IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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# Health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments[1]

## Executive Summary

[1] Translation of the executive summary of the final report "Kosten-Nutzen-Bewertung von Venlafaxin, Duloxetin, Bupropion und Mirtazapin im Vergleich zu weiteren verordnungsfähigen medikamentösen Behandlungen" (Version 1.0; Status: 3 September 2013). 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.

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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (*Sozialgesetzbuch*, SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts is presented in Appendix J of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| AMNOG | *Gesetz zur Neuordnung des Arzneimittelmarktes* (Act on the Reform of the Market for Medicinal Products) |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| G-BA | *Gemeinsamer Bundesausschuss* (Federal Joint Committee) |
| HRQoL | health-related quality of life |
| IQR | interquartile range |
| IQWiG | *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care) |
| MTC | mixed treatment comparison |
| NHB | net health benefit |
| QLDS | Quality of Life in Depression Scale |
| RCT | randomized controlled trial |
| SGB | *Sozialgesetzbuch* (Social Code Book) |
| SHI | statutory health insurance |
| SSRIs | selective serotonin reuptake inhibitors |
| TCAs | tricyclic antidepressants |

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## Background

In its letter of 17 December 2009, referring to § 35b SGB V in connection with § 10a (1, 2), Chapter 4 of the Code of Procedure of the Federal Joint Committee (G-BA), the G-BA commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with the health economic evaluation of venlafaxine, duloxetine, bupropion, and mirtazapine compared to further prescribable pharmaceutical treatments.

Due to a change in legal requirements for the Institute with the introduction of the Act on the Reform of the Market for Medicinal Products (AMNOG), the results of the preliminary report, which were based on the literature searches of the year 2010 (benefit data and health economic evaluations) and 2011 (cost data), were not updated. The results are contrasted with an overview of a potential need for updating.

## Research question

On the basis of the results of a benefit assessment of the test drugs venlafaxine, duloxetine, bupropion, and mirtazapine, the aim of the present investigation is to conduct a health economic evaluation of these test drugs in order to derive a recommendation for a reimbursement price. The relevant comparators of the therapeutic area (tricyclic antidepressants [TCAs] plus maprotiline, selective serotonin reuptake inhibitors [SSRIs], agomelatine, and trazodone) were included in the health economic evaluation. The study population consisted of previously untreated adult patients with depression.

## Methods of the benefit assessment

The benefit assessment was conducted by means of randomized controlled trials (RCTs) on the above-mentioned research question. This assessment was based on the results of the benefit assessments already conducted by IQWiG and published in the final reports A05-20A and A05-20C. In addition, to update the preceding benefit assessments, a systematic literature search for primary studies was conducted in the following databases: MEDLINE, EMBASE, BIOSIS, PsycINFO, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In this context, "update" refers to a search for publications reporting comparisons of venlafaxine, duloxetine, mirtazapine or bupropion in the period after the last update search of the benefit assessments (i.e. from January 2008 for A05-20A and from February 2009 for A05-20C). A search for relevant systematic reviews was conducted in parallel in the following databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The systematic reviews were scrutinized for further relevant studies. The searches were conducted on 1 December 2010.

The literature screening was carried out by 2 reviewers independently of each other. After assessing the risk of bias, the results of the single studies were presented for the relevant outcomes.

RCTs were considered that investigated patients in depression and compared venlafaxine, duloxetine, bupropion, and mirtazapine with placebo or other active comparators (including comparisons of the investigated antidepressants with each other), as well as St. John's Wort. Data from the relevant European Public Assessment Report (EPAR) of the European Medicines Agency (EMA) were specifically used for the drug agomelatine, as this is a new drug and the EPAR reflects the study status at the time of approval.

The information extracted was synthesized and analysed. This synthesis and analysis contained both a statistical summary of data, meta-analyses of pairwise drug comparisons, as well as an analysis of drug networks via adjusted indirect comparisons. The pairwise meta-analyses of single drug comparisons were examined for heterogeneity. Studies that could have contributed to heterogeneity due to the known effect modifiers from the preceding benefit assessments A05-20A and A05-20C were excluded from the study pool if relevant heterogeneity was present. For the analysis of the remaining studies forming the basis for the outcome-specific networks, either a mixed treatment comparison (MTC) meta-analysis or, if the network only covered a few comparators, an adjusted indirect comparison according to Bucher could be performed. The consistency assumption was tested for each MTC meta-analysis. To establish consistency, studies (or study arms in multi-arm studies) considerably contributing to inconsistency were selected according to predefined criteria and removed from the network. The impact of consistency checking on the informative value of the results of the MTC meta-analysis was checked in sensitivity analyses, both within the benefit assessment and the health economic evaluation.

No conclusions on benefit or added benefit were derived in the health economic evaluation. In fact, the results of the adjusted indirect comparisons were considered in the models for generating the efficiency frontier, taking the uncertainty related to this methodology into account.

Sensitivity analyses were conducted on both the benefit and on the cost-benefit level to assess the impact of the uncertainty of the results of the MTC meta-analyses in the context of the health economic evaluation. The sensitivity analyses contained the outcome-specific comparison of results using the effect estimates of the main result from the adjusted indirect comparisons with the alternative effect estimates. In the MTC meta-analyses these alternative effect estimates arose from the direct comparisons, the study pool containing all studies (before consistency checking), and the results based on alternative a priori distribution assumptions. The analyses of further sets of results, for example, for examining inexplicable heterogeneity leading to the exclusion of drugs from the network, was conducted where necessary (for instance, this was the case for the outcome "treatment discontinuation due to adverse events" in short-term studies). In contrast, the adjusted indirect comparisons according to Bucher were only based on star-shaped networks, so that consistency checking via a comparison of direct and indirect evidence within a closed loop was not possible and no corresponding sensitivity analyses could be calculated. Conclusions regarding the robustness of results from the adjusted indirect comparisons were as a matter of principle linked to the

standard consideration of appropriate sensitivity analyses within the health economic evaluation.

Due to a change in the legal situation the report was not updated. Nevertheless, a focussed literature search was conducted to gain an impression as to whether a relevant number of studies had been published between the last search date and the completion date of the final report in 2013. This focussed search did not correspond to the usual standards of the Institute in systematic literature searches, which is why there is no claim to completeness of this overview.

