IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A05-20C

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

Executive Summary

[1] Translation of the executive summary of the preliminary report "Bupropion, Mirtazapin und Reboxetin bei der Behandlung der Depression" (Version 1.0; Status: 29.05.2009). Please note: 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Bupropion, mirtazapine, and reboxetine in the treatment of depression

Contracting agency:
Federal Joint Committee

Commission awarded on:
22.02.2005

Internal Commission No.:
A05-20C

Publisher's address:
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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). Furthermore, bibliographic indexes of relevant secondary publications (systematic reviews, HTA reports), clinical trial registries, and publicly accessible drug approval documents were examined. Moreover, the manufacturers of the drugs approved in Germany were asked to provide information on published and unpublished trials (bupropion XL: GlaxoSmithKline; mirtazapine: Essex Pharma; reboxetine: Pfizer).

The manufacturers were initially asked to provide a comprehensive overview of all published and unpublished randomized controlled trials (RCTs) that they had sponsored on their drug for the indication of depression.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

RCTs were included that compared bupropion XL, mirtazapine or reboxetine with placebo or other chemically defined antidepressants (including the test drug) 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 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], individual or secondary symptoms of depression, relapse/recurrence/deterioration in depressive symptoms [trials on relapse prevention and recurrence prevention], mortality, suicidal tendencies, adverse drug effects, 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 the 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, is published on the Internet and interested parties are invited to submit written comments.

Results

Reboxetine

Despite several requests, 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. The manufacturer's documents could not, therefore, be used as a source for the collection of information. Due to this incomplete provision of information, CSRs on published and unpublished trials could not be requested.

Ten relevant trials for 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 the manufacturer of reboxetine (Pfizer) refused to provide full information on all trials with reboxetine.

Thus, out of the 10 included and 6 potentially relevant trials, a total of 9 could not be analysed (56%). When the size of the trials was considered, it emerged that data of at least 3023 patients in trials that in principle could have been included were unpublished or not analysable (information on size was missing in some identified trials), while data of 1607 patients were available in analysable form. As a result, the data of at least 65% of patients included in trials with reboxetine were not accessible.

Due to insufficient cooperation from the manufacturer of reboxetine, it remained unclear whether additional unpublished trials exist. It may well be that the identified data represent an even smaller portion of available evidence.

Thus, there were insufficient data available for the majority of potentially relevant trials and patients. This evaluation of the available evidence means that further assessment of the limited data available and drawing a conclusion from them on the benefit or harm of reboxetine would probably be severely biased and therefore cannot represent a valid decision basis for the Federal Joint Committee (G-BA). Based on the current state of knowledge, no proof of benefit or harm from reboxetine can be established, irrespective of whether the available data show an effect of reboxetine or not.

Mirtazapine

The manufacturer of mirtazapine (Essex Pharma) provided an overview of published and unpublished RCTs on mirtazapine for the indication of depression, which, according to the manufacturer, contained all the information available to them. Potentially relevant trials were identified from this overview and their full CSRs were then requested from the manufacturer.

The various stages of information collection identified 27 trials that could be included in the assessment. Out of these, 26 trials were acute treatment trials, one trial investigated mirtazapine in relapse prevention. There was no full publication available for 11 of the trials; however, it was possible to perform the assessment on the basis of the CSR, which was provided by the manufacturer of mirtazapine (Essex Pharma). In a further 11 trials, the full publication was complemented by a CSR from the manufacturer, and 5 trials were assessed exclusively on the basis of the full publication.

In addition to the 27 included trials, 4 potentially relevant trials were identified but no final decision could be made regarding their inclusion due to a lack of information. Despite a request to the manufacturer, no CSRs on these 4 trials were provided.

The manufacturer did not send the full CSRs for a large number of trials, instead only partial reports were provided without appendices containing the full analyses. In some cases, the

analyses available were only on limited patient populations. For this reason, the results of the benefit assessment on mirtazapine could be biased. Moreover, based on a current systematic review (Szegedi 2009), it is uncertain whether the manufacturer provided a full study list. Due to an incomplete transfer of data, the results of the assessment of mirtazapine must therefore be viewed with reservation.

