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Selective serotonin and norepinephrine reuptake inhibitors (SNRI) for patients with depression[1]

Executive Summary

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Selective serotonin and norepinephrine reuptake inhibitors (SNRI) for patients with depression

Executive summary

Background

In its letter of 22 February 2005 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out a benefit assessment of antidepressants for patients suffering from depression. On 27 April 2005 and 30 May 2005 the G-BA specified the commission in writing.

Research question

The aim of this research is to

- assess the benefit of the selective serotonin and norepinephrine reuptake inhibitors (SNRI) venlafaxine and duloxetine in treating the acute phase of depression, in maintenance therapy (relapse prevention), and in recurrence prevention compared to
    - treatment with placebo,
    - treatment with other antidepressants,
    - each other,

in each case in adult patients with depression with reference to patient-relevant outcomes.

Methods

A systematic literature search for relevant primary and secondary publications (systematic reviews, HTA reports) was carried out in the following databases: MEDLINE, EMBASE, PsycINFO, PSYNDEX plus and CENTRAL (unrestricted search period, last search in each case January 2008). In addition a search for primary publications was performed in PsiTri (last search in May 2007). A search for secondary publications was also carried out in the following specialized databases: CDSR, DARE and HTA (last search in each case January 2008). The bibliographic indexes of relevant secondary publications were searched as well as clinical trial registries and publicly accessible drug approval documents. Furthermore, the manufacturers of the drugs approved in Germany were asked to provide information on published and unpublished trials.

Randomized controlled trials were included that compared duloxetine or venlafaxine with placebo or other chemically defined antidepressants (including in each case the other test drug) and/or St. John’s Wort in the treatment of patients with depression. The minimum study

duration was 6 weeks for acute treatment, 6 months for relapse prevention and 12 months in the recovery stage for recurrence prevention.

The literature screening was carried out by 2 reviewers independently of each other. After assessing the study quality, the results of the individual trials were collated according to test drugs and outcomes, and subsequently described. Meta-analyses were carried out if this was considered feasible and useful. To prove a benefit, it was required that the effect exceeded a defined limit (relevance limit, Cohen's d/Hedges' g = 0.2) for results of continuous scales, in addition to the statistical significance of group difference.

Results

Duloxetine

A total of 16 relevant trials on duloxetine were identified. The designs of 15 of the trials included in the benefit assessment examined the effect in the acute phase of depression. One long-term trial covered therapy for relapse prevention. In total, the study and publication quality was good in the majority of studies. Several acute trials had minor flaws, mostly due to insufficient description concerning randomization, concealment of allocation to the treatment groups, and blinding methods. In the case of one trial, study and publication quality were graded as "grossly deficient" as the publication revealed relevant differences in favour of duloxetine in the results of the primary outcome when compared to the study report.

Table 1 gives an overview of the patient-relevant outcomes that were assessed in the included trials. The most important results of the trials with duloxetine are summarized in Table 2. Data on additional outcomes can be found in the following text. The summary focuses on the comparison of duloxetine with placebo and with the SSRI[2] drug class. Results from the comparison of duloxetine with individual drugs are only presented if they showed superiority or inferiority of one antidepressant. More detailed results on individual comparators can be found in the main part of the report.

[2] Selective serotonin reuptake inhibitors

Table 1: Overview of patient-relevant outcomes in the trials with duloxetine

	Depression	Individual and accompanying symptoms	Adverse events	Sexual dysfunction	Health-related quality of life	Social functioning level
Duloxetine versus placebo						
Acute trials	●	● anxiety, pain, cognition, somatization	●	●	●	●
Long-term trial (relapse prevention)	●	● pain, somatization	●		●	●
Duloxetine versus escitalopram						
Acute trials	●	● anxiety	●	●	●	●
Duloxetine versus fluoxetine						
Acute trials	●	● anxiety	●	●	●	
Duloxetine versus paroxetine						
Acute trials	●	● anxiety, pain, somatization	●	●	●	●
●: Data reported						

Table 2: Summary of the comparison of duloxetine with placebo and SSRI

Outcome	**Result of the meta-analyses and individual trials Group difference [95 % CI]**			
	DUL vs. plc[a]			**DUL vs. SSRI[a]**
	Short-term acute therapy	**Long-term acute therapy[b]**	**Relapse prevention[b]**	**Short-term acute therapy**
Remission[c]	1.91 [1.56; 2.34]		n. r.	1.11 [0.91; 1.34]
Response[c]	1.95 [1.61; 2.36]		n. r.	0.96 [0.80; 1.15]
Depression scale total score	-0.35 [-0.45; -0.24][d,f]	-2.49 [-4.55; -0.43] -0.25 [-0.45; -0.04][g]	not rep. [-5.86; -2.88] -0.70 [-0.95; -0.45][f]	-0.05 [-0.67; 0.58][e]
Relapse rates	n. r.	n. r.	p = 0.042	
AE[c]	1.91 [1.50; 2.43]	p = 0.107	p = 0.128	1.23 [1.01; 1.50]
SAE[c]	0.96 [0.39; 2.34]	p = 0.486	p = 0.246	1.65 [0.60; 4.54]
Discontinuation due to AE[c]	2.22 [1.55; 3.19]	p = 0.444	p = 0.997	1.53 [1.10; 2.13]
Sexual dysfunction (ASEX)	0.81 [0.12; 1.50][e] 0.2 [0.04; 0.37][g]	n. s.		-0.41 [-1.09; 0.27][e]
Anxiety (HAMA)	-1.51 [-2.15; -0.87][e] -0.26 [-0.40; -0.13][g]			-0.05 [-0.52; 0.42][e]

(continued)

Table 2 (continued): Summary of the comparison of duloxetine with placebo and SSRI

Outcome	**Result of the meta-analyses and individual studies Group difference [95 % CI]**			
	DUL vs. plc[a]			**DUL vs. SSRI[a]**
	Short-term acute therapy	**Long-term acute therapy[b]**	**Relapse prevention[b]**	**Short-term acute therapy**
Pain (VAS)	-4.56 [-6.79; -2.33][e] -0.20 [-0.30; -0.10][g]			
Cognition (MMSE)	0.04 [-0.48; 0.57][b]			
Somatic symptoms (SSI-28; SQ-SS: Relapse prevention)	-0.09 [-0.14; -0.04][e] -0.19 [-0.30; -0.08][g]		not rep. [-1.1; 0.26]	
Health-related quality of life (SF-36 psychological health; QLDS)	3.48 [1.30; 5.67][e] 0.28 [0.10; 0.45][g]; -3.08 [-4.40; -1.76][e] -0.34 [-0.49; -0.20][f]		-3.46 [-5.54; -1.37] -0.41 [-0.68; -0.13][g]	
Social functioning level (EWPS; SDS)	n. s.[b]; -3.26 [-4.49; -2.02][e] -0.46 [-0.64; -0.28][f]	n. s.	-4.12 [-6.06; -2.18] -0.55 [-0.83; -0.28][f]	