**Results of the benefit assessment**

The present results concerning the benefit assessment reflect the status of data from the year 2010.

Data from 109 studies from the underlying preceding benefit assessments were included in the benefit assessment of the present report. A total of 14 publications on 10 studies were identified by means of the update search. Of these 10 studies, 9 were already known from the preceding benefit assessment and relevant new data were only available for 1 of these 9 studies (comparison of mirtazapine vs. SSRIs). The newly identified study compared combinations of 2 drugs (venlafaxine plus mirtazapine, mirtazapine plus fluoxetine, bupropion plus mirtazapine) with fluoxetine plus placebo. The EPAR contained relevant data from 9 agomelatine studies, which were included in the benefit assessment. After application of the inclusion criteria for the research question of the health economic evaluation, 118 studies were considered in the study pool of the benefit assessment. In the following text the results are reported for the outcomes investigated in the benefit assessment. Acute studies with a minimum duration of 6 weeks were considered for the outcomes “remission”, “response”, “treatment discontinuation due to adverse events” (acute studies), and “health-related quality of life”. Long-term studies on relapse prevention were included for the outcomes “relapse” and “treatment discontinuation due to adverse events” (relapse prevention studies); in these studies a (controlled or uncontrolled) treatment phase was succeeded by a follow-up period of up to 6 months.

Seven drugs plus placebo formed the network for the outcome **“remission”**, so that 28 pairwise drug comparisons would have been possible. Results from 58 direct comparative studies were available for 14 of these possible drug comparisons: 42 of these studies contained 2 arms and 16 contained 3 arms, so that 90 pairwise comparisons from direct comparative studies could be considered. All 4 test drugs were contained in the MTC study pool (and thus in the network). Two studies and one study arm were excluded from the MTC study pool during consistency checking. The sensitivity analyses showed that, for the outcome “remission”, the main result of the MTC represented an adequate basis for further processing within the health economic evaluation. Table 1 shows the main result for the outcome “remission” from the adjusted indirect comparisons. The table also shows the results from the

direct comparisons as well as those based on the study pool containing all studies (before achieving consistency) are presented.

Table 1: Remission, results: direct comparison, MTC (all studies/consistent)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] All studies OR [95% CrI] | MTC[a] Consistent (main result) OR [95% CrI] |
|---|---|---|---|---|---|
| | DIC | | | 135,76 | 116,85 |
| Placebo | Duloxetine vs. placebo | 12 | 1.91 [1.56; 2.34] | 1.85 [1.60; 2.13] | 1.72 [1.48; 2.01] |
| | Venlafaxine vs. placebo | 9 | 1.97 [1.64; 2.35] | 1.79 [1.56; 2.08] | 1.74 [1.53; 2.00] |
| | Mirtazapine vs. placebo | 1 | 1.32 [0.69; 2.52] | 1.72 [1.38; 2.10] | 1.66 [1.32; 2.04] |
| | Bupropion vs. placebo | 4 | 1.46 [1.18; 1.82] | 1.38 [1.10; 1.74] | 1.39 [1.10; 1.76] |
| | SSRIs vs. placebo | 18 | 1.43 [1.24; 1.64] | 1.60 [1.41; 1.78] | 1.51 [1.32; 1.71] |
| | TCAs vs. placebo | 1 | 1.81 [1.06; 3.09] | 1.88 [1.22; 2.72] | 1.82 [1.17; 2.68] |
| | Agomelatine vs. placebo | 2 | 1.63 [0.97; 2.74] | 2.02 [1.34; 2.95] | 1.96 [1.31; 2.78] |
| Duloxetine | Venlafaxine vs. duloxetine | | | 0.97 [0.82; 1.17] | 1.01 [0.84; 1.20] |
| | Mirtazapine vs. duloxetine | | | 0.93 [0.74; 1.16] | 0.96 [0.75; 1.22] |
| | Bupropion vs. duloxetine | | | 0.75 [0.59; 0.96] | 0.81 [0.62; 1.05] |
| | SSRIs vs. duloxetine | 9 | 0.90 [0.75; 1.10] | 0.87 [0.74; 1.00][b] | 0.88 [0.75; 1.03] |
| | TCAs vs. duloxetine | | | 1.02 [0.64; 1.52] | 1.06 [0.67; 1.59] |
| | Agomelatine vs. duloxetine | | | 1.10 [0.72; 1.58] | 1.14 [0.74; 1.67] |
| Venlafaxine | Mirtazapine vs. venlafaxine | 1 | 0.98 [0.56; 1.69] | 0.96 [0.77; 1.17] | 0.96 [0.77; 1.17] |
| | Bupropion vs. venlafaxine | 2 | 0.72 [0.54; 0.96] | 0.77 [0.61; 0.98] | 0.80 [0.64; 1.01] |
| | SSRIs vs. venlafaxine | 17 | 0.89 [0.78; 1.02] | 0.90 [0.78; 1.01] | 0.87 [0.77; 0.98] |
| | TCAs vs. venlafaxine | 3 | 1.01 [0.58; 1.72] | 1.05 [0.66; 1.52] | 1.05 [0.69; 1.54] |
| | Agomelatine vs. venlafaxine | 1 | 1.33 [0.80; 2.22] | 1.13 [0.74; 1.59] | 1.13 [0.76; 1.60] |
| Mirtazapine | Bupropion vs. mirtazapine | | | 0.81 [0.60; 1.10] | 0.85 [0.63; 1.15] |
| | SSRIs vs. mirtazapine | 10 | 0.92 [0.76; 1.10] | 0.94 [0.77; 1.13] | 0.92 [0.77; 1.09] |
| | TCAs vs. mirtazapine | | | 1.10 [0.68; 1.69] | 1.11 [0.70; 1.70] |
| | Agomelatine vs. mirtazapine | | | 1.19 [0.75; 1.75] | 1.20 [0.76; 1.78] |
| Bupropion | SSRIs vs. bupropion | | | 1.17 [0.92; 1.44] | 1.10 [0.83; 1.39] |
| | TCAs vs. bupropion | | | 1.38 [0.83; 2.07] | 1.32 [0.80; 2.04] |
| | Agomelatine vs. bupropion | | | 1.48 [0.90; 2.30] | 1.43 [0.92; 2.17] |
| SSRIs | TCAs vs. SSRIs | | | 1.17 [0.76; 1.73] | 1.21 [0.79; 1.80] |
| | Agomelatine vs. SSRIs | | | 1.26 [0.84; 1.79] | 1.30 [0.87; 1.85] |
| TCAs | Agomelatine vs. TCAs | | | 1.12 [0.62; 1.92] | 1.13 [0.63; 1.95] |

a: The model specification for this outcome is described in the main text of the present assessment and presented in Appendix H of the full report.

b: The exact value of the upper limit of the CrI of the result based on all studies is 1.0030, and thus there is no change in significance (to the significance level $\alpha = 0.05$).

