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Bupropion, mirtazapine, and reboxetine in the treatment of depression[1]

Executive Summary

[1] Translation of the executive summary of the final report "Bupropion, Mirtazapin und Reboxetin bei der Behandlung der Depression" (Version 1.0; Status: 09.11.2009). Please note that this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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 in patients suffering from depression. On 30 October 2007 the G-BA specified the commission in writing.

Research question

The aim of this research is to

- assess the benefit of treatment with bupropion, mirtazapine or reboxetine in treating the acute phase of depression, in maintenance therapy (relapse prevention), and in recurrence prevention compared to
    - treatment with placebo
    - each other
    - treatment with other antidepressants

in each case in adult patients with depression. The focus of the investigation was on patient-relevant outcomes.

Methods

A systematic literature search was carried out in the following databases: MEDLINE, EMBASE, BIOSIS, CENTRAL, and PsycINFO (unrestricted search period, last search in each case in February 2009). In addition, a search for secondary publications was conducted in the following specialized databases: CDSR, DARE, and HTA (last search February 2009). Furthermore, bibliographic indexes of relevant secondary publications (systematic reviews, HTA reports), clinical trial registries, and publicly accessible drug approval documents were screened. Moreover, the manufacturers of the drugs approved in Germany were asked to provide information on published and unpublished trials (bupropion XL: GlaxoSmithKline; mirtazapine: Essex Pharma; reboxetine: Pfizer).

The manufacturers were initially asked to provide a comprehensive overview of all published and unpublished randomized controlled trials (RCTs) that they had sponsored on their drug for the indication of depression. These overviews were to be used to identify the relevant

trials for assessment. The manufacturers were then requested to provide full clinical study reports (CSRs) on the relevant published and unpublished trials.

Double-blinded RCTs were included that compared bupropion XL, mirtazapine or reboxetine with placebo or other chemically defined antidepressants (including the test drugs) or St. John's Wort in 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 trials had to report results on at least one of the pre-defined patient-relevant outcomes (remission, change in depressive symptoms [response or mean change on a depression scale], change in individual or secondary symptoms of depression, relapse/recurrence/deterioration in depressive symptoms [trials on relapse prevention and recurrence prevention], mortality, suicidal tendencies, suicide attempts and suicides, adverse drug effects, rate of complications from secondary diseases, health-related quality of life, social functioning level including working and earning capacity).

The literature screening was carried out by 2 reviewers independently of each other. After assessing the risk of bias, the results of the individual trials were collated according to test drugs and outcomes and described. Meta-analyses were carried out if this was considered feasible and useful. For results of continuous scales, for proof of benefit, in addition to statistical significance of the group difference, it was required that the effect exceeded a defined limit (relevance limit, Cohen's d=0.2). IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet and interested parties were invited to submit written comments.

Results

Reboxetine

During the preparation of the preliminary report on this assessment, the manufacturer of reboxetine (Pfizer) did not provide a full overview of all the Pfizer-sponsored published and unpublished trials on reboxetine for the indication of depression, despite several requests.

Ten relevant trials of reboxetine that could definitely be included were identified from the literature search in bibliographic databases, publicly accessible drug approval documents, and clinical trial registries. However, 3 of these trials could not be analysed with regard to the antidepressive effect of reboxetine because the publications only contained data on partial populations (for one multinational trial only data from the UK were published; one publication only showed results of a subpopulation for which data on cognition were recorded) or on selected outcomes (in one trial only data on sexual dysfunction were published). Furthermore, 6 potentially relevant trials were identified that could not be included because no full publication existed and, at the time of producing the preliminary report, the manufacturer of reboxetine (Pfizer) was not prepared to provide full information

on all trials of reboxetine. Due to insufficient cooperation from the manufacturer of reboxetine, it remained unclear whether additional unpublished trials existed.

Therefore, for the preparation of the preliminary report, there were insufficient data available for the majority of potentially relevant trials and patients. The assessment of the evidence at this point showed that further analysis of the limited data available would probably be seriously biased, as would any deduced conclusions on the proof of benefit or harm from reboxetine. Consequently, it could not represent a valid decision basis for the Federal Joint Committee. On the basis of these circumstances, no proof of benefit or harm from reboxetine could therefore be established, irrespective of whether the data available showed an effect of reboxetine or not.

During the commenting procedure on the preliminary report, the manufacturer of reboxetine (Pfizer) submitted a list – which it declared was complete – of all published and unpublished trials, as well as the CSRs for all trials except one. The documents also contained trials that had previously not been identified in the literature search conducted for the preliminary report. On the basis of the search results from the preliminary report and the submitted documents, 17 relevant trials were included in the benefit assessment (14 short-term acute trials, 1 long-term acute trial, and 2 relapse prevention trials).

The majority of the trials included used a flexible dosage scheme. In most trials, reboxetine was given in a dose of 8 to 10 mg. The comparator doses remained partly below the reboxetine dose when measured against the maximum recommended daily dose for each drug.

The risk of bias on a study level was mostly low (16 out of 17 trials). The risk of bias on an outcome level was assessed as being high in some cases, particularly due to inadequate intention-to-treat analyses. A high risk of bias existed in 4 out of 13 trials on remission, in 5 out of 15 trials on response, and in 6 out of 15 trials on mean change in depressive symptoms.

The most important results from the trials with reboxetine are summarized in Table 1. Data on additional outcomes are given in the text below. After the table, the results comparing reboxetine with placebo are described first. This is followed by a summary of results from active-controlled trials. The data are organized according to patient-relevant outcomes. The conclusions on the benefit assessment are summarized in “evidence maps” in Table 2 and Table 3.