Details of the results are contained in the main part of the report.
a: Result from one meta-analysis (if not otherwise designated)
b: Result from one individual study
c: Odds Ratio (if not otherwise designated)
d: Hedges' g
e: Mean difference

When interpreting the effect sizes, the confidence interval was set in relation to the relevance limit of 0.2 in Cohen's d/Hedges' g. If the confidence interval was completely above the relevance limit, a relevant effect size was assumed and proof or indication of benefit was attested. If the confidence interval lay partially or completely below this limit, the relevance of this effect could not be estimated with sufficient certainty. Thus, it remained unclear whether the effect size had attained a range that had relevance for benefit. In these cases, the benefit remained unclear and a benefit was not proven.
f: Relevant effect size (Cohen's d/Hedges' g)
g: Relevance of this effect cannot be estimated with sufficient certainty (Cohen's d/Hedges' g)

AE: adverse events; ASEX: Arizona Sexual Experience Questionnaire; CI: confidence interval; DUL: duloxetine; EWPS: Endicott Work Productivity Scale; HAMA: Hamilton Anxiety Scale; MMSE: Mini Mental State Examination; not rep.: not reported; n. r.: not relevant; n. s.: not significant; plc: placebo; QLDS: Quality of Life in Depression Scale; SAE: serious adverse events; SDS: Sheehan Disability Scale; SF-36: Short-Form-36; SQ-SS: Symptom Questionnaire Somatic Subscale; SSI-28: Somatic Symptom Inventory; SSRI: Selective Serotonin Reuptake Inhibitor; VAS: Visual Analogue Scale

Antidepressive effect

There was a statistically significant advantage for the **remission** outcome in the meta-analyses of duloxetine compared to placebo. In the comparison of duloxetine with SSRI, no statistically significant difference was observed in the remission rates. Thus, in outpatient

acute therapy for depression, there is proof of benefit compared to placebo, but no proof of additional benefit compared to the SSRI class.

The meta-analyses on the **response** outcome showed a statistically significant advantage of duloxetine compared to placebo. A comparison of duloxetine and SSRI did not yield a statistically significant difference. Thus, in summary, there was also a proof of benefit compared to placebo in outpatient acute therapy for depression, but no proof of additional benefit compared to SSRI.

For the mean change in depressive symptoms (**depression scale total score**) in outpatient acute therapy for depression, there was a statistically significant and relevant advantage for duloxetine compared to placebo. Thus, proof of a benefit from duloxetine compared to placebo existed. In the "long-term" acute therapy, the relevance of the present effect could not be estimated with certainty. The benefit remained unclear and was thus not proven. In the comparison of duloxetine and the SSRI class, there was no statistically significant difference. Thus, there was no proof of additional benefit from duloxetine.

With **relapse rates** of 23/132 participants (17.4 %) for duloxetine and 39/137 (28.5 %) for placebo, duloxetine was statistically significantly superior to placebo in preventing a relapse. The mean change in depressive symptoms (depression scale total score) on the HAMD-17[3] yielded a statistically significant difference in favour of duloxetine compared to placebo. The observed effect was relevant. Overall, the results of the long-term trial on relapse prevention showed an indication of benefit from duloxetine compared to placebo.

Adverse drug effects

There was a comparable pattern in the results of the **total rates of adverse events and therapy discontinuations due to adverse events**. Both outcomes showed proof of harm from duloxetine compared to placebo in outpatient acute therapy for depression. In the "long-term" acute trial, there was no proof of harm from duloxetine compared to placebo as the differences were not statistically significant. In the comparison of duloxetine with placebo, the long-term trial on relapse prevention did not provide proof of harm for the two outcomes, total rate of adverse events and therapy discontinuations due to adverse events. In outpatient acute therapy for depression, the comparison of duloxetine and SSRI showed proof of greater harm from duloxetine for these 2 outcomes.

For the **total rates of serious adverse events**, the comparison of duloxetine and placebo in outpatient acute therapy for depression yielded no proof of harm from duloxetine. There was also no proof of harm from duloxetine compared to placebo in the "long-term" acute trial that was not contained in the meta-analysis. This result was also evident in the only relapse-prevention trial. Furthermore, the meta-analyses of serious adverse events in the comparison

[3] Hamilton Depression Scale

of duloxetine and SSRI in acute therapy yielded no proof of greater or lesser harm from duloxetine.

The comparison of duloxetine and placebo in outpatient "short-term" acute therapy showed a statistically significant group difference for **sexual dysfunction**, measured using **ASEX**[4]. The relevance of the effect was uncertain. The data from the only study that documented **CSFQ**[5] for outpatient "short-term" acute therapy in women yielded a statistically significant result ($p < 0.05$, mean change compared to start of study [SD[6]]: duloxetine 1.12 [0.60], placebo 3.42 [0.85]), but its relevance could not be estimated. No statistically significant differences from duloxetine compared to placebo were reported in the male population in the "short-term" acute phase of the trial, nor in the male and female population in the "long-term" acute phase of the trial. The comparison of duloxetine with SSRI showed a group difference in **ASEX**, which was not statistically significant. In summary, for the sexual dysfunction outcome, there was an effect in acute therapy for depression, but its relevance could not be estimated with certainty. The harm from duloxetine remained unclear and was therefore not proven. There was also no proof of greater or lesser harm from duloxetine than from SSRI.

Based on the **number of patients with high blood pressure**, there was no proof of harm from duloxetine compared to placebo or of greater or lesser harm compared to the SSRI drug class. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on high blood pressure and low event rates). For this reason, no data on individual results are given here.

Change in individual symptoms and/or accompanying symptoms

The meta-analysis on **anxiety symptoms** using **HAMA**[7] yielded a statistically significant result in favour of duloxetine compared to placebo in outpatient acute therapy for depression. The relevance of this effect, however, could not be estimated with certainty. The benefit, therefore, remained unclear and was not proven. The comparison of duloxetine and SSRI did not show a statistically significant difference and thus no proof of additional benefit from duloxetine.

The meta-analysis on the influence on **pain symptoms** using **VAS**[8] yielded a statistically significant result in favour of duloxetine in the comparison of duloxetine and placebo in outpatient acute therapy for depression. However, the relevance of this effect could not be estimated with certainty. The benefit, therefore, remained unclear and there was no proof of

[4] Arizona Sexual Experience Questionnaire
[5] Changes in Sexual Functioning Questionnaire
[6] Standard deviation
[7] Hamilton Anxiety Scale
[8] Visual Analogue Scale

benefit. The result of the only relapse-prevention trial provided insufficient data on the comparison of duloxetine with placebo, thus preventing any further interpretation.

Data on **cognition** using the **MMSE**[9] showed a slight increase and thus improvement in score for duloxetine and placebo with no statistically significant difference in treatments in one trial. Thus, there is no proof of benefit from duloxetine compared to placebo of a positive influence on cognition in outpatient acute therapy for depression in older patients.