CI: confidence interval, CrI: credible interval, DIC: deviance information criterion, MTC: mixed treatment comparison, OR: odds ratio, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants (+ maprotiline)

Eight drugs plus placebo formed the network for the outcome **"response"**, so that 36 pairwise drug comparisons would have been possible. Results from 94 direct comparative studies were available for 21 of these possible drug comparisons: 73 of these studies contained 2 arms and 21 contained 3 arms, so that 136 pairwise comparisons from direct comparative studies could be considered. All 4 test drugs were contained in the MTC study pool (and thus in the network). During consistency checking, 2 placebo-controlled, 2 active-controlled and 2 active- and placebo-controlled studies (or study arms) were excluded from the MTC study pool, and no general limitation of the MTC results due to the achievement of consistency was expected. The sensitivity analyses showed that, for the outcome "response", the main result of the MTC represented an adequate basis for further processing within the health economic evaluation. Table 2 shows the main result for the outcome "response" from the adjusted indirect comparisons. The table also shows the results from the direct comparisons as well as those based on the study pool containing all studies (before achieving consistency).

Table 2: Response, results: direct comparison; MTC (all studies/consistent)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] All studies OR [95% CrI] | MTC[a] Consistent (main result) OR [95% CrI] |
|---|---|---|---|---|---|
| | DIC | | | 217,31 | 196,34 |
| Placebo | Duloxetine vs. placebo | 12 | 1.99 [1.65; 2.39] | 1.81 [1.58; 2.08] | 1.68 [1.43; 1.93] |
| | Venlafaxine vs. placebo | 18 | 2.15 [1.89; 2.45] | 2.06 [1.85; 2.29] | 2.08 [1.88; 2.30] |
| | Mirtazapine vs. placebo | 10 | 1.87 [1.36; 2.58] | 1.94 [1.61; 2.30] | 1.84 [1.58; 2.18] |
| | Bupropion vs. placebo | 4 | 1.48 [1.20; 1.82] | 1.48 [1.16; 1.86] | 1.51 [1.22; 1.82] |
| | SSRIs vs. placebo | 19 | 1.56 [1.37; 1.79] | 1.71 [1.53; 1.90] | 1.62 [1.46; 1.79] |
| | TCAs vs. placebo | 2 | 1.36 [0.90; 2.07] | 2.06 [1.60; 2.60] | 2.27 [1.76; 2.88] |
| | Agomelatine vs. placebo | 4 | 1.72 [1.34; 2.22] | 2.06 [1.64; 2.59] | 2.02 [1.63; 2.48] |
| | Trazodone vs. placebo | 2 | 1.22 [0.72; 2.07] | 1.17 [0.77; 1.71] | 1.21 [0.78; 1.70] |
| Duloxetine | Venlafaxine vs. duloxetine | 2 | 1.33 [0.93; 1.92] | 1.14 [0.98; 1.34] | 1.25 [1.07; 1.44] |
| | Mirtazapine vs. duloxetine | | | 1.07 [0.86; 1.31] | 1.11 [0.91; 1.36] |
| | Bupropion vs. duloxetine | | | 0.82 [0.62; 1.07] | 0.91 [0.69; 1.17] |
| | SSRIs vs. duloxetine | 9 | 1.02 [0.83; 1.23] | 0.95 [0.82; 1.09] | 0.97 [0.84; 1.11] |
| | TCAs vs. duloxetine | | | 1.14 [0.87; 1.47] | 1.36 [1.02; 1.75] |
| | Agomelatine vs. duloxetine | | | 1.14 [0.87; 1.48] | 1.22 [0.93; 1.57] |
| | Trazodone vs. duloxetine | | | 0.65 [0.41; 0.96] | 0.73 [0.44; 1.07] |
| Venlafaxine | Mirtazapine vs. venlafaxine | 1 | 1.30 [0.78; 2.13] | 0.94 [0.78; 1.12] | 0.89 [0.76; 1.06] |
| | Bupropion vs. venlafaxine | 2 | 0.70 [0.52; 0.94] | 0.72 [0.55; 0.91] | 0.73 [0.59; 0.89] |
| | SSRIs vs. venlafaxine | 23 | 0.83 [0.74; 0.94] | 0.83 [0.74; 0.92] | 0.78 [0.70; 0.86] |
| | TCAs vs. venlafaxine | 10 | 1.02 [0.74; 1.41] | 1.00 [0.79; 1.25] | 1.09 [0.84; 1.37] |
| | Agomelatine vs. venlafaxine | 2 | 1.25 [0.85; 1.85] | 1.00 [0.79; 1.28] | 0.97 [0.78; 1.22] |
| | Trazodone vs. venlafaxine | 2 | 0.71 [0.38; 1.33] | 0.57 [0.38; 0.83] | 0.58 [0.37; 0.82] |
| Mirtazapine | Bupropion vs. mirtazapine | | | 0.77 [0.57; 1.04] | 0.83 [0.63; 1.05] |
| | SSRIs vs. mirtazapine | 10 | 0.92 [0.72; 1.16] | 0.89 [0.75; 1.04] | 0.88 [0.75; 1.00][b] |
| | TCAs vs. mirtazapine | 1 | 1.45 [0.53; 3.85] | 1.07 [0.80; 1.39] | 1.24 [0.93; 1.61] |
| | Agomelatine vs. mirtazapine | | | 1.07 [0.80; 1.44] | 1.10 [0.85; 1.40] |
| | Trazodone vs. mirtazapine | 1 | 0.63 [0.27; 1.47] | 0.61 [0.38; 0.90] | 0.66 [0.42; 0.95] |
| Bupropion | SSRIs vs. bupropion | | | 1.17 [0.90; 1.50] | 1.08 [0.87; 1.34] |
| | TCAs vs. bupropion | | | 1.41 [1.02; 1.92] | 1.51 [1.11; 2.01] |
| | Agomelatine vs. bupropion | | | 1.40 [1.02; 1.89] | 1.35 [1.02; 1.77] |
| | Trazodone vs. bupropion | | | 0.80 [0.49; 1.22] | 0.80 [0.51; 1.17] |
| SSRIs | TCAs vs. SSRIs | | | 1.21 [0.95; 1.53] | 1.41 [1.10; 1.78] |
| | Agomelatine vs. SSRIs | 1 | 1.44 [0.90; 2.31] | 1.21 [0.94; 1.54] | 1.25 [1.00; 1.56][c] |
| | Trazodone vs. SSRIs | | | 0.69 [0.45; 1.01] | 0.75 [0.48; 1.06] |

