality in both mild/moderate and even more pronounced in severe depression. These results emphasize the impact of the treatment with venlafaxine on patients returning to normal social life.

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