Data on the influence on **somatic symptoms** were measured using **SSI**[10] and/or **SQ-SS**[11]. The meta-analysis of **SSI** in the comparison of duloxetine and placebo yielded a statistically significant result in favour of duloxetine. However, the relevance of this effect could not be estimated with certainty. The results of one trial on relapse prevention on **SQ-SS** did not provide a statistically significant difference for duloxetine compared to placebo. In summary, in the analysis of data on the influence on somatic symptoms, the benefit of duloxetine compared to placebo remained unclear in outpatient acute therapy for depression; a benefit was not proven. A placebo-controlled trial on long-term therapy/relapse prevention also produced no proof of benefit.

Mortality/suicidal tendency

Regarding the **mortality** and **suicidal tendency** outcomes, there was no proof of harm or of greater or lesser harm from duloxetine compared to placebo or compared to the SSRI drug class. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on mortality/suicidal tendency and event rates were very low). For this reason, no data on individual results are given here. The influence of duloxetine on mortality and suicidal tendency cannot be conclusively explained on the basis of the identified studies.

Health-related quality of life

In the total score for psychological health, the meta-analyses of **SF-36**[12] showed a statistically significant result in favour of duloxetine in the comparison of duloxetine and placebo for short-term therapy. However, the relevance of this effect could not be estimated with certainty. In the total score for physical health, no overall estimate was calculated in the comparison of duloxetine and placebo due to high heterogeneity. The results of the individual trials were contradictory in this respect. The meta-analyses of **QLDS**[13] also showed a statistically significant result in favour of duloxetine in the comparison of duloxetine and placebo in short-term therapy. The observed effect could be assumed to be relevant. Due to a lack of data, the benefit in the comparison of duloxetine compared to placebo was unclear for

[9] Mini Mental State Examination
[10] Somatic Symptom Inventory
[11] Symptom Questionnaire Somatic Subscale
[12] Short Form 36
[13] Quality of Life in Depression Scale

Q-LES-Q[14]. Only a statistically significant difference was reported, but its relevance could not be estimated.

In the only relapse-prevention trial, the comparison of duloxetine and placebo showed a statistically significant advantage for duloxetine for QLDS. However, the relevance of this effect could not be estimated with certainty.

Overall, the **health-related quality of life** outcome showed proof of benefit in outpatient acute therapy for depression. However, this benefit was only observed for **QLDS** and was thus obtained using a disease-specific scale. The generic quality of life scales, **SF-36** and **Q-LES-Q** either did not produce proof of benefit or the benefit of duloxetine remained unclear. The relapse prevention of depression yielded an effect, but its relevance could not be estimated with certainty due to a lack of data. In this case, too, the benefit remained unclear and was not proven.

Social functioning level including working and earning capacity

In "short-term" and "long-term" acute therapy, there was no statistically significant difference between duloxetine and placebo for **EWPS**[15]. In the comparison with placebo, the data on **SDS**[16] yielded a statistically significant and relevant result for the "short-term" acute therapy, but not for the "long-term" acute therapy (no statistically significant difference).

In one trial on relapse prevention there was a statistically significant and relevant difference compared to placebo on the **SDS**.

In summary, there was proof of benefit from duloxetine compared to placebo in outpatient acute therapy for depression ("short-term" acute trials) with regard to the influence on **social functioning level.** This benefit was also noted in the only long-term trial on relapse prevention (indication of benefit). It should be noted that the proof of benefit was produced from data on **SDS**, a scale that is used to assess the general social functioning level. The data on **EWPS**, a scale for assessing subjective work productivity specifically in psychiatric patients, did not produce proof of benefit. However, this result was only based on one study, which did not provide any figures. The same study (Nierenberg 2007) provided data on **SDS** that were similarly limited and did not indicate a benefit. These data could not be integrated into the meta-analysis. The total pool of other placebo-controlled trials on this scale produced a statistically significant result in the meta-analysis. Using both scales, there was no proof of benefit from duloxetine compared to placebo in "long-term" acute therapy.

[14] Quality of Life Enjoyment and Satisfaction Questionnaire
[15] Endicott Work Productivity Scale
[16] Sheehan Disability Scale

Subgroup analyses

In an interaction test using the available data on the mean change in depressive symptoms (depression scale total score) separated according to **gender,** there were no statistically significant results (at the significance level 0.2) in the comparison of duloxetine and placebo ($p = 0.27$), and duloxetine and SSRI ($p = 0.25$). As there was no interaction, no meta-analyses separated according to gender were carried out. As a result, the observed effect in the total population applies to men and women.

An interaction test using the baseline mean depression scale total scores (**severity** of disease when treatment started) yielded a statistically significant result (at the significance level 0.2) for remission and response in the comparison of duloxetine and SSRI ($p = 0.07$ and 0.06). Due to this interaction, further meta-analyses were carried out. They did not produce statistically significant differences between duloxetine and SSRI either for the subpool of trials with a mean baseline score of ≤ 37 % of the maximum score or for the subpool of the study population with a more severe disorder > 37 %. This result applied equally to remission and response (OR[17] [95 % CI[18]] of the meta-analyses ≤ 37 %, > 37 %; remission: 1.32 [1.00; 1.75], 0.96 [0.76; 1.20]; response: 1.15 [0.91; 1.47], 0.81 [0.64; 1.02]). In summary, there was no proof of additional benefit from duloxetine compared to SSRI in outpatient acute therapy for depression, either at higher or lower baseline severity of disease. This result has limitations due to the generally averaged-out baseline severity of disease (on average consistently moderate depression) in the study pool included. There was no indication of a relevant interaction between the severity of disease and the treatment effect in the comparison of duloxetine and placebo. Thus, the observed effect in the total population compared to placebo applies equally to the investigated severity of disease.

An interaction test on the influence of **age** between trials with younger patients and those with older patients in the comparison of duloxetine and placebo (outcome: therapy discontinuations due to adverse events) did not produce a statistically significant result (at the significance level 0.2). The observed effect in the total population thus applies both to the younger and the older patients treated in the trials.

An interaction test using the available data on 2 trials with patients suffering from **pain** compared to the remaining placebo-controlled trials did not show a statistically significant value (at the significance level 0.2) ($p = 0.73$). The observed effect in the total population thus applies equally to the patients treated in the studies with and without explicit pain symptoms.

[17] Odds ratio
[18] Confidence interval

Venlafaxine

A total of 62 relevant trials on venlafaxine were identified. In 51 of the study phases included in the benefit assessment, the effect of venlafaxine was examined in acute therapy for patients over 18 years of age. An additional 7 trials addressed acute therapy for older patients and a further 2 trials addressed the treatment of therapy-resistant patients. Three long-term trials could be included in this benefit assessment: one trial on relapse prevention and 2 trials on recurrence prevention. Overall, the study and publication quality of the majority of the studies was more or less average: 17 out of 60 acute trials had major flaws. Only 3 acute trials were assessed as having "no flaws". The 3 long-term trials were assessed as having minor flaws.

Table 3 gives an overview of the patient-relevant outcomes that were assessed in the included studies. The most important results of the studies on venlafaxine are summarized in Table 4. Data on further outcomes can be found in the text that follows. The summary concentrates on the comparison of venlafaxine with placebo and with the SSRI and TCA[19] drug classes. Results on the comparison of venlafaxine with individual drugs are only presented if they showed the superiority or inferiority of one antidepressant. More detailed results on individual comparators can be found in the main part of the report.