(continued)

Table 2: Response, results: direct comparison; MTC (all studies/consistent) (continued)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] | |
|---|---|---|---|---|---|
| | | | | All studies OR [95% CrI] | Consistent (main result) OR [95% CrI] |
| TCAs | Agomelatine vs. TCAs | | | 1.01 [0.71; 1.38] | 0.91 [0.64; 1.25] |
| | Trazodone vs. TCAs | 1 | 0.27 [0.12; 0.61] | 0.58 [0.35; 0.86] | 0.54 [0.35; 0.78] |
| Agomelatine | Trazodone vs. agomelatine | | | 0.58 [0.36; 0.87] | 0.60 [0.38; 0.94] |

a: The model specification for this outcome is described in the main text of the present assessment and presented in Appendix H of the full report.
b: The exact value of the upper limit of the CrI of the main result is 1.0002168, and thus includes the zero effect.
c: The exact value of the lower limit of the CrI of the main result is 0.9976651, and thus includes the zero effect.
CI: confidence interval, CrI: credible interval, DIC: deviance information criterion, MTC: mixed treatment comparison, OR: odds ratio, SSRIs: selective serotonin reuptake inhibitors, TCAs: tricyclic antidepressants (+ maprotiline)

Twelve drugs plus placebo formed the network for the outcome **"treatment discontinuation due to adverse events" (acute studies)**, so that 78 pairwise drug comparisons would have been possible. Results from 89 direct comparative studies were available for 31 of these possible drug comparisons: 70 of these studies contained 2 arms and 19 contained 3 arms, so that 127 pairwise comparisons from direct comparative studies could be considered. All 4 test drugs were covered in the network. During consistency checking, 6 studies and 2 study arms were excluded from the MTC study pool, and no general limitation of the MTC results due to the achievement of consistency was expected. The sensitivity analyses showed that for the outcome "treatment discontinuation due to adverse events", the main result of the MTC represented an adequate basis for further processing within the health economic evaluation. Table 3 shows the main result for the outcome "treatment discontinuation due to adverse events" from the adjusted indirect comparisons. The table also shows the results from the direct comparisons as well as those based on the study pool containing all studies (before achieving consistency).

Table 3: "Treatment discontinuation due to adverse events" (acute studies), results: direct comparison; MTC (all studies/consistent)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] All studies OR [95% CrI] | MTC[a] Consistent (main result) OR [95% CrI] |
|---|---|---|---|---|---|
| | DIC | | | 197,18 | 167,31 |
| Placebo | Duloxetine vs. placebo | 12 | 2.22 [1.55; 3.19] | 2.89 [2.16; 3.80] | 3.53 [2.66; 4.59] |
| | Venlafaxine vs. placebo | 18 | 2.47 [1.81; 3.37] | 2.28 [1.87; 2.79] | 2.41 [1.99; 2.87] |
| | Mirtazapine vs. placebo | 2 | 2.75 [1.28; 5.93] | 2.23 [1.53; 3.16] | 2.18 [1.56; 2.96] |
| | Bupropion vs. placebo | 4 | 1.00[b] [0.61; 1.65] | 1.33 [0.79; 2.05] | 1.25 [0.75; 1.95] |
| | Fluoxetine vs. placebo | 11 | 1.27 [0.88; 1.84] | 1.41 [1.08; 1.82] | 1.37 [1.07; 1.73] |
| | Escitalopram vs. placebo | | | 1.81 [0.60; 4.22] | 1.84 [0.71; 3.87] |
| | Paroxetine vs. placebo | 7 | 2.13 [1.43; 3.17] | 2.40 [1.76; 3.17] | 2.76 [2.08; 3.59] |
| | Sertraline vs. placebo | 1 | 3.36 [1.17; 9.70] | 1.40 [0.81; 2.23] | 0.77 [0.35; 1.38] |
| | Fluvoxamine vs. placebo | | | 1.62 [0.68; 3.22] | 1.55 [0.73; 2.83] |
| | TCAs vs. placebo | 1 | 2.25 [0.88; 5.75] | 2.50 [1.62; 3.68] | 2.35 [1.56; 3.43] |
| | Agomelatine vs. placebo | 4 | 0.95 [0.47; 1.91] | 0.89 [0.50; 1.47] | 0.94 [0.53; 1.48] |
| | Trazodone vs. placebo | 1 | 2.27 [0.95; 5.44] | 2.60 [1.19; 4.96] | 2.63 [1.27; 4.78] |
| Duloxetine | Venlafaxine vs. duloxetine | 2 | 0.56 [0.36; 0.86] | 0.80 [0.59; 1.07] | 0.69 [0.52; 0.91] |
| | Mirtazapine vs. duloxetine | | | 0.78 [0.50; 1.17] | 0.63 [0.42; 0.90] |
| | Bupropion vs. duloxetine | | | 0.47 [0.26; 0.76] | 0.36 [0.20; 0.60] |
| | Fluoxetine vs. duloxetine | 2 | 0.60 [0.19; 1.92] | 0.50 [0.35; 0.69] | 0.39 [0.28; 0.54] |
| | Escitalopram vs. duloxetine | | | 0.64 [0.20; 1.51] | 0.53 [0.19; 1.16] |
| | Paroxetine vs. duloxetine | 5 | 0.76 [0.50; 1.15] | 0.84 [0.59; 1.15] | 0.79 [0.58; 1.07] |
| | Sertraline vs. duloxetine | | | 0.49 [0.27; 0.82] | 0.22 [0.10; 0.42] |
| | Fluvoxamine vs. duloxetine | | | 0.57 [0.23; 1.14] | 0.45 [0.21; 0.83] |
| | TCAs vs. duloxetine | | | 0.88 [0.53; 1.36] | 0.68 [0.43; 1.04] |
| | Agomelatine vs. duloxetine | | | 0.31 [0.17; 0.54] | 0.27 [0.15; 0.44] |
| | Trazodone vs. duloxetine | | | 0.92 [0.40; 1.82] | 0.76 [0.35; 1.44] |
| Venlafaxine | Mirtazapine vs. venlafaxine | 1 | 0.69 [0.37; 1.28] | 0.98 [0.68; 1.36] | 0.91 [0.66; 1.22] |
| | Bupropion vs. venlafaxine | 2 | 0.83 [0.43; 1.61] | 0.59 [0.34; 0.91] | 0.52 [0.30; 0.83] |
| | Fluoxetine vs. venlafaxine | 16 | 0.67 [0.54; 0.83] | 0.62 [0.49; 0.77] | 0.57 [0.46; 0.70] |
| | Escitalopram vs. venlafaxine | 1 | 0.71 [0.32; 1.56] | 0.79 [0.27; 1.82] | 0.76 [0.30; 1.59] |
| | Paroxetine vs. venlafaxine | 4 | 0.93 [0.50; 1.72] | 1.06 [0.77; 1.40] | 1.15 [0.83; 1.49] |
| | Sertraline vs. venlafaxine | 4 | 0.77 [0.47; 1.25] | 0.62 [0.36; 0.96] | 0.32 [0.15; 0.57] |
| | Fluvoxamine vs. venlafaxine | 1 | 1.34 [0.30; 6.02] | 0.71 [0.30; 1.42] | 0.65 [0.31; 1.18] |
| | TCAs vs. venlafaxine | 10 | 1.03 [0.71; 1.49] | 1.10 [0.74; 1.56] | 0.98 [0.68; 1.38] |
| | Agomelatine vs. venlafaxine | 2 | 0.27 [0.13; 0.55] | 0.39 [0.22; 0.64] | 0.39 [0.22; 0.61] |
| | Trazodone vs. venlafaxine | 2 | 1.11 [0.56; 2.22] | 1.15 [0.53; 2.17] | 1.09 [0.53; 1.97] |