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 in part 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 10 out of 24 studies on response, and in 10 out of 26 trials on mean change in depressive symptoms.

The most important results from the trials with mirtazapine are summarized in Table 1. 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 benefit assessment are summarized in “evidence maps” in Table 2 and Table 3.

Table 1: Summary of the results of trials with mirtazapine (all results to be viewed with reservation, as the data supplied by the manufacturer of mirtazapine were incomplete and unpublished data can potentially challenge the result)

Outcome	**Results of the meta-analyses and individual trials Group difference [95% CI], p value**								
	MIR vs. Plc[a]	**MIR vs. SSRI[a]**	**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; 1.42] p=0.084	1.25 [0.86; 1.83] p=0.241	1.24 [0.89; 1.71] p=0.202	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]	1.84 [1.34; 2.53] p<0.001	1.09 [0.87; 1.37] p=0.445	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)	-0.19 [-0.43; 0.06] p=0.133[h]	-0.07 [-0.21; 0.07] p=0.338[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	no data	no data p=0.558
AE[d]	heterogeneous results	0.97 [0.79; 1.19] p=0.781	1.28 [0.71; 2.31] p=0.416	0.98 [0.70;1.37] p=0.902	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-continuation due to AE[d]	2.75 [1.28; 5.93] p=0.010	heterogeneous results	1.81 [1.03; 3.18] p=0.039	0.63 [0.40; 0.98] p=0.042	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 (ASEX / CSFQ)	no data p=0.300[c]	meta-analysis not possible	no data p=0.854[c]	not recorded	not recorded	no data; p=0.536/0.279[e,l] no data; p=0.704/0.773[f,l]	p=0.967 / 0.305[l]	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 treatment 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 depressive 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: result for men/women
AE: adverse event; 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 effects; TRA: trazodone; VEN: venlafaxine XR

Mirtazapine in acute therapy compared to placebo

All placebo-controlled trials investigated the 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, no benefit from mirtazapine with regard to remission could be proven.

In a meta-analysis of short-term acute treatment trials, the rate of patients with **response** was statistically significantly higher with mirtazapine than with placebo. This provides proof of the benefit of mirtazapine with regard to the response in short-term acute therapy. However, this proof must be viewed with reservation, as the data for the assessment supplied by the manufacturer of mirtazapine were incomplete and unpublished data could potentially challenge the result. It is probable that the effect is exaggerated on the basis of the data available for the benefit assessment. In contrast, there is no proof of benefit for mirtazapine compared to placebo for the **mean change in depressive symptoms**, measured on the HAMD.[2]

A trial with depressive patients 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). There is no proof of benefit for mirtazapine in acute therapy for these outcomes in this population.

In respect of design and study duration, none of the trials were aimed at investigating **suicidal tendency, suicides** or **mortality**. An interpretation of the results for these outcomes is therefore limited in its validity and does not provide a conclusive answer. Taking account of the limited validity, there was no proof of harm of mirtazapine 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 with mirtazapine than with placebo. This provides proof of harm from mirtazapine for this outcome. However, this proof must be viewed with reservation due to a potential bias in the results through incomplete data (see above). 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 remained unclear. 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. There is therefore no proof of harm from mirtazapine with regard to sexual dysfunction.

[2] Hamilton Depression Scale

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 revealed a statistically significant difference in the **remission** rate between mirtazapine and one of the active comparators. There is therefore no proof of additional benefit from mirtazapine with regard to remission.

Nor could any statistically significant differences be observed between mirtazapine and the active controls for the **response** rate. There is therefore no proof of additional benefit from mirtazapine for the response. Nor is there any proof of additional benefit from mirtazapine with regard to the **mean change in depressive symptoms** measured using the HAMD.

These results were also confirmed in a sertraline-controlled short-term acute treatment trial with SSRI-resistant patients (see Table 1), and in the paroxetine-controlled long-term acute treatment 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 from mirtazapine with regard to 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 from mirtazapine with regard to the social functioning level outcome.