Table 1: Summary of the results of trials with reboxetine

Outcome	**Results of the meta-analyses and individual trials** **Group difference [95% CI], p value**								
	RBX vs. plc[a]	**RBX vs. SSRI[a,b]**	**SSRI – individual agents**				**RBX vs. TCA[a]**	**TCA – indiv. agents**	
			RBX vs. FLU[a]	**RBX vs. PAR[a]**	**RBX vs. CIT[b,c]**	**RBX vs. CIT[c,d]**		**RBX vs. IMI[a]**	**RBX vs. DOT[c]**
Remission[e]	1.17 [0.91; 1.51] p=0.216	0.80 [0.67; 0.96] p=0.015	0.85 [0.62; 1.16] p=0.306	0.79 [0.59; 1.05] p=0.104	0.64 [0.26; 1.57] p=0.362	0.51 [0.32; 0.83] p=0.003[g]	-	heterogeneous results	no data
Response[e]	H: 11.43 [3.10; 42.12] p<0.001[c] O: 1.05 [0.73; 1.50] p=0.796	0.80 [0.67; 0.95] p=0.010	0.82 [0.60; 1.12] p=0.212	0.79 [0.64; 0.99] p=0.040	0.67 [0.26; 1.70] p=0.53	0.60 [0.35; 1.03] p=0.058	heterogeneous results	heterogeneous results	0.60 [0.38; 0.96] p=0.04[g]
HAMD total score	H: −1.52 [−2.14; −0.90] p<0.001[c,f,g] O: −0.18 [−0.46; 0.09] p=0.193[c,f]	heterogeneous results	−0.09 [−0.27; 0.10] p=0.375[f]	no data p=0.035[c] 0.24 [0.02; 0.46][f]	no data	1.9 [0.1; 3.6] p=0.034 0.22 [0.00; 0.44][f]	heterogeneous results	−0.06 [−0.25; 0.12] p=0.486[f]	3.5 [1.7; 5.2] p<0.001 0.47 [0.23; 0.70] p<0.001[f,g]
SAE	0.00 [−0.01; 0.01] p=0.776[h]	0.00 [−0.01; 0.01] p=0.990[h]	0.00 [−0.02; 0.01] p=0.578[h]	0.00 [−0.01; 0.02] p=0.554[h]	no data	0.97 [0.24; 3.95] p=1.0[e]	heterogeneous results	−0.02 [−0.05; 0.02] p=0.356[h]	2.64 [0.50; 13.84] p=0.24[e]
AE[e]	2.11 [1.54; 2.90] p<0.001	1.06 [0.82; 1.36] p=0.667	1.25 [0.89; 1.76]; p=0.192 M: 2.76 [1.28; 5.93]; p=0.010 W: 0.90 [0.51; 1.59]; p=0.724	0.90 [0.61;1.33] p=0.600	no data	1.57 [1.03; 2.38] p=0.04	1.31 [0.92; 1.86] p=0.137	1.12 [0.73; 1.73] p=0.591	1.76 [0.96; 3.24] p=0.07
Dis-continuations due to AE[e]	2.21 [1.45; 3.37] p<0.001	heterogeneous results	1.79 [1.06; 3.05] p=0.031	heterogeneous results	no data	4.61 [2.15; 9.89] p<0.001	heterogeneous results	0.69 [0.40; 1.21] p=0.199	2.03 [1.12; 3.68] p=0.02

(continued)

Table 1 (continued): Summary of the results of trials with reboxetine

The main part of the report contains more detailed information on the results.

a: result of a meta-analysis (if not otherwise designated); b: without long-term acute trial; c: result(s) from individual trial(s); d: long-term acute trial; e: odds ratio (if not otherwise designated); f: Cohen's d; g: no proof of benefit or additional benefit due to high risk of bias; h: risk difference

AE: adverse events; CI: confidence interval; CIT: citalopram; DOT: dothiepin; FLU: fluoxetine; H: hospitalized patients; HAMD: Hamilton Depression Scale; IMI: imipramine; M: men; O: outpatients; PAR: paroxetine; plc: placebo; RBX: reboxetine; SAE: serious adverse events; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; vs.: versus; W: women

Reboxetine in acute therapy compared to placebo

All placebo-controlled trials on acute therapy investigated short-term acute therapy (6 to 8 weeks). Data on **remission** were available from all placebo-controlled trials, apart from one trial with severely depressed inpatients. In these 7 trials there was no statistically significant difference between the remission rates with reboxetine and placebo. Therefore, in short-term acute therapy, a benefit of reboxetine was not proven for the outcome remission.

Data on **response** were available from all 8 placebo-controlled trials. The meta-analysis of trials showed a high level of heterogeneity. A meta-regression analysis to investigate this heterogeneity revealed that the care setting was a probable effect modifier (p value of the corresponding interaction test: 0.001). In the trial with patients treated in hospital (N=52), the response rate under reboxetine was statistically significantly higher than under placebo. In the pool of the remaining 7 trials and that of the 2 trials with patients receiving outpatient treatment, there were no statistically significant differences. As a result, in short-term acute therapy, there is an indication of a benefit of reboxetine for the outcome response in hospitalized patients, whereas a benefit is not proven in outpatients.

Due to the high heterogeneity in the meta-analysis, inpatients and outpatients treated in the trial were also considered separately with regard to the **mean change in depressive symptoms.** Due to the high risk of bias, no proof of benefit was derived from the statistically significant effect of reboxetine in the trial including inpatients. In short-term acute therapy, the analysis of the trial including outpatients produced no proof of benefit of reboxetine compared to placebo for the mean change in depressive symptoms.

Data on the effect of reboxetine on the **social functioning level** were only collected in 2 placebo-controlled trials. There was a statistically significant difference in favour of reboxetine (group difference 1.3 points on the SASS; p=0.010). Measured in standard deviations, the effect size (0.16 [0.04; 0.29]) was below a small effect. The relevance of the effect cannot be estimated with certainty; thus, in short-term acute therapy there is no proof of benefit of reboxetine for the outcome social functioning level.

The effect of reboxetine on **health-related quality of life** was only measured in 2 trials. There was no statistically significant difference between reboxetine and placebo. Thus, there is no proof of benefit in short-term acute therapy.

There were no analysable data on the effect of reboxetine compared to placebo on **individual and secondary symptoms** in depression.

With respect to study design and duration, none of the trials were aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results for these outcomes is therefore limited and the data do not provide conclusive clarification. Taking the limited validity into account, there was no proof of harm from reboxetine compared to placebo for the above-mentioned outcomes.

The analysis of **adverse events** (see Table 1) showed a statistically significantly higher rate of therapy discontinuations due to adverse events and of patients with at least one adverse event under reboxetine than under placebo. Thus, in short-term acute therapy, there is proof of harm from reboxetine for these outcomes. There was no statistically significant difference in the rate of serious adverse events between reboxetine and placebo. Thus, in short-term acute therapy, there is no proof of harm from reboxetine for this outcome.

Reboxetine in acute therapy compared to other antidepressants

The majority of active-controlled trials investigated short-term acute therapy (6 to 12 weeks). A citalopram-controlled trial was identified in long-term acute therapy (24 weeks).

In the comparison of reboxetine with SSRI in the short-term acute trials, there was a statistically significant difference in favour of SSRI both in the **remission** rate and in the **response** rate (see Table 1). Thus, in short-term acute therapy, there is proof of a lesser benefit of reboxetine compared to SSRI for remission and response. In addition, there was a statistically significant difference in the response rate in favour of paroxetine compared to reboxetine. Thus, in short-term acute therapy, there is proof of a lesser benefit of reboxetine compared to paroxetine for the outcome response. In long-term acute therapy there was also a statistically significant advantage in favour of the comparator, citalopram, for remission. However, due to a high risk of bias for this outcome, this does not signify an indication of a lesser benefit.

In short-term acute therapy there was no proof of additional benefit or lesser benefit of reboxetine compared to TCA or the individual agents. Although the response rate under reboxetine was statistically significantly lower compared to dothiepin, the risk of bias for this outcome was high, thus no proof of lesser benefit of reboxetine could be shown in short-term acute therapy.

With regard to the **mean change in depressive symptoms**, measured using the Hamilton Depression Scale (HAMD), a high level of heterogeneity (due to different effects of the individual agents) was present in the meta-analysis of trials comparing reboxetine and SSRI in short-term acute therapy. A conclusion on the benefit of reboxetine compared to the SSRI drug class was therefore dispensed with.