(continued)

Table 3: "Treatment discontinuation due to adverse events" (acute studies), results: direct comparison; MTC (all studies/consistent) (continued)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] All studies OR [95% CrI] | MTC[a] Consistent (main result) OR [95% CrI] |
|---|---|---|---|---|---|
| Mirtazapine | Bupropion vs. mirtazapine | | | 0.62 [0.32; 1.04] | 0.59 [0.32; 0.99] |
| | Fluoxetine vs. mirtazapine | 3 | 0.55 [0.31; 0.97] | 0.65 [0.44; 0.93] | 0.64 [0.45; 0.87] |
| | Escitalopram vs. mirtazapine | | | 0.83 [0.26; 2.02] | 0.86 [0.31; 1.88] |
| | Paroxetine vs. mirtazapine | 4 | 1.56 [1.01; 2.38] | 1.10 [0.74; 1.55] | 1.29 [0.93; 1.75] |
| | Sertraline vs. mirtazapine | 1 | 0.23 [0.08; 0.61] | 0.64 [0.35; 1.06] | 0.36 [0.17; 0.64] |
| | Fluvoxamine vs. mirtazapine | 2 | 0.60 [0.31; 1.18] | 0.73 [0.33; 1.36] | 0.71 [0.36; 1.26] |
| | TCAs vs. mirtazapine | 1 | 0.95 [0.06; 15.54] | 1.15 [0.67; 1.84] | 1.10 [0.67; 1.72] |
| | Agomelatine vs. mirtazapine | | | 0.41 [0.21; 0.73] | 0.44 [0.24; 0.73] |
| | Trazodone vs. mirtazapine | | | 1.20 [0.51; 2.42] | 1.23 [0.56; 2.37] |
| Bupropion | Fluoxetine vs. bupropion | | | 1.13 [0.65; 1.87] | 1.16 [0.67; 1.95] |
| | Escitalopram vs. bupropion | | | 1.44 [0.43; 3.66] | 1.55 [0.53; 3.57] |
| | Paroxetine vs. bupropion | | | 1.92 [1.07; 3.22] | 2.35 [1.31; 3.90] |
| | Sertraline vs. bupropion | | | 1.12 [0.53; 2.09] | 0.65 [0.25; 1.34] |
| | Fluvoxamine vs. bupropion | | | 1.29 [0.47; 2.85] | 1.32 [0.51; 2.74] |
| | TCAs vs. bupropion | | | 1.99 [1.04; 3.54] | 1.99 [1.05; 3.43] |
| | Agomelatine vs. bupropion | | | 0.71 [0.33; 1.37] | 0.80 [0.36; 1.48] |
| | Trazodone vs. bupropion | | | 2.08 [0.81; 4.48] | 2.24 [0.89; 4.65] |
| Fluoxetine | Escitalopram vs. fluoxetine | | | 1.29 [0.43; 3.04] | 1.35 [0.52; 2.91] |
| | Paroxetine vs. fluoxetine | | | 1.73 [1.19; 2.38] | 2.04 [1.47; 2.75] |
| | Sertraline vs. fluoxetine | | | 1.00[c] [0.56; 1.62] | 0.57 [0.26; 1.03] |
| | Fluvoxamine vs. fluoxetine | | | 1.16 [0.48; 2.31] | 1.14 [0.53; 2.10] |
| | TCAs vs. fluoxetine | | | 1.79 [1.13; 2.67] | 1.73 [1.12; 2.58] |
| | Agomelatine vs. fluoxetine | 1 | 1.03 [0.20; 5.20] | 0.64 [0.35; 1.07] | 0.69 [0.38; 1.10] |
| | Trazodone vs. fluoxetine | | | 1.87 [0.83; 3.63] | 1.94 [0.93; 3.56] |
| Escitalopram | Paroxetine vs. escitalopram | | | 1.70 [0.55; 4.03] | 1.81 [0.68; 3.98] |
| | Sertraline vs. escitalopram | | | 0.98 [0.29; 2.46] | 0.51 [0.15; 1.33] |
| | Fluvoxamine vs. escitalopram | | | 1.14 [0.27; 3.16] | 1.02 [0.29; 2.58] |
| | TCAs vs. escitalopram | | | 1.76 [0.55; 4.26] | 1.54 [0.56; 3.46] |
| | Agomelatine vs. escitalopram | | | 0.62 [0.18; 1.60] | 0.62 [0.20; 1.46] |
| | Trazodone vs. escitalopram | | | 1.82 [0.46; 4.94] | 1.71 [0.53; 4.25] |