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 2 trials on short-term acute therapy. A statistically significant difference in favour of mirtazapine was observed in the long-term acute treatment trial (group difference 4 points on the QLDS;[3] p=0.021). The 95% confidence interval for Cohen's d for the group difference extended into the range below a small effect (Cohen's d -0.35 [-0.65; -0.05]). Consequently, the relevance of the effect cannot be estimated with certainty. There is therefore no proof of additional benefit.

The trials on individual and secondary symptoms showed no statistically significant difference between mirtazapine and paroxetine with regard to **anxiety,** and between mirtazapine and amitriptyline with regard to **cognition**. Thus, there is no proof of additional benefit from mirtazapine for the outcomes anxiety and cognition.

In respect of design or duration, none of the trials were aimed at investigating **suicidal tendencies, suicides** or **mortality**. An interpretation of the results of these outcomes therefore

[3] Quality of Life in Depression Scale

has limited validity and does not provide conclusive clarification. In view of this limited validity, there was no proof of greater or lesser harm from mirtazapine compared to active comparators for the above-mentioned outcomes.

For some comparisons and some outcomes, the analyses of **adverse events** showed statistically significant differences between mirtazapine and the other antidepressants (Table 1). In the short-term acute therapy with mirtazapine, there were more therapy discontinuations due to adverse events compared to fluoxetine and fewer compared to paroxetine. This provides proof of greater harm from mirtazapine compared to fluoxetine and lesser harm from mirtazapine compared to paroxetine in short-term acute therapy. In contrast, in the long-term acute therapy there was no proof of lesser (or greater) harm from mirtazapine compared to paroxetine with reference 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. From this result, an indication can be deduced of greater harm from mirtazapine compared to venlafaxine XR for serious adverse events. Due to a potential bias in the results through an incomplete provision of data, all proofs and indications mentioned must be viewed with reservation (see above). 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, 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). In this trial, 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 from mirtazapine with regard to relapse prevention. Due to a potential bias in the results through incomplete provision of data, however, this indication must be viewed with reservation.

Due to a lack of data (measures of statistical dispersion and p values), it was not possible to assess the effect of mirtazapine on **health-related quality of life**. A benefit from mirtazapine with regard to this outcome is therefore not proven.

With reference to design and duration, the relapse prevention trial was not aimed at investigating **suicidal tendencies, suicides** or **mortality**. An interpretation of the results on these outcomes therefore has limited validity and does not provide conclusive clarification. In view of the limited validity of the data, 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). This provides an indication of harm from mirtazapine with reference to therapy discontinuations due to adverse events. Due to a potential bias in the results through incomplete provision of data, however, this indication must be viewed with reservation (see above). There is no proof of harm in relapse prevention with reference to the total rate of adverse events or serious adverse events.

Evidence maps for mirtazapine

Table 2: Mirtazapine – evidence map for acute treatment trials (all results to be viewed with reservation)

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				↔ ↔					
Anxiety				↔ no data					
Cognition									↔
Mortality	(↔) (↔)	(↔)	(↔)	(↔) no data	(↔) (↔)	(↔)	(↔)	(↔)	
Suicidal tendency	(↔) no data	(↔)	(↔)	(↔) no data	(↔) (↔)	(↔)	(↔)	(↔)	(↔)
Suicide attempts & suicides	(↔) no data	(↔)	(↔)	(↔) no data	(↔) (↔)	(↔)	(↔)	(↔)	(↔)
SAE	↔ ↔	↔	↔	↔ no data	↔ ↔	↔	(M−)		↔
Total rate AE	↔ no data	↔	↔	↔ ↔	↔ ↔	↔	↔		
Discontinuation due to AE	M− no data	No statement[e]	M−	M+ ↔	(M−) (M−)	↔	↔		↔
Sexual dysfunction	↔ no data	No statement[f]	↔	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 treatment trials, lower: trial after acute heart attack
b: Findings from the only long-term acute treatment trial not included
c: 2 symbols in each cell: upper: short-term acute treatment trials, lower: long-term acute treatment 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
f: Meta-analysis not possible