There was no statistically significant difference in the meta-analysis of the 3 fluoxetine-controlled trials, while the paroxetine-controlled trial (052) revealed a statistically significant difference in favour of paroxetine (see Table 1). However, the relevance of the effect could not be estimated with certainty. Thus, in short-term acute therapy there is no proof of a lesser benefit of reboxetine compared to paroxetine with regard to the mean change in depressive symptoms. There was a statistically significant advantage for citalopram in long-term acute therapy. The relevance of the effect was uncertain here as well (see Table 1). Thus, there is no proof of a lesser benefit of reboxetine compared to citalopram.

The meta-analysis of TCA also revealed heterogeneity for the above outcome, while no heterogeneous results were observed with the individual agents. There was no statistically significant difference between reboxetine and imipramine. Consequently, there is no proof of additional benefit of reboxetine. The difference between reboxetine and dothiepin was statistically significant in favour of dothiepin (see Table 1). There was even an effect of relevant size. However, the risk of bias for this outcome was high, so that in short-term acute therapy proof of a lesser benefit of reboxetine compared to dothiepin could not be asserted.

For the comparison with SSRI in short-term acute therapy, data on the effect of reboxetine on the **social functioning level** were collected in 3 trials. The meta-analysis of the 3 trials did not show a statistically significant difference between the treatment options. Nor were there any statistically significant differences when compared to the individual agents, fluoxetine and paroxetine. Therefore, in short-term acute therapy, there is no proof of additional benefit of reboxetine compared to SSRI or to the individual agents, fluoxetine or paroxetine, for the outcome social functioning level. The only dothiepin-controlled trial revealed the same result.

There was also no statistically significant difference between reboxetine and citalopram in long-term acute therapy. Thus, there is no proof of additional benefit of reboxetine.

Compared to active comparators, there were no analysable data on the effect of reboxetine on **health-related quality of life** or **individual and secondary symptoms** in depression.

With respect to study design and duration, none of the trials were aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results for these outcomes is therefore limited and the data do not provide conclusive clarification. Taking the limited validity into account, there was no proof of greater or lesser harm of reboxetine compared to active comparators for the above-mentioned outcomes.

The analyses of **adverse events** showed statistically significant differences between reboxetine and the other antidepressants in some comparisons and for some outcomes (see Table 1). In short-term acute therapy, more therapy discontinuations due to adverse events occurred under reboxetine compared to fluoxetine and dothiepin. Consequently, in short-term acute therapy there is proof of greater harm from reboxetine compared to fluoxetine and an indication of greater harm from reboxetine compared to dothiepin. There was also proof from the subgroup analyses of greater harm from reboxetine compared to fluoxetine in male patients with regard to the number of patients who had experienced at least one adverse event. There was no proof of greater harm for this outcome in women. In long-term acute therapy there were indications of greater harm from reboxetine compared to citalopram, both with regard to therapy discontinuations due to adverse events and to the total number of adverse events.

Reboxetine in relapse prevention compared to placebo

In the relapse prevention trial with patients without further restriction, statistically significantly fewer patients suffered a **relapse** under reboxetine than under placebo (reboxetine 21.8%, placebo 56.0%, $p < 0.001$). The increase in depressive symptoms, measured as **mean change on the HAMD**, was statistically significant and relevantly smaller under reboxetine than under placebo (mean value at end of study: mirtazapine 7.9, placebo 13.9, $p < 0.001$; Cohen's d: −0.71 [−0.96; −0.46]). Consequently, there is an indication of a benefit of reboxetine in relapse prevention.

However, in the trial with fluoxetine-resistant patients who had responded to reboxetine, there was no statistically significant difference in the relapse rate between reboxetine and placebo. There were insufficient data on the mean change on the HAMD. Accordingly, there is no proof of benefit of reboxetine in this respect.

With regard to study design and duration, the relapse prevention trials were not aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results for these outcomes is therefore limited and the data do not provide conclusive clarification. Taking the limited validity into account, there was no proof of harm from reboxetine compared to placebo for the above-mentioned outcomes.

The treatment groups in the 2 trials showed no difference in the total number of patients with **adverse events**, with serious adverse events, and the number of therapy discontinuations due to adverse events. In relapse prevention, there is therefore no proof of harm from reboxetine for these outcomes.

The following 2 tables show the "evidence maps" for reboxetine.

Evidence maps for reboxetine

Table 2: Reboxetine – evidence map for acute trials

Outcome	RBX vs. plc	RBX vs. SSRI[a]	RBX vs. FLU	RBX vs. PAR	RBX vs. CIT	RBX vs. CIT long-term	RBX vs. TCA	RBX vs. IMI	RBX vs. DOT
Remission	↔	R−	↔	↔	↔	↔		↔	
Response	H: (R+) O: ↔	R−	↔	R−	↔	↔	no statement[b]	↔	↔
Depression scale total score	H: ↔ O: ↔	no statement[b]	↔	↔	no data	↔	no statement[b]	↔	↔
Social functioning level	↔	↔	↔	↔	no data	↔			↔
Health-related quality of life	↔								
Mortality	(↔)	(↔)	(↔)	(↔)	no data	(↔)	(↔)	(↔)	(↔)
Suicidal tendencies	(↔)	(↔)	(↔)	(↔)	no data	(↔)	(↔)	(↔)	(↔)
Suicide attempts & suicides	(↔)	(↔)	(↔)	(↔)	no data	(↔)	(↔)	(↔)	(↔)
SAE	↔	↔	↔	↔	no data	↔	no statement[b]	↔	↔
AE	R−	↔	all: ↔ M: R− / W: ↔	↔	no data	(R−)	↔	↔	↔
Discontinuations due to AE	R−	no statement[b]	R−	↔	no data	(R−)	no statement[b]	↔	(R−)

R+ / R-: proof of superiority/inferiority of reboxetine
(R+) / (R-): indication of superiority/inferiority of reboxetine
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data
Empty cells: no data available
a: Findings from the only long-term acute trial not included
b: Due to heterogeneity, no statement on benefit compared to the drug class

AE: adverse events; CIT: citalopram; DOT: dothiepin; FLU: fluoxetine; H: hospitalized patients; IMI: imipramine; M: men; O: outpatients; PAR: paroxetine; plc: placebo; SAE: serious adverse events; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants; vs.: versus; W: women

Table 3: Reboxetine – evidence map for relapse prevention trial

Outcome	RBX vs. plc Non-therapy-resistant population	RBX vs. plc Fluoxetine-resistant population
Relapse rate at end of study	(R+)	↔
Depression scale total score	(R+)	no data
Mortality	(↔)	(↔) (no events)
Suicidal tendencies	(↔)	(↔) (no events)
Suicide attempts & suicides	(↔)	(↔) (no events)
Total rate of SAE	↔	↔
Total rate of AE	↔	↔
Discontinuations due to AE	↔	↔

R+ / R−: superiority/inferiority of reboxetine
(R+) / (R−): indication of superiority/inferiority of reboxetine
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data

AE: adverse events; plc: placebo; RBX: reboxetine; SAE: serious adverse events

Mirtazapine

The various stages of the literature search identified 27 trials that could be included in the assessment. Out of these, 26 trials were acute (25 short-term acute trials, 1 long-term acute trial); one trial investigated mirtazapine in relapse prevention.