[19] Tri- and tetracyclic antidepressants

Table 3: Overview of the patient-relevant outcomes in the studies on venlafaxine

	Depression	Individual and accompanying symptoms	Adverse events	Sexual dysfunction	Health-related quality of life	Social functioning level
Venlafaxine versus placebo						
Acute trials	●	● anxiety, energy	●	●	●	●
Long-term trials (relapse/ recurrence prevention)	● / ●	- / ● anxiety	● / ●		- / ●	- / ●
Venlafaxine versus SSRI[a]						
Acute trials	●	● anxiety, pain, cognition, sleep	●	●	●	●
Venlafaxine versus TCA[b]						
Acute trials	●	● anxiety, cognition	●		●	●
Venlafaxine versus agomelatine						
Acute trials	●		●			
Venlafaxine versus bupropion						
Acute trials	●	● anxiety, energy	●	●	●	●
Venlafaxine versus mirtazapine						
Acute trials	●		●			
Venlafaxine versus moclobemide						
Acute trials	(●)		●			
Venlafaxine versus trazodone						
Acute trials	●		●			

a: Data on at least one of the following drugs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
b: Data on at least one of the following drugs: amitriptyline, clomipramine, dosulepin, imipramine, maprotiline, nortriptyline
●: Data reported
(●): Data collected but not reported
SSRI: selective serotonin reuptake inhibitors; TCA: tri- and tetracyclic antidepressants

Table 4: Summary of the comparison of venlafaxine with placebo and with SSRI, TCA

Outcome	**Result of meta-analyses and individual studies Group difference [95 % CI]**			
	VEN vs. plc[a]		**VEN vs. SSRI[a]**	**VEN vs. TCA[a]**
	Short-term acute therapy	**Relapse[b] / recurrence prevention**	**Short-term acute therapy**	**Short-term acute therapy**
Remission[c]	1.97 [1.64; 2.35]	n. r.	1.12 [0.98; 1.28]	0.99 [0.58; 1.71]
Response[c]	2.04 [1.74; 2.38]	n. r.	1.20 [1.07; 1.35]	0.98 [0.71; 1.35]
Depression scale total score	-0.40 [-0.47; -0.32][d,h]	-4.2 [-6.24; -2.16] -0.50 [-0.75; -0.25][h] / high heterogeneity	-0.09 [-0.16; -0.02][d,i]	0.47 [-0.73; 1.68][e]
Relapse/ recurrence rates[c]	n. r.	p < 0.001 / 0.27 [0.18; 0.40]	n. r.	n. r.
AE[c]	high heterogeneity	p = 0.112 / 1.20 [0.83; 1.73]	1.31 [1.14; 1.50]	0.65 [0.49; 0.86]
SAE[c]	1.27 [0.81; 2.00]	p = 0.171 / high heterogeneity	0.96 [0.68; 1.34]	0.00 [-0.03; 0.04][g]
Discontinuation due to AE[c]	2.47 [1.81; 3.37][f]	p = 0.796 / 0.51 [0.26; 1.01]	1.38 [1.15; 1.66]	-0.01 [-0.04; 0.02][g]
Sexual dysfunction (CSFQ)	-0.08 [-1.33; 1.17][e]			
Anxiety (HAMA; HADS; BSA; Covi)	-2.85 [-3.90; -1.80][e] -0.35 [-0.48; -0.22][h]; relevance uncertain due to lack of data[b]; n. s.[b]; relevance uncertain due to lack of data[b]	/ p = 0.03[b] -0.26 [-0.50; -0.01][i]	0.21 [-0.34; 0.76][e]	0.09 [-0.98; 1.16][e]
Energy (MEI)	7.19 [4.27; 10.12][e] 0.36 [0.18; 0.53][i]			
Health-related quality of life (SF-36 psychological; physical health; Q-LES-Q; GLF)	5.30 [2.58; 8.02][e] 0.29 [0.14; 0.44][i]; p = 0.002[b] 0.43 [0.12; 0.74][i]	/ p = 0.020[b] 0.27 [0.03; 0.52][i]; p = 0.490[b]; p = 0.004[b] 0.34 [0.09; 0.58][i]	-0.47 [-1.94; 1.00][e]	
Social functioning level (SAS-SR; SDS)	relevance uncertain due to lack of data[b]; -3,06 [-4.19; -1.93][e] -0.40 [-0.55; -0.25][h]	/p = 0.006[b] -0.33 [-0.58; -0.08][i]		

(continued)

Table 4 (continued): Summary of the comparison of venlafaxine with placebo and with SSRI, TCA

Details of the results are contained in the main part of the report. a: Result from one meta-analysis (if not otherwise designated) b: Result from one individual study c: Odds Ratio (if not otherwise designated) d: Hedges' g e: Mean difference f: Result from a sensitivity analysis without studies having major flaws g: Risk difference See Table 2 for explanation of the following footnotes: h: Relevant effect size (Cohen's d/Hedges' g) i: Relevance of this effect cannot be estimated with sufficient certainty (Cohen's d/Hedges' g) AE: adverse events; BSA: Brief Scale for Anxiety; CI: Confidence Interval; Covi: Covi Scale; CSFQ: Changes in Sexual Functioning Questionnaire; GLF: General Life Functioning Scale; HADS: Hospital Anxiety and Depression Scale; HAMA: Hamilton Anxiety Scale; MEI: Motivation and Energy Inventory; n. r.: not relevant; plc: placebo; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SAE: serious adverse events; SAS-SR: Social Adjustment Scale-Self-Report; SDS: Sheehan Disability Scale; SF-36: Short-Form-36; SSRI: Selective Serotonin Reuptake Inhibitors; TCA: tri- and tetracyclic antidepressants; VEN: Venlafaxine

Antidepressive effect

The meta-analyses showed a statistically significant advantage for venlafaxine compared to placebo for the **remission** outcome. No statistically significant differences were observed in the remission rates in the comparison of venlafaxine with active comparators in SSRI and TCA drug classes. There was a statistically significant advantage for venlafaxine in the comparison of bupropion and venlafaxine (OR [95 % CI] of the meta-analysis: 1.39 [1.04; 1.84]). The comparison with placebo produced proof of benefit from venlafaxine in acute therapy for depression for the **remission** outcome. The comparison of venlafaxine with the SSRI and TCA drug classes produced no proof of additional benefit from venlafaxine. There was proof of additional benefit from venlafaxine in the comparison of venlafaxine and bupropion.

In the **response rates** there was a statistically significant advantage from venlafaxine compared to placebo, as was the case with remission. Similarly, a statistically significant advantage from venlafaxine was observed for the comparison with SSRI and the individual substance, fluoxetine (OR [95 % CI] of the meta-analysis: 1.26 [1.07; 1.48]). There was no statistically significant difference in the comparison of venlafaxine with TCA. The second individual substance comparison that demonstrated a statistically significant advantage for venlafaxine was in the comparison with bupropion (OR [95 % CI] of the meta-analysis: 1.43 [1.06; 1.91]). Thus, there was proof of benefit from venlafaxine in the comparison with placebo for the response outcome in acute therapy for depression. The comparison of venlafaxine with the SSRI drug class produced proof of additional benefit from venlafaxine, which was also observed in the analysis compared to fluoxetine. The comparison of

venlafaxine with the TCA drug class did not produce proof of additional benefit from venlafaxine. However, the comparison of venlafaxine and bupropion showed proof of additional benefit from venlafaxine.