AE: adverse event; AMI: amitriptyline; FLU: fluoxetine; FLUV: fluvoxamine; PAR: paroxetine; Plc: placebo; SAE: serious adverse event; SER: sertraline; SSRI: selective serotonin reuptake inhibitors; TRA: trazodone; VEN: venlafaxine

Table 3: Mirtazapine – evidence map for the relapse prevention trial (all results to be viewed with reservation)

Outcome	MIR vs. Plc
Relapse rate at end of study	(M+)
Depression scale Total score	(M+)
Health-related quality of life	data missing
Mortality	(↔) (no events)
Suicidal tendency	(↔) (no events)
Suicide attempts & suicides	(↔) (no events)
Total rate SAE	↔
Total rate AE	↔
Discontinuation 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
Empty cells: no data available

AE: adverse event; MIR: mirtazapine; Plc: placebo; SAE: serious adverse event

Bupropion XL

The manufacturer of bupropion XL (GlaxoSmithKline) provided an overview of published and unpublished RCTs with bupropion XL sponsored by GlaxoSmithKline for the indication of depression. During the search, no trials beyond this overview were identified that were primarily sponsored by GSK. Potentially relevant trials were identified from this overview and the corresponding full CSRs were then requested from the manufacturer.

Overall, 6 relevant trials were identified during the various search stages of the collection of information and were all included in the assessment. One of the trials was unpublished, the remaining 5 were published. The full CSR for all 6 trials was provided by the manufacturer.

The trials comprised 3 trials on short-term acute therapy (treatment duration: 8 to 10 weeks). One of the trials was 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 standard in all trials, bupropion XL between 150 and 300 mg/day, 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 (approval status in Germany).

The risk of bias on a study level was low in all 6 trials. The risk of bias on an outcome level was classified as low for all outcomes in all trials except one. The risk of bias was rated as high for the “social functioning level” outcome in 2 out of 3 trials.

Table 4 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 described. Thereafter, the results of the comparison of bupropion XL with placebo in trials on the prevention of SAD are described. The conclusions on benefit assessment are summarized in “evidence maps” in Table 5 and Table 6.

Table 4: Summary of the results of trials with bupropion XL

	Result of meta-analyses Group difference [95% CI], p value		
	Short-term acute therapy		**Prevention of relapse into SAD**
Outcome	**Bupropion vs. placebo**	**Bupropion vs. venlafaxine**	**Bupropion vs. placebo**
Remission[a]	1.44 [1.13; 1.84] p=0.003	0.72 [0.54; 0.96] p=0.025	not relevant
Response[a]	1.47 [1.17; 1.85] p=0.001	0.70 [0.52; 0.94] p=0.018	not relevant
Depression scale Total score (MADRS)[b]	-1.84 [-2.97; -0.71] p=0.001 Cohen's d: -0.18 [-0.30; -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[a]	0.35 [0.12; 1.01] p=0.052	0.51 [0.09; 2.94] p=0.449	0.00 [-0.01; 0.01] p=0.718[c]
AE[a]	0.85 [0.68; 1.07] p=0.176	heterogeneous results	1.21 [0.86; 1.70] p=0.274
Discontinuation due to AE[a]	0.82 [0.52; 1.31] p=0.414	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
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]	-1.23 [-2.12; -0.34] p=0.007 Cohen's d: -0.16 [-0.28; -0.05]	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[b]	not recorded	not recorded	-0.03 [-0.60; 0.55] p=0.921

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

AE: adverse events; CI: confidence interval; CSFQ: Changes in Sexual Function Questionnaire; HAMA: Hamilton Anxiety Scale,; HAMD: Hamilton Depression Scale; HAMD-24-SAD: Hamilton Depression Scale Seasonal Affective Disorder Version; 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

Bupropion XL in short-term acute therapy

In the trials on short-term acute therapy a statistically significantly higher proportion of patients with bupropion XL achieved **remission** or responded to the therapy (**response**) than with placebo. This proves a benefit from bupropion XL for the remission and response compared to placebo. The **mean change in depressive symptoms** measured on the MADRS[4] was statistically significantly greater with bupropion XL than with placebo, however, the relevance of the difference could not be evaluated with certainty. The benefit with reference to the mean change in depressive symptoms is thus not proven.