The majority of the trials included used a flexible dosage scheme. Most trials had a target dose of 15 to 45 mg/day or 30 to 45 mg/day. In almost all trials with active controls, the comparator dose remained partly well below the mirtazapine dose when measured against the maximum recommended daily dose for each drug.

The risk of bias on a study level was mostly low (25 out of 27 trials). The risk of bias on an outcome level was assessed as being high in some cases, particularly due to inadequate intention-to-treat analyses. A high risk of bias existed in 4 out of 13 trials on remission, in 7 out of 24 studies on response, and in 7 out of 26 trials on mean change in depressive symptoms.

The most important results from the trials with mirtazapine are summarized in Table 4. Data on additional outcomes are given in the text below. After the table, the results comparing mirtazapine with placebo are described first. This is followed by a summary of results from active-controlled trials. The data are organized according to patient-relevant outcomes. The conclusions on the benefit assessment are summarized in "evidence maps" in Table 5 and Table 6.

Table 4: Summary of the results of acute trials with mirtazapine

Outcome	Results of the meta-analyses and individual trials Group difference [95% CI], p value								
	MIR vs. plc[a]	MIR vs. SSRI[a,b]	SSRI – individual agents				MIR vs. VEN[c]	MIR vs. TRA[c]	MIR vs. AMI[c]
			MIR vs. FLU[a]	MIR vs. PAR[a,b]	MIR vs. FLUV[a]	MIR vs. SER[c]			
Remission[d]	no data p=0.458[c]	1.18 [0.98; 1.43] p=0.076	1.25 [0.86; 1.83] p=0.241	1.25 [0.90; 1.73] p=0.175	1.17 [0.79; 1.73] p=0.433	no data; p=0.798[e] no data; p=0.079[f]	−0.4 [−11.9; 11.0] p=0.942[g]	no data	no data
Response[d]	1.87 [1.36; 2.58] p<0.001	1.10 [0.87; 1.38] p=0.430	1.17 [0.82; 1.67] p=0.388	heterogeneous results	heterogeneous results	no data; p=0.824[e] no data; p=0.891[f]	6.4 [−6.1; 18.9] p=0.317[g]	no data p=0.39	no data p=0.531
Depression scale total score (HAMD)	heterogeneous results	−0.06 [−0.19; 0.07] p=0.376[h]	−0.16 [−0.39; 0.07] p=0.182[h]	heterogeneous results	heterogeneous results	−0.65 [−2.26; 0.97] p=0.431[e,i] −0.60 [−2.48; 1.28] p=0.821[f,i]	−0.91 [−2.77; 0.96] p=0.338[i]	no data p=0.05	no data "n.s."
SAE[d]	0.00 [−0.01; 0.02] p=0.561[j]	0.00 [−0.01; 0.01] p=0.983[j]	0.89 [0.28; 2.87] p=0.848	0.00 [−0.02; 0.02] p=0.659[j]	1.37 [0.17; 11.37] p=0.768	no data; p=0.480[e] no data; p=0.575[f]	no data p=0.015[k]	no data	no data p=0.558
AE[d]	heterogeneous results	1.00 [0.81; 1.22] p=0.972	1.28 [0.71; 2.31] p=0.416	1.06 [0.74;1.51] p=0.760	0.85 [0.54; 1.33] p=0.468	no data; p=0.548[e] no data; p=0.506[f]	no data p=0.904	no data	no data
Dis-continuations due to AE	2.75 [1.28; 5.93] p=0.010	heterogeneous results	1.81 [1.03; 3.18] p=0.039	0.64 [0.42; 0.99] p=0.046	1.66 [0.85; 3.23] p=0.137	no data; p=0.002[e,k] no data; p=0.041[f,k]	no data p=0.22	no data	no data p=1.0
Sexual dysfunction[l]	no data p=0.300[c]	0.06 [−0.11; 0.22] p=0.512[h]	no data p=0.854[c]	not recorded	not recorded	p=0.536/0.279[e,m] p=0.642/0.196[f,m]	p=0.967/0.305[m]	not recorded	not recorded

The main part of the report contains more detailed information on the results.

a: result of a meta-analysis (if not otherwise designated); b: without long-term acute trial; c: result(s) from individual trial(s); d: odds ratio (if not otherwise designated); e: trial with depressed patients with no other restriction; f: trial with SSRI-resistant depressed patients; g: group difference in %; h: Cohen's d; i: group difference for HAMD total score; j: risk difference; k: higher rate with mirtazapine; l: using CSFQ or ASEX; m: result for men/women
AE: adverse events; AMI: amitriptyline; ASEX: Arizona Sexual Experience Questionnaire; CI: confidence interval; CSFQ: Changes in Sexual Function Questionnaire; FLU: fluoxetine; FLUV: fluvoxamine; HAMD: Hamilton Depression Scale; MIR: mirtazapine; n.s.: not significant; PAR: paroxetine; plc: placebo; SER: sertraline; SSRI: selective serotonin reuptake inhibitors; SAE: serious adverse events; TRA: trazodone; VEN: venlafaxine XR.

Mirtazapine in acute therapy compared to placebo

All placebo-controlled trials investigated short-term acute therapy (6 to 8 weeks). Data on **remission** were only available from one placebo-controlled trial. In this trial there was no statistically significant difference between the remission rates with mirtazapine and placebo. Therefore, in short-term acute therapy, a benefit of mirtazapine for the outcome remission is not proven.

In a meta-analysis of short-term acute trials, the rate of patients showing **response** was statistically significantly higher with mirtazapine than with placebo. In short-term acute therapy, this provides proof of benefit of mirtazapine for the outcome response. In contrast, there is no proof of benefit of mirtazapine compared to placebo for the **mean change in depressive symptoms**, measured on the HAMD.

A trial with patients suffering from depression following an acute heart attack showed no statistically significant difference between mirtazapine and placebo for the following outcomes: remission, response and mean change in depressive symptoms (p=0.08; p=0.18; p=0.09). In acute therapy, there is no proof of benefit of mirtazapine for these outcomes in this population.

With respect to study design and duration, none of the trials were aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results for these outcomes is therefore limited and the data do not provide a conclusive answer. Taking the limited validity into account, there was no proof of harm from mirtazapine compared to placebo for the above-mentioned outcomes.

The analysis of **adverse events** (see Table 4) showed a statistically significantly higher rate of therapy discontinuations due to adverse events with mirtazapine than with placebo. In short-term acute therapy this provides proof of harm from mirtazapine for this outcome. There was no statistically significant difference in the rate of serious adverse events between mirtazapine and placebo; the total rate of adverse events showed heterogeneous results. Consequently, the effect of mirtazapine on this outcome remains unclear. In short-term acute therapy, there is therefore no proof of harm from mirtazapine for these outcomes.

The placebo-controlled trial on **sexual dysfunction** showed no statistically significant difference between mirtazapine and placebo. In short-term acute therapy, there is therefore no proof of harm from mirtazapine for the outcome sexual dysfunction.