For the mean change in depressive symptoms (**depression scale total score**) there was a statistically significant advantage for venlafaxine in the comparison of venlafaxine and placebo in acute therapy for depression. The observed effect could be assumed to be relevant. The comparison of venlafaxine and SSRI also produced a statistically significant difference in favour of venlafaxine. However, the relevance of this effect could not be estimated with certainty. The comparison of venlafaxine with the TCA drug class did not show a statistically significant difference. Based on the mean change in depressive symptoms (depression scale total score), the studies thus produced proof of benefit from venlafaxine compared to placebo in acute therapy for depression. The comparison of venlafaxine with the TCA drug class did not produce proof of additional benefit from venlafaxine. The comparison of venlafaxine with the SSRI drug class produced a result, the relevance of which could not be estimated with certainty. Additional benefit remained unclear and there was no proof of additional benefit.

With a **relapse probability** of 28 % for venlafaxine and 52 % for placebo, the analysis of a relapse-prevention trial showed venlafaxine to be statistically significantly superior in preventing relapses. At the end of the study a statistically significant difference was observed in favour of venlafaxine in the mean change of the HAMD-21 score in respect of the mean change in depressive symptoms (**depression scale total score**). Smaller mean changes and therefore more stable values occurred over time when patients were treated with venlafaxine. This result produced a relevant effect in relation to the mean difference.

With regard to **recurrence**, the long-term trials on recurrence prevention showed statistically significant differences in favour of the active substance in the comparison of venlafaxine and placebo. There was high heterogeneity in the result of the meta-analysis on the mean change in depressive symptoms (**depression scale total score**) for these trials. The results of the individual trials showed an effect in favour of venlafaxine, but its relevance could not be estimated with certainty. Overall, the results of the only long-term trial included on relapse prevention showed an indication of benefit from venlafaxine compared to placebo. The results of the 2 long-term trials included on recurrence prevention produced proof of benefit from venlafaxine compared to placebo.

Adverse drug effects

The results for the **total rates of adverse events** and **therapy discontinuations due to adverse events** are as follows: with high heterogeneity in the relevant meta-analysis, there was no proof of harm from venlafaxine for the total rates in its comparison with placebo in acute therapy for depression. The analysis of therapy discontinuations produced proof of harm from venlafaxine (high heterogeneity of initial meta-analysis; analysis without studies having major flaws was statistically significant). For relapse and recurrence prevention there was no

proof of harm (no statistically significant differences between venlafaxine and placebo). The comparison of venlafaxine with the SSRI drug class yielded a statistically significant difference to the disadvantage of venlafaxine and thus proof of greater harm for both outcomes, which was also observed in the individual drug analysis in comparison with fluoxetine (OR [95 % CI] of the meta-analyses: 1.33 [1.14; 1.56] for adverse events and 1.46 [1.17; 1.83] for therapy discontinuations due to adverse events). The comparison of venlafaxine with the TCA drug class and with other individual drugs revealed several differences between the two outcomes and for this reason the results are presented separately: for the total rate of adverse events, the TCA comparison produced a statistically significant result in favour of venlafaxine and proof of lesser harm, which was also evident in the analyses when compared to the individual drugs, amitriptyline and clomipramine (OR [95 % CI] of the meta-analyses: 0.47 [0.24; 0.93] and 0.55 [0.32; 0.95]). In the comparison of venlafaxine and trazodone there was a statistically significant advantage from venlafaxine in older patients and thus an indication of lesser harm from venlafaxine (20 vs. 37 %, p = 0.049). In the comparison of venlafaxine with the TCA drug class, on the other hand, there was no proof of greater or lesser harm from venlafaxine for therapy discontinuations due to adverse events. Only the comparison of maprotiline and venlafaxine produced a statistically significant advantage for venlafaxine and thus an indication of a lesser harm (RD[20] [95 % CI] of the individual trial: -0.09 [-0.17; -0.01]). The comparison on the individual drug, agomelatine, produced proof of greater harm from venlafaxine (OR [95 % CI] of the meta-analysis: 3.76 [1.82; 7.75]).

The results for the **total rate of serious adverse events** differed from the above results for the two other outcomes insofar as no comparison produced a statistically significant difference; thus no harm, or greater or lesser harm, from venlafaxine was proven. Thus, there was no proof of harm from venlafaxine in the comparison with placebo either in acute therapy or in relapse or recurrence prevention (high heterogeneity) of depression. The comparison of venlafaxine with the SSRI and TCA drug classes produced no proof of greater or lesser harm with respect to serious adverse events.

The data on **CSFQ** with reference to **sexual dysfunction** showed no statistically significant difference in acute therapy for depression in the comparison with placebo. Thus, there was no proof of harm from venlafaxine in acute therapy for depression for the sexual dysfunction outcome.

On the basis of the **number of patients with high blood pressure**, there was no proof of harm from venlafaxine compared to placebo. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on high blood pressure and event rates were low). For this reason, no data on individual results are given here.

[20] Risk difference

Change in individual symptoms and/or accompanying symptoms

In the comparison with placebo, the meta-analysis of **HAMA** for **anxiety symptoms** produced a statistically significant result in favour of venlafaxine in acute therapy for depression. The relevance of the effect was in this case provided. For the **HADS**[21] anxiety sub-scale, the relevance of the effect could not be estimated due to a lack of data in the comparison of venlafaxine and placebo in one trial. The data of one trial on **BSA**[22] produced a statistically non-significant difference between the treatment groups (venlafaxine, imipramine and placebo) for the total score. For the **Covi scale**, a statistically significant superiority of venlafaxine compared to placebo was reported in one trial, but this could not be confirmed by data. The relevance of this effect could not be estimated with certainty.

A statistically significant difference between venlafaxine and placebo was reported for **HAMA** in the recurrence prevention therapy. However, the relevance of this effect could not be estimated with certainty.

The comparison with the SSRI drug class did not show a statistically significant difference for **HAMA**. The comparison of venlafaxine and TCA for the **HADS** anxiety subscale also did not show a statistically significant difference between the treatments.

In summary, the various measurement instruments produced a heterogeneous picture for the **anxiety symptoms** outcome in the comparison of placebo and venlafaxine in acute therapy for depression. However, it should be noted that in 3 out of the 4 scales there was data on the placebo comparison only in one trial in each case and consequently the conclusion for this scale was determined by one trial in each case. Morever, a statistically significant result was reported in 2 cases, but its relevance remained in doubt due to a lack of data. The strongest evidence for the comparison of the influence on anxiety symptoms compared to placebo was supplied by the meta-analysis of **HAMA**. Overall, proof of benefit from venlafaxine compared to placebo can thus be assumed for acute therapy. In contrast, the benefit of venlafaxine remained unclear in therapy for recurrence prevention, thus providing no proof of benefit. There was no proof of additional benefit from venlafaxine compared to the SSRI and TCA drug classes in acute therapy.