Compared to venlafaxine XR, the proportion of patients with remission or response in treatment with bupropion XL was statistically significantly smaller. Thus, 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 reference to the mean change in depressive symptoms on the MADRS is not proven.

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 reference to these outcomes is not proven. In the comparison of bupropion XL and venlafaxine XR, no statistically significant differences occurred with reference to the above-mentioned outcomes (see Table 4).

With reference to study design and duration, the trials were not aimed at investigating **suicidal tendencies, suicides** or **mortality**. An interpretation of the results of these outcomes therefore has limited validity, and does not provide conclusive clarification. In view of the limited validity of the data, 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.

The differences in the rates of **adverse events**, serious adverse events, and of therapy discontinuations due to adverse events between bupropion XL and placebo were not statistically significant. Between bupropion XL and venlafaxine XR there was also no statistically significant difference in serious adverse events and in therapy discontinuations due to adverse events. With reference to 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, there is no proof of harm from bupropion XL compared to placebo or of greater or lesser harm compared to venlafaxine XR. With reference to **sexual dysfunction**, the group differences

[4] Montgomery-Åsberg Depression Rating Scale

between bupropion XL and placebo or venlafaxine XR were not statistically significant either. Thus, 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. With reference to preventing a relapse, a benefit from 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, a benefit from bupropion XL with reference to the main change in depressive symptoms is not proven.

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

Allowing for the limited validity of the data, there was no proof of harm from bupropion XL compared to placebo for **suicidal tendency**, **suicide** 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. There is therefore no proof of harm from bupropion XL with reference to adverse events in patients with SAD.

Evidence maps for bupropion XL

Table 5: Bupropion XL – evidence map for acute treatment trials

Outcome	Bupropion vs. placebo			Bupropion vs. venlafaxine
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 tendency	(↔)			(↔)
Suicide attempts & suicides	(↔)			(↔)
SAE	↔			↔
Total rate AE	↔			↔
Discontinuation 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 start of study ≤ 30; severe depression: MADRS at start of study > 30

AE: adverse event; MADRS: Montgomery-Åsberg Depression Rating Scale; SAE: serious adverse event

Table 6: Bupropion – Evidence map for relapse prevention trials on SAD

Outcome	Bupropion 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 tendency	(↔) (no events)
Suicide attempts & suicides	(↔) (no events)
SAE	↔
Total rate AE	↔
Discontinuation 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 event; HAMD-17: Hamilton Depression Rating Scale 17-item version; HAMD-SAD: 24-item Structured Interview Guide for the Hamilton Depression Rating Scale; Seasonal Affective Disorder version; SAD: seasonal affective disorder; SAE: serious adverse event

Conclusions

Reboxetine

Due to inadequate cooperation from the manufacturer of reboxetine (Pfizer), there was insufficient data available on a large proportion of potentially relevant trials with reboxetine. There is proof that a relevant volume of data is not available through incomplete provision of data by Pfizer. This evaluation of the available evidence means that further assessment of the limited data available and drawing conclusions from them on the benefit or harm of reboxetine would probably be severely biased and therefore cannot represent a valid decision basis for the Federal Joint Committee (G-BA). Based on the current state of knowledge, no proof of benefit or harm from reboxetine can be established.

Mirtazapine

Due to incomplete provision of data by the manufacturer of mirtazapine (Essex Pharma), it is suspected that a relevant volume of data on mirtazapine is not available. The analysis of the available data is therefore possibly biased. Thus, the results of the assessment of mirtazapine must generally be viewed with reservation, because unpublished data can challenge them. This also in particular applies to findings on aspects of harm, for which no proof or indications of differences between mirtazapine and placebo or other antidepressants were confirmed.