Mirtazapine in acute therapy compared to other antidepressants

The majority of active-controlled trials investigated short-term acute therapy (6 to 8 weeks). A paroxetine-controlled trial was identified in long-term acute therapy (24 weeks). None of the active-controlled trials and no meta-analysis revealed a statistically significant difference in the **remission** rate between mirtazapine and one of the active comparators. In short-term

acute therapy, there is therefore no proof of additional benefit of mirtazapine for the outcome remission. Nor could any statistically significant differences in the **response** rate be observed between mirtazapine and the active controls. In short-term acute therapy, there is therefore no proof of additional benefit of mirtazapine for the outcome response. Nor is there any proof of additional benefit of mirtazapine for the **mean change in depressive symptoms** measured using the HAMD.

These results were also confirmed in a sertraline-controlled short-term acute trial with SSRI-resistant patients (see Table 4) and in the paroxetine-controlled long-term acute trial over 24 weeks (remission: p=0.10; response: p=0.31; mean change in symptoms: p=0.16). Thus, for SSRI-resistant patients and in long-term acute therapy, there is also no proof of additional benefit of mirtazapine for the outcomes remission, response, and the mean change in depressive symptoms.

Data on the effect of mirtazapine on the **social functioning level** were only collected in the sertraline-controlled trial with SSRI-resistant patients. The trial showed no statistically significant difference between the treatment options. There is therefore no proof of additional benefit of mirtazapine for the outcome social functioning level.

The effect of mirtazapine compared to paroxetine on **health-related quality of life** was investigated both in short-term and long-term acute therapy. There was no statistically significant difference between mirtazapine and paroxetine in the 3 trials on short-term acute therapy. A statistically significant difference in favour of mirtazapine was observed in the long-term acute trial (both on the QLDS[2] and in the total score of mental health in SF-36). The 95% confidence intervals for Cohen's d for the group difference extended in both cases into the range below a small effect (Cohen's d −0.37 [−0.68; −0.06] and 0.32 [0.01; 0.64]). Consequently, the relevance of the effect cannot be estimated with certainty. In short-term and long-term acute therapy, there is therefore no proof of additional benefit of mirtazapine.

The results on individual and secondary symptoms showed no statistically significant difference between mirtazapine and paroxetine with regard to **anxiety.** Concerning **cognition,** there were no statistically significant differences between mirtazapine and amitriptyline and between mirtazapine and paroxetine (in each case in older patients). In the trials on individual and secondary symptoms, evidence of benefit was lacking with regard to the outcome changes in depressive symptoms. The results on individual and secondary symptoms are therefore not included in the benefit assessment, but are merely presented here as additional information.

With respect to study design and duration, none of the trials were aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results on these outcomes is therefore limited and the data do not provide conclusive clarification. Taking this limited

[2] Quality of Life in Depression Scale

validity into account, for the above-mentioned outcomes there was no proof of greater or lesser harm from mirtazapine compared to active comparators.

For some comparisons and some outcomes, the analyses of **adverse events** showed statistically significant differences between mirtazapine and the other antidepressants (Table 4). In short-term acute therapy with mirtazapine, there were more therapy discontinuations due to adverse events compared to fluoxetine and fewer compared to paroxetine. In short-term acute therapy, this provides proof of greater harm from mirtazapine compared to fluoxetine and lesser harm from mirtazapine compared to paroxetine. In contrast, in long-term acute therapy there was no proof of lesser (or greater) harm from mirtazapine compared to paroxetine with regard to therapy discontinuations due to adverse events. In the sertraline-controlled trials, more patients using mirtazapine discontinued the trial due to adverse events than those using sertraline (trial with depressed patients with no further restriction: mirtazapine 12%, sertraline 3%; trial with SSRI-resistant depressed patients: mirtazapine 19%, sertraline 9%). This provided an indication of greater harm from mirtazapine compared to sertraline for these two patient populations. An additional statistically significant difference was found for serious adverse events when comparing mirtazapine and venlafaxine XR. In the trial, the rate of serious adverse events was 5% in the mirtazapine group and there were no serious adverse events with venlafaxine XR. In short-term acute therapy, an indication can be deduced from this result of greater harm from mirtazapine compared to venlafaxine XR with regard to serious adverse events. The other active comparisons did not show any differences in adverse events between mirtazapine and the other agents investigated.

The data on sexual dysfunction did not yield any statistically significant differences between mirtazapine and fluoxetine, sertraline or venlafaxine XR. Thus, in short-term therapy, there is no proof of greater or lesser harm from mirtazapine with regard to this outcome.

Mirtazapine in relapse prevention compared to placebo

In the relapse prevention trial, statistically significantly fewer patients suffered a relapse with mirtazapine than with placebo (mirtazapine: 20%, placebo: 44%, p=0.001). The increase in depressive symptoms, measured as mean change on the HAMD, was statistically significantly and relevantly smaller with mirtazapine than with placebo (mean value at end of study: mirtazapine 6.1. placebo 10.7. p=0.01; Cohen's d: −0.57 [−0.89; −0.25]). This provides an indication of benefit for the use of mirtazapine in relapse prevention.

However, it was not possible to show a positive effect of mirtazapine on **health-related quality of life**; there was no statistically significant difference in the Q-LES-Q score on general activity. A benefit of mirtazapine for this outcome is therefore not proven.

With regard to study design and duration, the relapse prevention trial was not aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results on these outcomes is therefore limited and the data do not provide conclusive clarification. Taking the

limited validity of the data into account, there was no proof of harm from mirtazapine compared to placebo for the above-mentioned outcomes.

The total rate of patients with **adverse events** (mirtazapine 72%, placebo 68%, p=0.53) or with serious adverse events (1 event each for mirtazapine and placebo) did not differ between the treatment groups. The study discontinuations due to adverse events, however, were statistically significantly more frequent with mirtazapine than with placebo (mirtazapine 11%, placebo 3%, p=0.029). In relapse prevention, this provides an indication of harm from mirtazapine with regard to therapy discontinuations due to adverse events; there is no proof of harm with regard to the total rate of adverse events or serious adverse events.

Evidence maps for mirtazapine

Table 5: Mirtazapine – evidence map for acute trials

Outcome	MIR vs. plc[a]	MIR vs. SSRI[b]	MIR vs. FLU	MIR vs. PAR[c]	MIR vs. SER[d]	MIR vs. FLUV	MIR vs. VEN	MIR vs. TRA	MIR vs. AMI
Remission	↔ ↔	↔	↔	↔ ↔	↔ ↔	↔	↔		
Response	M+ ↔	↔	↔	↔ ↔	↔ ↔	↔	↔	↔	↔
Depression scale total score	↔ ↔	↔	↔	↔ ↔	↔ ↔	↔	↔	↔	↔
Social functioning level					no data ↔				
Health-related quality of life				↔ ↔					
Mortality	(↔) (↔)	(↔)	(↔)	(↔) no data	(↔) (↔)	(↔)	(↔)	(↔)	
Suicidal tendencies	(↔) no data	(↔)	(↔)	(↔) (↔)	(↔) (↔)	(↔)	(↔)	(↔)	(↔)
Suicide attempts & suicides	(↔) no data	(↔)	(↔)	(↔) (↔)	(↔) (↔)	(↔)	(↔)	(↔)	(↔)
SAE	↔ no data	↔	↔	↔ no data	↔ ↔	↔	(M−)		↔
AE	↔ no data	↔	↔	↔ ↔	↔ ↔	↔	↔		
Discontinuations due to AE	M− no data	No statement[e]	M−	M+ ↔	(M−) (M−)	↔	↔		↔
Sexual dysfunction	↔ no data	↔	↔		↔ ↔		↔		