The meta-analysis of **MEI**[23] on **energy and motivation** produced a statistically significant result in favour of venlafaxine in the comparison of venlafaxine and placebo. However, the relevance of this effect could not be estimated with certainty. On the basis of the data analysed, therefore, the benefit from venlafaxine compared to placebo on the influence on energy and motivation in acute therapy for depression remained unclear and there was no proof of benefit.

[21] Hospital Anxiety and Depression Scale
[22] Brief Scale for Anxiety
[23] Motivation and Energy Inventory

Mortality/suicidal tendency

With regard to the **mortality and suicidal tendency** outcomes, there was no proof of harm from venlafaxine compared to placebo, nor was there proof of greater or lesser harm compared to the SSRI and TCA drug classes. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on mortality/suicidal tendency and event rates were low). For this reason, no data on individual results are given here. The influence of venlafaxine on mortality and suicidal tendency cannot be explained conclusively on the basis of the trials identified.

Health-related quality of life

The meta-analyses of **Q-LES-Q** showed a statistically significant result in favour of venlafaxine in the comparison of venlafaxine and placebo for "short-term" acute therapy, but its relevance could not be estimated with certainty. For **GLF**[24], one trial on "short-term" acute therapy showed statistically significantly better outcome scores in the venlafaxine group compared to placebo. However, the relevance of the effect could not be estimated with certainty either.

The trial on recurrence prevention reported a statistically significant difference between venlafaxine and placebo for the **Q-LES-Q**, but its relevance could not be estimated with certainty. The same applied to the statistically significant difference between venlafaxine and placebo for the total score of psychological health for **SF-36** (relevance uncertain). For the **SF-36** total score of physical health, there was a non-statistically significant difference in the comparison of venlafaxine and placebo.

The comparison of venlafaxine with the SSRI drug class produced no statistically significant difference for **Q-LES-Q**.

In summary, the benefit from venlafaxine remained unclear for the health-related quality of life outcome both in acute therapy and in recurrence prevention therapy for depression. There was no proof of benefit. A proof of additional benefit from venlafaxine compared to the SSRI drug class for health-related quality of life in acute therapy was not observed.

Social functioning level including working and earning capacity

In "short-term" acute therapy, statistically significant advantages were reported for venlafaxine compared to placebo for **SAS-SR**[25], but the relevance of the effect remained uncertain due to a lack of data. For **SDS**, the meta-analysis showed a statistically significant

[24] General Life Functioning Scale
[25] Social Adjustment Scale - Self-Report

result in favour of venlafaxine in the comparison of venlafaxine and placebo. The relevance of the effect could be assumed in this case.

For the **SAS-SR**, a statistically significant difference between venlafaxine and placebo was reported in long-term therapy for recurrence prevention. However, its relevance could not be estimated with certainty.

In summary, with regard to the influence on the social functioning level, there was proof of benefit from venlafaxine compared to placebo in outpatient acute therapy for depression ("short-term" acute trials). It should be noted that the proof of benefit was produced using data from **SDS**, a scale that assesses the general social functioning level. The results on **SAS-SR** could not be conclusively interpreted due to a lack of data. The benefit remained unclear and was not proven. In the comparison of venlafaxine and placebo, the benefit also remained unclear in recurrence prevention and thus was not proven.

Subgroup analyses

An interaction test of the available data on mean change in depression symptoms (depression scale total score) separated according to **gender** did not produce a statistically significant result (at the significance level 0.2) for the comparison of venlafaxine versus placebo, SSRI and bupropion (p = 0.203; 0.91; 0.33). As no interaction existed, no meta-analyses separated according to gender were carried out either. The effect observed in the total population thus applies to men and women.

There were no indications from the trials on the comparison of venlafaxine with placebo, with TCA, with bupropion or with agomelatine that the **severity** of the disease had an influence on the treatment effect. There was an indication in the comparison of venlafaxine and SSRI of a relationship between the treatment effect and the severity of the depression for the response outcome (interaction test based on the baseline score on the depression scale: p = 0.08). Due to this interaction, more meta-analyses were carried out. No statistically significant difference between the treatment options was found for the subpool of trials with mean baseline score of < 50 % of the maximum score (OR [95 % CI] of the meta-analysis: 1.10 [0.97; 1.25]). For the study population subpool with a more severe disorder (> 50 % of the maximum score), a statistically significant difference in favour of venlafaxine was shown (OR [95 % CI] of the meta-analysis: 1.46 [1.10; 1.95]). This influence of the severity on the treatment effect was not observed for the mean change in depressive symptoms outcome (depression scale total score). The data concerning a relevant interaction between severity and treatment effect consistent with an additional benefit of venlafaxine compared to SSRI exclusively in patients with more severe depression were thus ambiguous. The results were thus not considered as proof, but as an indication that the additional benefit of venlafaxine applies more to patients with higher severity of depression than to patients with lower severity of depression.

An interaction test using the available data from 2 trials with **therapy-resistant patients** compared to the remaining SSRI-controlled trials did not show a statistically significant value (at the significance level 0.2) and thus no relevant interaction between therapy resistance and the effect on the response outcome (p = 0.93). Thus, no further investigation of benefit/additional benefit was carried out. The effect observed in the total population compared to SSRI thus applied equally to therapy-resistant patients (according to the selection criteria of the two trials) and not explicitly therapy-resistant populations (according to the selection criteria of the other trials).

For the subgroup on **treatment setting**, the study pool contained a total of 3 trials exclusively with inpatients. These were active-controlled trials with the comparators, fluoxetine, imipramine and nortriptyline, so that it was possible to carry out a comparison with the outpatient trials for the TCA pool. Overall, the individual result of the trial with fluoxetine as comparator was in major agreement with the conclusions of proof for the total meta-analyses on remission, response and mean change in depressive symptoms (depression scale total score) (in the comparisons with both SSRI and fluoxetine). An interaction test on venlafaxine and TCA in the comparison of inpatients and outpatients produced a statistically significant interaction (at the significance level 0.2) between provision setting and treatment effect for the response outcome (p = 0.08). Due to this interaction, further meta-analyses were carried out. For both subpools of trials (outpatient and inpatient), there were no statistically significant differences between venlafaxine and TCA for the response outcome (OR [95 %] of the meta-analyses: 1.27 [0.82; 1.96] and 0.65 [0.39; 1.08]). In summary, there was no proof of additional benefit from venlafaxine compared to TCA for inpatients and outpatients in acute therapy for depression. With reference to one relevant inpatient trial, no clear difference was established in the antidepressive effect compared to the remaining SSRI and fluoxetine-controlled trials.