(continued)

Table 3: "Treatment discontinuation due to adverse events" (acute studies), results: direct comparison; MTC (all studies/consistent) (continued)

| | Drug comparisons | Studies | Direct comparison OR [95% CI] | MTC[a] All studies OR [95% CrI] | MTC[a] Consistent (main result) OR [95% CrI] |
|---|---|---|---|---|---|
| Paroxetine | Sertraline vs. paroxetine | | | 0.59 [0.33; 0.98] | 0.28 [0.13; 0.54] |
| | Fluvoxamine vs. paroxetine | | | 0.68 [0.29; 1.35] | 0.57 [0.27; 1.05] |
| | TCAs vs. paroxetine | | | 1.06 [0.65; 1.66] | 0.87 [0.54; 1.42] |
| | Agomelatine vs. paroxetine | 1 | 0.97 [0.31; 3.09] | 0.38 [0.20; 0.65] | 0.34 [0.19; 0.56] |
| | Trazodone vs. paroxetine | | | 1.10 [0.48; 2.20] | 0.97 [0.44; 1.81] |
| Sertraline | Fluvoxamine vs. sertraline | | | 1.22 [0.46; 2.65] | 2.24 [0.84; 4.98] |
| | TCAs vs. sertraline | | | 1.90 [0.99; 3.37] | 3.41 [1.52; 6.76] |
| | Agomelatine vs. sertraline | | | 0.68 [0.31; 1.32] | 1.36 [0.56; 2.88] |
| | Trazodone vs. sertraline | | | 1.98 [0.78; 4.30] | 3.84 [1.33; 8.77] |
| Fluvoxamine | TCAs vs. fluvoxamine | | | 1.80 [0.72; 3.84] | 1.71 [0.75; 3.46] |
| | Agomelatine vs. fluvoxamine | | | 0.64 [0.23; 1.46] | 0.68 [0.27; 1.41] |
| | Trazodone vs. fluvoxamine | | | 1.88 [0.58; 4.63] | 1.91 [0.66; 4.36] |
| TCAs | Agomelatine vs. TCAs | | | 0.37 [0.18; 0.67] | 0.41 [0.21; 0.69] |
| | Trazodone vs. TCAs | 1 | 1.02 [0.24; 4.29] | 1.08 [0.46; 2.17] | 1.16 [0.51; 2.23] |
| Agomelatine | Trazodone vs. agomelatine | | | 3.16 [1.17; 6.95] | 2.97 [1.25; 6.03] |

a: The model specification for this outcome is described in the main text of the present assessment and presented in Appendix H of the full report.

b: The exact value of the direct effect estimate is 1.003.

c: The exact value of the effect estimate of the MTC meta-analysis based on all studies is 1.0020.

CI: confidence interval, CrI: credible interval, DIC: deviance information criterion, MTC: mixed treatment comparison, OR: odds ratio, TCAs: tricyclic antidepressants (+ maprotiline)

The results of 7 studies were available for the outcome **"relapse"**. However, after applying the information synthesis methods, the agomelatine studies had to be removed from the study pool because of relevant heterogeneity. Finally, for the outcome "relapse", the network contained 3 placebo-controlled studies from the preceding benefit assessments (one each on venlafaxine, duloxetine and mirtazapine). The network was thus star-shaped. Correspondingly, the adjusted indirect comparison according to Bucher was chosen as the approach for data synthesis. Consistency checking was not possible, as this would have required a closed loop in the network. No sensitivity analyses could therefore be performed.

As with the results from the adjusted comparisons for which sensitivity analyses could be conducted, it was assumed here that the result for the outcome "relapse" from the adjusted indirect comparisons represented an adequate basis for further processing in the health economic evaluation. Table 4 shows the result for the outcome "relapse" from the direct and adjusted indirect comparisons according to Bucher.

Table 4: Relapse, results: direct comparison; adjusted indirect comparison according to Bucher

| | **Drug comparisons** | **Studies** | **Direct comparison OR [95% CI]** | **Adjusted indirect comparison according to Bucher OR [95% CI]** |
|---|---|---|---|---|
| Placebo | Duloxetine vs. placebo | 1 | 0.53 [0.30; 0.95] | |
| | Venlafaxine vs. placebo | 1 | 0.42 [0.26; 0.68] | |
| | Mirtazapine vs. placebo | 1 | 0.33 [0.16; 0.68] | |
| Duloxetine | Venlafaxine vs. duloxetine | | | 0.79 [0.37; 1.69] |
| | Mirtazapine vs. duloxetine | | | 0.63 [0.25; 1.58] |
| Venlafaxine | Mirtazapine vs. venlafaxine | | | 0.79 [0.33; 1.89] |
| CI: confidence interval, OR: odds ratio | | | | |

The results of 13 studies were available for the outcome **"treatment discontinuation due to adverse events" (relapse prevention studies)**. After applying the information synthesis methods described above, the outcome-specific network with 3 placebo-controlled studies was star-shaped. All test drugs, except for bupropion, were contained in the network. An adjusted indirect comparison according to Bucher was performed. Consistency checking was not possible, as this would have required a closed loop in the network. No sensitivity analyses could therefore be conducted. As with the results from the adjusted comparisons for which sensitivity analyses could be conducted, it was assumed here that the result for the outcome "treatment discontinuation due to adverse events" (relapse prevention studies) from the adjusted indirect comparisons represented an adequate basis for further processing within the health economic evaluation. Table 5 shows the result for the outcome "treatment discontinuation due to adverse events" (relapse prevention studies) from the direct and adjusted indirect comparisons according to Bucher.