M+ / M-: proof of superiority/inferiority of mirtazapine
(M+) / (M-): indication of superiority/inferiority of mirtazapine
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data
Empty cells: no data available

a: 2 symbols in each cell: upper: short-term acute trials, lower: trial after acute heart attack
b: Findings from the only long-term acute trial not included
c: 2 symbols in each cell: upper: short-term acute trials, lower: long-term acute trial
d: 2 symbols in each cell: upper: patients with no additional restriction, lower: SSRI-resistant patients
e: Due to heterogeneity, no statement on benefit compared to the drug class of SSRI

AE: adverse events; AMI: amitriptyline; FLU: fluoxetine; FLUV: fluvoxamine; PAR: paroxetine; plc: placebo; SAE: serious adverse events; SER: sertraline; SSRI: selective serotonin reuptake inhibitors; TRA: trazodone; VEN: venlafaxine; vs.: versus

Table 6: Mirtazapine – evidence map for the relapse prevention trial

Outcome	MIR vs. plc
Relapse rate at end of study	(M+)
Depression scale total score	(M+)
Health-related quality of life	↔
Mortality	(↔) (no events)
Suicidal tendencies	(↔) ((no events)
Suicide attempts & suicides	(↔) ((no events)
SAE	↔
AE	↔
Discontinuations due to AE	(M−)

M+ / M-: proof of superiority/inferiority of mirtazapine
(M+) / (M-): indication of superiority/inferiority of mirtazapine
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data

AE: adverse events; MIR: mirtazapine; plc: placebo; SAE: serious adverse events

Bupropion XL

Overall, 7 relevant trials were identified during the various stages of the literature search and were all included in the assessment.

The trials comprised 4 trials on short-term acute therapy (treatment duration: 8 to 10 weeks). Two of the trials were placebo-controlled, 2 trials were placebo and venlafaxine-controlled. Another 3 placebo-controlled trials investigated bupropion XL for the prevention of a relapse into seasonal affective disorder (SAD) (treatment duration: 12 to 29 weeks).

Flexible dosing was applied in 6 trials; 1 trial used a fixed dose. The dose for bupropion XL was between 150 and 300 mg/day and for venlafaxine XR between 75 and 150 mg/day. This corresponded to 50% to 100% of the approved maximum daily dose for bupropion XL, and 20% to 40% for venlafaxine XR.

The risk of bias on a study level was low in all 7 trials. On an outcome level the risk of bias was classified as low for all outcomes in all trials except 2. The risk of bias was rated as high in 1 out of 3 trials investigating the social functioning level and in 1 out of 3 trials investigating sexual dysfunction (in both cases due to inadequate intention-to-treat analyses).

Table 7 summarizes the most important results from the trials with bupropion XL. Additional outcomes are presented in the text below. After the table, the results of the comparison of bupropion XL with placebo and of bupropion XL with venlafaxine XR in short-term acute therapy are first described. Thereafter, the results of the comparison of bupropion XL with placebo in trials on the prevention of SAD are presented. The conclusions on the benefit assessment are summarized in “evidence maps” in Table 8 and Table 9.

Table 7: Summary of the results of trials with bupropion XL

Outcome	Result of meta-analyses Group difference [95% CI], p value		
	Short-term acute therapy		Prevention of relapse into SAD
	Bupropion XL vs. placebo	Bupropion XL vs. venlafaxine XR	Bupropion XL vs. placebo
Remission[a]	1.46 [1.18; 1.82] p=0.001	0.72 [0.54; 0.96] p=0.025	not relevant
Response[a]	1.48 [1.20; 1.82] p<0.001	0.70 [0.52; 0.94] p=0.018	not relevant
Depression scale total score (MADRS)[b]	−1.70 [−2.72; −0.68] p=0.001 Cohen's d: −0.17 [−0.27; −0.07]	1.66 [0.24; 3.08] p=0.022 Cohen's d: 0.17 [0.03; 0.31]	not recorded
Relapse into SAD[a]	not relevant	not relevant	0.48 [0.35; 0.65] p<0.001
Depression scale total score (HAMD-24-SAD)[b]	not relevant	not relevant	−1.89 [−3.11; −0.67] p=0.002 Cohen's d: −0.19 [−0.31; −0.07]
Depression scale Total score (HAMD-17)[b]	not recorded	not recorded	−1.19 [−1.96; −0.42] p=0.002 Cohen's d: −0.19 [−0.31; −0.07]
SAE	0.39[a] [0.16; 0.94] p=0.037	0.51[a] [0.09; 2.94] p=0.449	0.00[c] [−0.01; 0.01] p=0.718
AE[a]	heterogeneous results	heterogeneous results	1.21 [0.86; 1.70] p=0.274
Discontinuations due to AE[a]	1.00 [0.61; 1.65] p=0.992	0.84 [0.44; 1.60] p=0.588	heterogeneous results
Sexual dysfunction (CSFQ)[b]	0.62 [−0.63; 1.87] p=0.329	0.71 [−0.54; 1.96] p=0.266	not recorded
Sexual dysfunction (ASEX)[d]	−0.27 [−0.53; −0.01] p=0.045	not recorded	not recorded
Social functioning level (SDS)[b]	−2.11 [−3.02;−1.20] p<0.001 Cohen's d: −0.28 [−0.40; −0.16]	0.96 [−0.17; 2.08] p=0.097	not recorded
Health-related quality of life (Q-LES-Q)[b]	4.03 [1.90; 6.15] p<0.001 Cohen's d: 0.22 [0.11; 0.34]	−0.72 [−3.95; 2.50] p=0.660	not recorded
Anxiety (HAMA)[b]	−1.24 [−2.03; −0.46] p=0.002 Cohen's d: −0.17 [−0.28; −0.06]	1.17 [−0.06; 2.39] p=0.062	not recorded
Motivation and energy (MEI)[b]	5.55 [2.66; 8.44] p<0.001 Cohen's d: 0.27 [0.12; 0.41]	−2.08 [−5.01; 0.85] p=0.164	not recorded
Pain (VAS)[b]	not recorded	not recorded	−0.03 [−0.60; 0.55] p=0.921

(continued)

Table 7 (continued): Summary of the results of trials with bupropion XL

More detailed information on the results can be found in the main part of the report. a: Odds ratio (if not otherwise defined); b: weighted mean value difference; c: risk difference; d: Cohen's d AE: adverse events; ASEX: Arizona Sexual Experience Scale; CI: confidence interval; CSFQ: Changes in Sexual Function Questionnaire; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MEI: Motivation and Energy Inventory; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SAD: seasonal affective disorder; SAE: serious adverse events; SDS: Sheenan Disability Scale; VAS: visual analogue scale; XL, XR: extended release

Bupropion XL in short-term acute therapy

In the trials on short-term acute therapy, a statistically significantly higher proportion of patients using bupropion XL achieved **remission** or responded to the therapy (**response**) than patients using placebo. In short-term acute therapy, this proves a benefit of bupropion XL versus placebo for the outcomes remission and response.