There was one trial in the benefit assessment pool which explicitly included patients with a specific **comorbidity** using an appropriate diagnosis criterion (ICD-10, DSM). The participants in this placebo-controlled trial with older patients had to meet the criterion of mild or moderate dementia according to DSM-IV in addition to the MDD diagnosis according to DSM-IV. The individual results of the trial deviated from the corresponding total result of meta-analyses on response and mean change in depressive symptoms (depression scale total score). As the study population consisted of older patients with dementia, it was not clear whether the deviating effectiveness results of the trial were the result of dementia, age or both characteristics of the population (see below for result for the age subgroup). It thus remained unclear whether the dementia comorbidity had an influence on the antidepressive effect.

With an **age** limit of 60/65 years of age, the venlafaxine study pool comprised 16 trials, which only included younger patients, and 7 trials with patients ≥ 60/65 years of age. For adverse events, the meta-regressions on venlafaxine and placebo, TCA and SSRI did not produce statistically significant interactions (at the significance level 0.2) between the age and the

treatment effect (outcome: therapy discontinuations due to adverse events; placebo: p = 0.98; TCA: p = 0.44; SSRI: p = 0.60). For the antidepressive effect, there were no statistically significant interactions in the comparison of venlafaxine and SSRI (at the significance level 0.2) for the response rate (SSRI: p = 0.71). In the comparison versus placebo and TCA, there were statistically significant interactions between age and treatment effect (placebo: p = 0.001; TCA: p = 0.18) for the response outcome. These effects were evaluated separately in meta-analyses for a study pool of older and younger patients in the comparison of venlafaxine versus placebo and versus TCA.

In the comparison of venlafaxine and placebo there was a statistically significant advantage from venlafaxine for the response outcome for the subpool of the younger study population (OR [95 % CI] of the meta-analysis: 2.26 [1.85; 2.77]). In contrast, the analysis for the subpool of the older study population did not produce a statistically significant difference (OR [95 % CI] of the meta-analysis: 0.83 [0.48; 1.42]). In summary, in acute therapy for depression, there was proof of benefit from venlafaxine compared to placebo in younger patients. In the therapy for older patients there was no proof of benefit from venlafaxine compared to placebo.

The comparison of venlafaxine and TCA did not produce statistically significant differences for the response outcome in either subpool (younger and older patients) (OR [95 % CI] of the meta-analyses: younger: 1.15 [0.80; 1.64]; older: 0.65 [0.39; 1.06]). Thus, there was no proof of additional benefit from venlafaxine compared to TCA for either age group in acute therapy for depression.

One study designated a concrete inclusion of patients with a **defined individual symptom**. This active- and placebo-controlled trial (comparator: fluoxetine) explicitly included patients with baseline anxiety symptoms measured using Covi scores. Overall, the individual result was in major agreement with the conclusions on proof for the total meta-analyses on remission, response and mean change in depressive symptoms (depression scale total score) (in each case in the placebo, SSRI and fluoxetine comparison). Thus, no clear difference could be established in the antidepressant effect between the patient population suffering from anxiety included in one trial and the remaining placebo-controlled and SSRI/fluoxetine-controlled trials.

Direct comparison between duloxetine and venlafaxine

Two relevant trials were identified on the direct comparison of duloxetine and venlafaxine. Both studies were used for assessing benefit in acute therapy. Overall, both studies were assessed as being free of flaws.

Table 5 gives an overview of the patient-relevant outcomes that were assessed in the included studies on direct comparison. The most important results of the studies are summarized in Table 6. Data on further outcomes can be found in the text that follows.

Table 5: Overview of patient-relevant outcomes in the trials on direct comparison

	Depression	Individual and accompanying symptoms	Adverse events	Sexual dysfunction	Health-related quality of life	Social functioning level
Duloxetine versus venlafaxine						
Acute trials	●	● anxiety, sleep	●	●	●	●
●: Data reported						

Table 6: Summary of results of trials on direct comparison of duloxetine and venlafaxine

Outcome	Result of meta-analyses and individual trials on direct comparison Group difference [95 % CI][a]
Remission[b]	heterogeneous results
Response[b]	0.75 [0.52; 1.08]
Depression scale total score	0.99 [-0.02; 2.,00][c]
AE[b]	heterogeneous results
SAE[b]	0.34 [0.03; 4.18]
Discontinuation due to AE[b]	1.79 [1.16; 2.78]
Sexual dysfunction (CSFQ)	0.76 [-0.86; 2.37][c]
Anxiety (HAMA)	0.71 [-0.19; 1.62][c]
Sleep (PSQI)	0.58 [-0.09; 1.26][c]
Health-related quality of life (SF-36 psychological; physical health; EQ-5D; QLDS)	-1.69 [-3.61; 0.23][c]; -1.90 [-3.01; -0.80][c,e], -0.26 [-0.41; -0.11][e]; -0.06 [-0.09; -0.02][c], -0.,23 [-0.38; -0.09][e]; 1.60 [0.34; 2.85][c], 0.19 [0.04; 0.34][e]
Social functioning level (SDS)	1.60 [0.46; 2.75][c], 0.21 [0.06; 0.35][e]

Details of the results are contained in the main part of the report.
a: Result from one meta-analysis (if not otherwise designated)
b: Odds Ratio (if not otherwise designated)
c: Mean difference

See Table 2 for explanation of the following footnotes:
d: Relevant effect size (Cohen's d/Hedges' g)
e: Relevance of this effect cannot be estimated with sufficient certainty (Cohen's d/Hedges' g)

AE: adverse events; CI: Confidence Interval; CSFQ: Changes in Sexual Functioning Questionnaire; EQ-5D: Euroqol; HAMA: Hamilton Anxiety Scale; PSQI: Pittsburgh Sleep Quality Index; QLDS: Quality of Life in Depression Scale; SAE: serious adverse events; SDS: Sheehan Disability Scale; SF-36: Short-Form-36

Antidepressive effect

In the meta-analyses there was a very heterogeneous result for the **remission** outcome. Thus, in the comparison of duloxetine and venlafaxine, there was no proof of additional benefit

from either of the two drugs for the remission outcome in outpatient acute therapy for depression.

The analysis of the **response** outcome did not produce a statistically significant difference between venlafaxine and duloxetine. Thus, in the comparison of duloxetine and venlafaxine, there was no proof of additional benefit from either of the two drugs in outpatient acute therapy for depression.

Moreover, the analysis of the mean change in depressive symptoms (**depression scale total score**) did not produce a statistically significant difference between duloxetine and venlafaxine. In summary there was also no proof here of additional benefit from either of the two drugs in outpatient acute therapy for depression.

Adverse drug effects

One of the 3 meta-analyses carried out produced heterogeneous results (**total rates of adverse events**). The analysis of the **serious adverse events** outcome did not produce a statistically significant difference between the treatment options, whereas there was a statistically significant result in favour of venlafaxine for **discontinuation due to adverse events**. Overall, in the direct comparison of duloxetine and venlafaxine in outpatient acute therapy for depression, there was no proof of greater or lesser harm from either of the two drugs with reference to the total rates of adverse and serious adverse events. In contrast, there was proof of lesser harm from venlafaxine compared to duloxetine and consequently proof of greater harm from duloxetine compared to venlafaxine for therapy discontinuation due to adverse events.