Table 5: "Treatment discontinuation due to adverse events" (relapse prevention studies), results: direct comparison; adjusted indirect comparison according to Bucher

| | **Drug comparisons** | **Studies** | **Direct comparison OR [95% CI]** | **Adjusted indirect comparison according to Bucher OR [95% CI]** |
|---|---|---|---|---|
| Placebo | Duloxetine vs. placebo | 1 | 1.05 [0.30; 3.70] | |
| | Venlafaxine vs. placebo | 1 | 0.91 [0.45; 1.84] | |
| | Mirtazapine vs. placebo | 1 | 5.08 [1.06; 24.30] | |
| Duloxetine | Venlafaxine vs. duloxetine | | | 0.87 [0.21; 3.70] |
| | Mirtazapine vs. duloxetine | | | 4.86 [0.65; 36.29] |
| Venlafaxine | Mirtazapine vs. venlafaxine | | | 5.57 [1.00; 30.99][a] |

a: The exact value of the lower CI of the result of the adjusted indirect comparison according to Bucher is 1.001499, thus yielding a statistically significant difference.
CI: confidence interval, OR: odds ratio

Three drugs plus placebo formed the network for the only continuous outcome "**health-related quality of life"** operationalized by the Quality of Life in Depression Scale (QLDS), so that 6 pairwise drug comparisons would have been possible. Results from 6 direct comparative studies were available for 4 of these possible drug comparisons: 4 of these studies contained 2 arms and 2 contained 3 arms, so that 10 pairwise comparisons from direct comparative studies could be considered. Two of the 4 test drugs were contained in the network (duloxetine, venlafaxine). For this outcome, an MTC meta-analysis was calculated, by means of which consistency checking was performed. No exclusion of a study was necessary due to the inconsistency criterion and thus there was no limitation of the MTC results in connection with the achievement of consistency. Table 6 shows the main result for the outcome "health-related quality of life" from the adjusted indirect comparisons. In addition, an overview of the results from the direct comparisons is presented.

Table 6: Health-related quality of life (QLDS), results: direct comparison; MTC (all studies/consistent)

| | Direct comparisons | Studies | Direct comparison MD [95% CI] | MTC[a] All studies, consistent (main result) MD [95% CrI] |
|---|---|---|---|---|
| | DIC | | | 11,98 |
| Placebo | Duloxetine vs. placebo | 4 | -3.08 [-4.40; -1.76] | -3.06 [-4.90; -1.22] |
| | Venlafaxine vs. placebo | | | -4.62 [-7.47; -1.75] |
| | Paroxetine vs. placebo | 2 | -2.65 [-4.58;-0.72] | -2.92 [-5.42; -0.41] |
| Duloxetine | Venlafaxine vs. duloxetine | 2 | -1.60 [-2.85; -0.34] | -1.56 [-3.75; 0.68] |
| | Paroxetine vs. duloxetine | 2 | -0.17 [-2.12; 1.77] | 0.14 [-2.31; 2.64] |
| Venlafaxine | Paroxetine vs. venlafaxine | | | 1.70 [-1.61; 5.05] |

Negative change during course of study: improvement in quality of life.

a: The model specification for this outcome is described in the main text of the present assessment and presented in Appendix I of the full report.

CI: confidence interval, CrI: credible interval, DIC: deviance information criterion, MD: mean difference, MTC: mixed treatment comparison, QLDS: Quality of Life in Depression Scale

As only studies on one pairwise drug comparison were available for the outcome "**recurrences"**, no adjusted indirect comparisons could be calculated. For the same reason, the outcome could not be considered in the health economic evaluation.

**Methods of health economic evaluation and budget impact analysis**

A health economic evaluation was conducted on the basis of the results of the preceding and updated benefit assessments. This was an exemplary evaluation limited to a population of adult patients with moderate to severe depression aged 18 to 65 years; for the effect estimates of the benefit assessment, studies including patients without age restrictions were also considered. An incremental cost-effectiveness analysis based on a decision-analytic model was chosen as the health economic study type. The analysis was conducted with the efficiency frontier approach.

To generate the concept of the model for the health economic evaluation, a systematic literature search was conducted in the following databases: MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), the Health Technology Assessment Database (Technology Assessments), the National Health Service (NHS) Economic Evaluation

Database (Economic Evaluation), and the Health Economic Evaluations Database (HEED). The last search was conducted on 3 January 2011.

In addition, the websites of various reimbursement institutions and guideline providers were screened.

Furthermore, for cost estimation, a systematic literature search was conducted in the same databases on 31 March 2011.

Statutory health insurance (SHI) claims data were used as a further important source for cost estimation. These data were used for the calculation of costs in the single cost sectors (primarily inpatient care and incapacity for work), as well as for the examination of patient numbers and assumptions.

The following additional sources were used:

- Uniform Value Scale (*Einheitlicher Bewertungsmaßstab)* for determination of outpatient and psychotherapy services
- The Pharmacy Price Schedule (*Lauer Taxe*), Summaries of Product Characteristics of drug manufacturers, and the Pharmaceutical Prescriptions Report (*Arzneiverordungs-Report*) for the calculation of drug costs
- Statistics of the German Pension Insurance (*Deutsche Rentenversicherung*) 2009 for estimation of rehabilitation costs
- National accounts 2010 of the Federal Statistical Office (*Statistisches Bundesamt*) for calculation of indirect costs

Data on the issue of further treatment in the case of non-response or relapse, as well as the distribution of general practitioner and specialist treatment, were collected via an expert survey.

Costs were determined from the SHI insurants' perspective. In this perspective, the cost parameters for the model were determined according to the bottom-up approach for the health service sectors of outpatient care, drugs, inpatient care, and psychotherapy. For drugs, lead compounds were determined as representatives of drug classes, insofar as drug classes had been formed in the preceding benefit assessment. In addition, co-payments were determined for outpatient services, drugs and inpatient services. Furthermore, costs from the societal perspective in the narrower sense were determined. For this purpose, costs for productivity losses due to incapacity for work were calculated. Moreover, from the societal perspective in the narrower sense, rehabilitation costs from the pension insurance perspective were also considered. Indirect costs and rehabilitation costs from the pension insurance perspective were determined with a top-down approach. Indirect costs were estimated with the human capital approach. The index year was 2011. If prices were not available for 2011, they were adapted to 2011 by means of the Consumer Price Index.