The **mean change in depressive symptoms** measured on the MADRS[3] was statistically significantly greater with bupropion XL than with placebo; however, the relevance of the difference could not be evaluated with certainty. In short-term acute therapy, a benefit with regard to the mean change in depressive symptoms is thus not proven. This also applies to the subgroups differentiated according to degree of disease severity. Although there was an indication of an interaction between treatment and degree of severity, none of the meta-analyses within the subgroups with greater or less severe depression yielded proof of a benefit of bupropion in short-term acute therapy with regard to the mean change in depressive symptoms.

Compared to venlafaxine XR, the proportion of patients with remission or response during treatment with bupropion XL was statistically significantly smaller. Thus, in short-term acute therapy, this provides proof of lesser benefit of bupropion XL compared to venlafaxine XR for remission and response. The mean change in depressive symptoms on the MADRS was also less with bupropion XL than with venlafaxine XR. However, because the relevance of the effect cannot be estimated with certainty, a lesser benefit with regard to the mean change in depressive symptoms on the MADRS is therefore not proven in short-term acute therapy.

The effect of bupropion XL on the **social functioning level**, **health-related quality of life**, **anxiety symptoms** as well as **motivation and energy of patients** was statistically significantly greater than that of placebo. However, because the relevance of the effects cannot be estimated with certainty, the benefit with regard to these outcomes is not proven in short-term acute therapy. In the comparison of bupropion XL and venlafaxine XR, no

[3] Montgomery-Åsberg Depression Rating Scale

statistically significant differences occurred with regard to the above-mentioned outcomes (see Table 7). Thus, there was no proof of additional benefit in short-term acute therapy.

With regard to study design and duration, the trials were not aimed at investigating **suicidal tendencies, suicides** or **mortality**. The validity of the results on these outcomes is therefore limited, and the data do not provide conclusive clarification. Taking the limited validity of the data into account, there was no proof of harm from bupropion XL compared to placebo or of greater or lesser harm compared to venlafaxine XR for the above-mentioned outcomes.

In short-term acute therapy, the differences in the rates of **adverse events** and the rate of therapy discontinuations due to adverse events between bupropion XL and placebo were not statistically significant. There is thus no proof of harm from bupropion XL with regard to these outcomes. The statistically significant advantage of bupropion XL compared to placebo with regard to serious adverse events produced proof of a lesser harm in short-term acute therapy. This finding was caused by many cases in the placebo group (10/18), which presented deterioration in the underlying disease (SAE regarding suicidal tendencies and deterioration of depression); in this respect, this finding matches specific proof of benefit (e.g. response).

Between bupropion XL and venlafaxine XR there was no statistically significant difference in serious adverse events and in therapy discontinuations due to adverse events. Concerning the total rate of adverse events, the comparison of bupropion XL and venlafaxine XR showed heterogeneous results (one trial with a statistically significant advantage for bupropion XL, one trial without a group difference). Thus, in short-term acute therapy, there is no proof of greater or lesser harm from bupropion XL compared to venlafaxine XR. With regard to **sexual dysfunction**, the group differences between bupropion XL and placebo or venlafaxine XR were not statistically significant on the CSFQ, and statistically significant but of uncertain relevance on the ASEX (for placebo only). Thus, in short-term acute therapy, for this outcome as well, there is no proof of harm from bupropion XL compared to placebo or of greater or lesser harm compared to venlafaxine XR.

Bupropion XL for the prevention of a relapse into SAD

In the trials on prevention of a **relapse** into SAD, statistically significantly lower relapse rates were observed with bupropion XL than with placebo. In relapse prevention, a benefit of bupropion XL is proven. The **mean changes in depressive symptoms** on the HAMD-24 SAD and the HAMD-17 were also statistically significant, but the relevance of the group difference could not be estimated. Thus, in relapse prevention a benefit of bupropion XL with regard to the mean change in depressive symptoms is not proven (see Table 7).

There was no statistically significant difference between the effect of bupropion XL and that of placebo on **pain symptoms**. Thus, in relapse prevention a benefit of bupropion XL with regard to pain symptoms in depressed patients is not proven.

Taking the limited validity of the data into account, there was no proof of harm from bupropion XL compared to placebo for the outcomes **suicidal tendencies**, **suicides** or **mortality**.

There were no statistically significant differences in the rate of **adverse events** or serious adverse events between bupropion XL and placebo. The analysis of therapy discontinuations due to adverse events showed heterogeneous results. Thus, in relapse prevention in patients with SAD, there is no proof of harm from bupropion XL with regard to adverse events.

Evidence maps for bupropion XL

Table 8: Bupropion XL – evidence map for acute trials

Outcome	Bupropion XL vs. placebo			Bupropion XL vs. venlafaxine XR
Remission	B+			B−
Response	B+			B−
Depression scale total score	all: ↔	mild / moderate depression[a]: ↔	severe depression[a]: ↔	↔
Social functioning level	↔			↔
Health-related quality of life	↔			↔
Anxiety	↔			↔
Motivation and energy	↔			↔
Mortality	(↔)			(↔)
Suicidal tendencies	(↔)			(↔)
Suicide attempts & suicides	(↔)			(↔)
SAE	B+[b]			↔
AE	↔			↔
Discontinuations due to AE	↔			↔
Sexual dysfunction	↔			↔

B+ B-: proof of superiority/inferiority of bupropion
(B+) / (B-): indication of superiority/inferiority of bupropion
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data

a: Definitions: mild/moderate depression: MADRS at baseline ≤ 30; severe depression: MADRS at baseline > 30
b: The lesser harm of bupropion XL compared to placebo refers to serious adverse events in the placebo group, which were associated with deterioration in the underlying disease (SAE regarding suicidal tendencies and deterioration of depression). This difference also reflects a benefit aspect, which was also observed in the relevant outcomes (e.g. response).

AE: adverse events; MADRS: Montgomery-Åsberg Depression Rating Scale; SAE: serious adverse events; vs.: versus; XL, XR: extended release

Table 9: Bupropion XL – Evidence map for relapse prevention trials on SAD

Outcome	Bupropion XL vs. placebo
Relapse rate at end of study	B+
Depression scale total score (HAMD-24-SAD)	↔
Depression scale total score (HAMD-17)	↔
Pain	↔
Mortality	(↔) (no events)
Suicidal tendencies	(↔) (no events)
Suicide attempts & suicides	(↔) (no events)
SAE	↔
AE	↔
Discontinuations due to AE	↔

B+ / B-: proof of superiority/inferiority of bupropion
(B+) / (B-): indication of superiority/inferiority of bupropion
↔: no proof of superiority or inferiority of one of the 2 treatment options
(↔): no proof of superiority or inferiority of one of the 2 treatment options, with insufficient data

AE: adverse events; HAMD-17: Hamilton Depression Rating Scale (17-item version); HAMD-24-SAD: HAMD (24-item version); SAD: seasonal affective disorder; SAE: serious adverse events; XL: extended release

Conclusions

Reboxetine

Reboxetine in acute therapy

In outpatients receiving short-term acute therapy, there is no proof of benefit of reboxetine versus placebo for the following outcomes: remission, response to therapy, and mean change in depressive symptoms on the HAMD. In inpatients receiving short-term acute therapy, there is an indication of a benefit for the outcome response; however, a benefit for the outcomes remission or mean change in depressive symptoms is not proven.