Mirtazapine in acute therapy

There is proof of a benefit from mirtazapine compared to placebo for response to short-term acute therapy. However, this proof must be viewed with reservation, as the data for the assessment that were provided by the manufacturer of mirtazapine were incomplete and unpublished data could potentially challenge the result. A benefit from mirtazapine is not proven for the remission of depression and for the mean change in depressive symptoms measured on the HAMD.

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

Allowing for the limitations of the data, there was no proof of harm from mirtazapine compared to placebo for suicidal tendency, suicide or mortality or for greater or lesser harm from mirtazapine compared to other antidepressants.

There is proof of harm from mirtazapine compared to placebo for therapy discontinuations due to adverse events. However, this proof must be viewed with reservation (see above). There is no proof that adverse events and serious adverse events occur more frequently with

mirtazapine than with placebo. With reference to sexual dysfunction, a harm from mirtazapine is not proven.

Compared to other antidepressants, for therapy discontinuations due to adverse events there is proof in short-term acute therapy of greater harm from mirtazapine compared to fluoxetine, and lesser harm from mirtazapine compared to paroxetine. In addition, for therapy discontinuations due to adverse events, there is an indication of greater harm from mirtazapine compared to sertraline in depressed patients with no additional restriction and in SSRI-resistant depressed patients. With reference to serious adverse events, there is an indication of greater harm from mirtazapine compared to venlafaxine XR. However, these proofs and indications must be viewed with reservation (see above). With reference to adverse events, the other active comparisons did not show any proof of greater or lesser harm from mirtazapine. With reference to sexual dysfunction, there is no proof of greater or lesser harm from mirtazapine compared to other antidepressants.

Mirtazapine in relapse prevention

With reference to relapse prevention (relapse rate and mean change in depressive symptoms), there is an indication of benefit from mirtazapine compared to placebo. However, this indication must be viewed with reservation (see above). A benefit from mirtazapine in treatment for relapse prevention is not proven for health-related quality of life.

Allowing for the limitations of the data, there was no proof of harm from mirtazapine compared to placebo for suicidal tendency, suicide or mortality. There is an indication of harm from mirtazapine with reference to therapy discontinuations due to adverse events. However, this indication must be viewed with reservation (see above). With reference to the total rate of adverse events or serious adverse events, there is no proof of harm from mirtazapine.

Bupropion XL

Bupropion XL in short-term acute therapy

In short-term acute therapy there is proof of benefit from bupropion XL compared to placebo for the outcomes remission and response. With reference to the mean change in depressive symptoms on the MADRS, there is no proof of benefit.

Compared to venlafaxine XR, a lesser benefit from bupropion XL is proven for remission and response. With reference to the mean change in depressive symptoms measured on the MADRS, no additional benefit or lesser benefit is proven.

With reference to social functioning level, health-related quality of life, anxiety symptoms, and the patient's motivation and energy, a benefit from bupropion XL compared to placebo is not proven. A comparison of bupropion XL with venlafaxine XR does not produce proof of additional benefit from bupropion XL for these afore-mentioned outcomes.

Allowing for the limitations of the data, there was no proof of harm from bupropion XL compared to placebo for suicidal tendency, suicide or mortality or for greater or lesser harm compared to venlafaxine.

There is no proof of harm from bupropion XL compared to placebo or of greater or lesser harm compared to venlafaxine XR for adverse events, serious adverse events, therapy discontinuations due to adverse events or sexual dysfunction.

Bupropion XL for the prevention of relapse into SAD

A benefit from bupropion XL compared to placebo is proven in the prevention of relapse into SAD. A benefit with reference to the mean change in depressive symptoms is not proven.

There is no proof of benefit from bupropion XL with reference to pain symptoms in depressed patients.

Allowing for the limitations of the data, there was no proof of harm from bupropion XL compared to placebo for suicidal tendency, suicide or mortality.

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

Concluding comment

This report on the 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.

Key words: depression, bupropion, mirtazapine, reboxetine, dopamine reuptake inhibitors, NARI, norepinephrine reuptake inhibitor, NaSSA, norepinephrine and selective serotonin reuptake inhibitors, systematic review

The full preliminary report (German version) is available under
http://www.iqwig.de/index.582.html