The data on **sexual dysfunction** obtained from the **CSFQ** from the comparison of both drugs did not produce a statistically significant difference between the treatment options. Thus, with regard to the sexual dysfunction outcome, there was no proof of greater or lesser harm from duloxetine or venlafaxine in the direct comparison in outpatient acute therapy for depression.

Based on the **number of patients with high blood pressure**, there was no proof of greater or lesser harm from duloxetine or venlafaxine in the direct comparison in outpatient acute therapy for depression. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on high blood pressure and event rates were low). For this reason, no data on individual results are given here.

Change in individual symptoms and/or accompanying symptoms

The results of the **HAMA** on **anxiety symptoms** did not produce a statistically significant difference between the treatment options. Thus, there was no proof of additional benefit from either of the two drugs with respect to the influence on anxiety symptoms in outpatient acute therapy for depression.

In the comparison of duloxetine and venlafaxine, there was no statistically significant difference for the **sleep** outcome based on the **PSQI**[26]. Thus, there was also no proof of additional benefit from either of the two drugs with respect to the influence on sleep in outpatient acute therapy for depression.

Mortality/suicidal tendency

With regard to the **mortality and suicidal tendency** outcomes, there was no proof of greater or lesser harm from duloxetine or venlafaxine in outpatient acute therapy for depression. This result must be interpreted in the light of the limited validity of the data (no studies primarily focused on mortality/suicidal tendency and event rates were low or non-existent). For this reason, no data on individual results are given here. The influence of duloxetine and venlafaxine on mortality and suicidal tendency cannot be conclusively confirmed on the basis of the trials identified.

Health-related quality of life

For the **SF-36** total score of psychological health, there was no statistically significant difference between the treatment options in the comparison of duloxetine and venlafaxine. In contrast, there was a statistically significant difference in favour of venlafaxine in the total score of physical health, but its relevance could not be estimated with certainty. The comparison of venlafaxine and duloxetine in **EQ-5D**[27] produced a statistically significant result in favour of venlafaxine, but its relevance could also not be estimated with certainty. The analysis of **QLDS** produced a statistically significant result in favour of venlafaxine compared to duloxetine. The relevance of the observed effect could also not be estimated with certainty.

In summary, the additional benefit of duloxetine or venlafaxine remained for the most part unclear for the health-related quality of life outcome in outpatient acute therapy for depression. There was no proof of additional benefit.

Social functioning level including working and earning capacity

The data on **SDS** in outpatient acute therapy for depression produced a statistically significant result in favour of venlafaxine in the comparison of the 2 drugs, but its relevance could not be estimated with certainty. The additional benefit of duloxetine or venlafaxine with regard to the influence on the social functioning level in outpatient acute therapy for depression remained unclear. There was no proof of additional benefit.

[26] Pittsburgh Sleep Quality Index
[27] Euroqol EQ-5D

Conclusions

The patient-relevant outcomes investigated in this report were remission, change in depressive symptoms (response and mean change in depressive symptoms measured on a scale), relapse and recurrence, individual and accompanying symptoms of depression, health-related quality of life, social functioning level, mortality, suicidal tendency, total rates of adverse events and serious adverse events, therapy discontinuations due to adverse events, sexual dysfunction and high blood pressure.

Data were available on the direct comparison of duloxetine and venlafaxine, on the comparison of duloxetine with placebo and with the SSRI drug class (3 individual drugs), and on the comparison of venlafaxine with placebo, with the SSRI and TCA drug classes (6 individual drugs in each case), and with the drugs, agomelatine, bupropion, mirtazapine, moclobemide and trazodone.

The studies investigated short-term acute therapy (direct comparison, duloxetine, venlafaxine), long-term acute therapy (duloxetine, venlafaxine), as well as relapse prevention (duloxetine, venlafaxine) and recurrence prevention (venlafaxine).

The data on the available combinations of these outcomes, therapy comparisons and therapeutic goals provided the following proofs or indications:

Direct comparison

- Proof of greater harm from duloxetine and consequently lesser harm from venlafaxine with reference to therapy discontinuations due to adverse events

Duloxetine

- Proof of benefit when compared to placebo with reference to remission and to change in depressive symptoms (response and mean change in depressive symptoms) in short-term acute therapy
- Indication of benefit when compared to placebo in relapse prevention
- Proof of benefit when compared to placebo for health-related quality of life in short-term acute therapy
- Proof of benefit when compared to placebo with reference to an improvement in general social functioning level in short-term acute therapy, indication of benefit with reference to an improvement in general social functioning level for relapse prevention

- Proof of harm when compared to placebo and of greater harm when compared to SSRI for the total rate of adverse events and therapy discontinuations due to adverse events in short-term acute therapy

Venlafaxine

- Proof of benefit when compared to placebo with reference to remission and to change in depressive symptoms (response and mean change in depressive symptoms) in short-term acute therapy
- Proof of benefit when compared to placebo in recurrence prevention
- Indication of benefit when compared to placebo in relapse prevention
- Proof of additional benefit when compared to the SSRI drug class (on an individual drug level for fluoxetine) for change in depressive symptoms (response) in short-term acute therapy
- Proof of additional benefit when compared to bupropion for remission and for change in depressive symptoms (response) in short-term acute therapy
- Indication that, for change in depressive symptoms (response), the additional benefit from venlafaxine compared to SSRI applies more to patients with higher severity of depression than to those with lower severity of depression
- Proof of benefit when compared to placebo in younger patients in acute therapy for depression with reference to change in depressive symptoms (response), no proof of benefit in therapy for older patients
- Proof of benefit when compared to placebo for treatment of anxiety in short-term acute therapy
- Proof of benefit when compared to placebo with reference to an improvement in social functioning level in short-term acute therapy
- Proof of harm when compared to placebo for therapy discontinuations due to adverse events in short-term acute therapy
- Proof of greater harm when compared to SSRI (on an individual drug level for fluoxetine) for the total rate of adverse events and therapy discontinuations due to adverse events in short-term acute therapy
- Proof of greater harm when compared to agomelatine for therapy discontinuations due to adverse events in short-term acute therapy

- Proof of lesser harm when compared to TCA, amitriptyline and clomipramine for the total rate of adverse events in short-term acute therapy
- Indication of lesser harm when compared to maprotiline for therapy discontinuations due to adverse events in short-term acute therapy
- Indication of lesser harm when compared to trazodone for the total rate of adverse events in short-term acute therapy

There were no proofs or indications of benefit/additional benefit or harm/greater or lesser harm from duloxetine or venlafaxine in comparisons with placebo or active comparators in any other available combinations of outcomes, therapy comparisons and therapeutic goals.

Due to the limited data records on the two drugs, it is not possible to draw a conclusion concerning the mortality and suicidal tendency outcomes. There were no data available for assessing the influence on complications of potential depression-concomitant diseases.

Keywords: depression, duloxetine, venlafaxine, SNRI, selective serotonin and norepinephrine reuptake inhibitors, systematic review

The full report (in German) is available on www.iqwig.de/index.560.html