In short-term acute therapy, there is no proof of benefit of reboxetine for the outcomes social functioning level and health-related quality of life, as well as for the individual and secondary symptoms of depression.

In short-term acute therapy, there is proof of a lesser benefit of reboxetine versus SSRI for the outcomes remission and response. On the level of individual agents, a lesser benefit of reboxetine versus paroxetine is proven for response. In short-term or long-term acute therapy, further proof of differences in benefit outcomes between reboxetine and other antidepressants is not available.

Taking the limited validity of the data into account, there was no proof of harm from reboxetine versus placebo or of greater or lesser harm from reboxetine versus other antidepressants for the outcomes suicidal tendencies, suicides or mortality.

In short-term acute therapy, there is proof of harm from reboxetine versus placebo for the outcomes adverse events and therapy discontinuations due to adverse events, but not for serious adverse events.

In short-term acute therapy, there is proof of greater harm from reboxetine versus fluoxetine for adverse events in men and for therapy discontinuations due to adverse events in men and women. In addition, there is an indication of greater harm from reboxetine versus dothiepin for the outcome therapy discontinuations due to adverse events. In long-term acute therapy, there is an indication of greater harm from reboxetine versus citalopram (adverse events and therapy discontinuation due to adverse events).

Reboxetine in relapse prevention

In relapse prevention (relapse rate and mean change in depressive symptoms), there is an indication of a benefit of reboxetine versus placebo. There is no proof of benefit in relapse prevention in fluoxetine-resistant patients.

Taking the limited validity of the data on suicidal tendencies, suicides or mortality into account, in relapse prevention there is no proof of harm from reboxetine versus placebo. Nor is there proof of harm from reboxetine for the outcomes adverse events, serious adverse events and therapy discontinuations due to adverse events.

Mirtazapine

Mirtazapine in acute therapy

In short-term acute therapy, there is proof of benefit of mirtazapine versus placebo for the outcome response. A benefit of mirtazapine is not proven for the outcomes remission of depression or mean change in depressive symptoms measured on the HAMD.

In short-term or long-term acute therapy, there is no proof of additional benefit of mirtazapine versus other antidepressants for the following outcomes: remission, response, and mean change in depressive symptoms. Nor is there any proof of additional benefit of mirtazapine for the outcomes social functioning level or health-related quality of life.

Taking the limited validity of the data into account, there was no proof of harm from mirtazapine versus placebo or of greater or lesser harm from mirtazapine versus other antidepressants for the outcomes suicidal tendencies, suicides or mortality.

In short-term acute therapy, there is proof of harm from mirtazapine versus placebo for the outcome therapy discontinuations due to adverse events. There is no proof that adverse events and serious adverse events occur more frequently with mirtazapine than with placebo. Harm from mirtazapine is not proven with regard to the outcome sexual dysfunction.

Compared to other antidepressants, in short-term acute therapy there is proof of greater harm from mirtazapine versus fluoxetine and lesser harm from mirtazapine versus paroxetine for the outcome therapy discontinuations due to adverse events. In addition, for the same outcome, there is an indication of greater harm from mirtazapine versus sertraline in depressed patients with no additional restriction and in SSRI-resistant depressed patients.

In short-term acute therapy, there is an indication of greater harm from mirtazapine versus venlafaxine XR for the outcome serious adverse events. For adverse events, the other active comparisons did not show any proof of greater or lesser harm from mirtazapine. Regarding sexual dysfunction, there is no proof of greater or lesser harm from mirtazapine versus other antidepressants.

Mirtazapine in relapse prevention

In relapse prevention (relapse rate and mean change in depressive symptoms), there is an indication of a benefit for the use of mirtazapine versus placebo; a benefit is not proven for the outcome health-related quality of life.

Taking the limited validity of the data into account, there was no proof of harm from mirtazapine versus placebo for suicidal tendencies, suicides or mortality. There is an indication of harm from mirtazapine with regard to therapy discontinuations due to adverse events. In relapse prevention, there is no proof of harm from mirtazapine with regard to the total rate of adverse events or serious adverse events.

Bupropion XL

Bupropion XL in short-term acute therapy

In short-term acute therapy, there is proof of benefit of bupropion XL versus placebo for the outcomes remission and response; benefit is not proven for the mean change in depressive symptoms on the MADRS.

In short-term acute therapy, a lesser benefit of bupropion XL versus venlafaxine XR is proven for remission and response; no additional or lesser benefit is proven for the mean change in depressive symptoms measured on MADRS.

In short-term acute therapy, a benefit of bupropion XL versus placebo is not proven for the outcomes social functioning level, health-related quality of life, anxiety symptoms, and patients' motivation and energy. A comparison of bupropion XL and venlafaxine XR does not produce proof of additional benefit of bupropion XL for the outcomes mentioned above.

Taking the limited validity of the data into account, in short-term acute therapy there was no proof of harm from bupropion XL versus placebo or of greater or lesser harm versus venlafaxine XR with regard to the outcomes suicidal tendencies, suicides or mortality.

In short-term acute therapy, there is no proof of harm from bupropion XL versus placebo or of greater or lesser harm versus venlafaxine XR for the outcomes adverse events, therapy discontinuations due to adverse events or sexual dysfunction. For serious adverse events, there was proof of lesser harm from bupropion XL versus placebo (caused by deterioration in the underlying disease in the placebo group). For the same outcome, there was no proof of greater or lesser harm from bupropion XL versus venlafaxine XR.

Bupropion XL for the prevention of relapse into SAD

In the prevention of relapse into SAD, a benefit of bupropion XL versus placebo is proven. A benefit is not proven with regard to the mean change in depressive symptoms. In relapse prevention, there is no proof of benefit of bupropion XL for the outcome pain symptoms in depressed patients.

Taking the limited validity of the data into account, there was no proof of harm from bupropion XL versus placebo for the outcomes suicidal tendencies, suicides or mortality.

When using bupropion XL in the prevention of relapse into SAD, there is no proof of harm from bupropion XL for the outcomes adverse events, serious adverse events, and therapy discontinuations due to adverse events.

Concluding comment

The progress of this benefit assessment of bupropion, mirtazapine, and reboxetine shows that the aim of a valid benefit assessment is put at risk if existing knowledge is not made available. The problem can only be solved by making it compulsory by law to publish and provide all study results.

Keywords: depression, bupropion, mirtazapine, reboxetine, dopamine reuptake inhibitors, NARI, noradrenalin reuptake inhibitors, NaSSA, noradrenergic and specific serotonergic antidepressants, systematic review, publication bias

The full report (in German) is available on www.iqwig.de