A Markov model with a 2-month cycle length was developed for the health economic evaluation and analysed by means of cohort simulation. The following 8 states were considered in the model: acute treatment of depression in first-line therapy, further treatment of response in first-line therapy, further treatment of remission in first-line therapy, further treatment of depression after relapse in first-line therapy, depression in second-line therapy after treatment discontinuation due to adverse events, depression after lack of response in second-line therapy, response/remission after discontinuation in second-line therapy, and depression after relapse in second-line therapy. In the base case, the main results from the MTC meta-analyses based on a consistent network or from direct comparisons (if no MTC meta-analysis could be calculated) were included in the model as effect estimates of the benefit assessment. Scenarios were modelled covering the period of the studies (on average about 8 weeks) and a period of 12 months. The latter was conducted both from the SHI perspective and from the societal perspective in the narrower sense. In the base case analysis it was planned to generate efficiency frontiers for the following outcomes: remission, response, treatment discontinuations due to adverse events, quality of life measured with the QLDS, and relapse. The costs adjusted by the benefit difference for the efficiency frontier and the test drug reimbursement prices inferred from them (in short: "added-benefit-adjusted reimbursement prices") were calculated by means of the net health benefit (NHB) approach. Due to the short-term horizons no discounting was performed.

Comprehensive sensitivity analyses were conducted within the examination of uncertainty in the estimation of added-benefit-adjusted reimbursement prices. The influence of specific attributes of all parameters (except drug costs) on the NHB was examined in deterministic sensitivity analyses. In addition, the NHB for the different basic probabilities was examined in sensitivity analyses for the respective outcomes. Moreover, it was determined in scenario analyses how the analysis results for the respective outcomes behaved when considering the results of the sensitivity analyses of the benefit assessment. For this purpose, instead of the main results underlying the base case analysis in the health economic evaluation the following results were used in the model: MTC results from MTC meta-analyses with deviating a priori distributions, MTC results from analyses including all studies in the study pool (before consistency checking), or the estimates from direct comparisons (homogeneous study pool, before consistency checking). In this context, a priori distributions were varied for the study-specific baseline probabilities, the basic parameters, and the between-study variance. The influence on the NHB was described. Finally, probabilistic sensitivity analyses were conducted and interquartile regions were designated around the outcome-specific NHB of the test drugs and the added-benefit-adjusted reimbursement prices resulting from them. The interquartile regions cover those 50% of simulations in the probabilistic sensitivity analyses that lie above the 25% lowest results and below the 25% highest results for the added-benefit-adjusted reimbursement price.

The added-benefit-adjusted reimbursement prices were considered in the budget impact analysis calculated for a population with moderate to severe depression who approximately

corresponded to the population in the benefit assessments. On the one hand, on the basis of the results of the health economic evaluation, changes when applying the added-benefit-adjusted reimbursement price to the test drugs were calculated over the years 2010 to 2013. For this purpose, it was assumed that the dominated comparators and test drugs in the health economic evaluation were substituted between 25 and 100% up to the year 2013, depending on the scenario. On the other hand, the change in the drug budget was determined across all prescriptions of antidepressants in the SHI.

Due to a change in the legal situation the report was not updated. Nevertheless, a focussed literature search for cost studies and health economic evaluations was conducted to gain an impression as to whether a relevant number of studies had been published between the last search date and the completion date of the final report in 2013. These focussed searches did not correspond to the usual standards of the Institute in systematic literature searches, which is why there is no claim to completeness of this overview. In addition, the changed costs were compiled for drug costs and further cost sectors.

**Results of the health economic evaluation**

The present results concerning the health economic evaluation represent the status of the data of the year 2010 (health economic evaluations) and 2011 (cost data).

***Interim results for cost estimation***

*Sources for cost estimation*

The systematic literature search identified 11 cost studies that, according to the congruent opinion of both reviewers, fulfilled the study inclusion criteria defined for the preliminary report. However, no study results could be used from this search to calculate cost parameters for the health economic model. This was due to the fact that, on the one hand, no study completely included the population relevant here, and on the other, the costs from the cost studies referred to different observation periods and basic years. For this reason, in comparison with the costs calculated in this report, results from the studies retrieved in the literature search are only discussed with regard to methodological approaches and results.

In each case, for all health states and cycles of the Markov model, the cost parameters were determined by means of the Institute's own calculations. The sources differed depending on the health service sectors. The assumptions for health care paths and options for action were primarily drawn on the basis of the National Health Care Guideline (*Nationale Versorgungsleitlinie*) and the expert survey.

*Generation of state-related costs*

The amount of the cost parameters in the health states per average patient were on the one hand determined by the assumptions about the use of health services in the respective sector (e.g. the number of outpatient visits, costs of the prescribed drug etc.), and on the other, by the proportions of patients in this health service sector. In the case of inclusion in absorbing

states, transition costs were calculated once in order to prevent an overestimation of costs for patients remaining in the states for several cycles.

*Estimation of drug-related costs in the states of the model*

Except for increased monitoring costs for TCAs due to electrocardiograms (ECGs) in the outpatient sector, no strategy-specific cost differences could be reliably presented for the various health service sectors. For instance, differences in cost parameters depending on the drug strategy mainly arose from the different drug costs themselves (including co-payments). All further cost sectors have no relation to the strategy and thus were equally considered in the cost parameters as base amounts for all drugs.

*Results for cost parameters*

The following tables provide an overall overview of the costs considered in the Markov model per state and drug (class).

Table 7: Model of health economic evaluation – Cost parameters for drugs and co-payments for drugs

| Drug class | Drug | Markov states→ / Cost parameters ↓ | Depression FT (acute) | Response FT (cont.) | Remission FT (cont.) | Depression FT (cont.) after relapse | Depression ST after discontinuation | Depression ST No response | Response / Remission ST after discontinuation | Depression ST after relapse |
|---|---|---|---|---|---|---|---|---|---|---|
| SNRIs | Venlafaxine (test drug) | Drug costs (€) | 49.80 | 50.05 | 50.30 | 49.30 | 22.24 | 29.26 | 22.58 | 29.26 |
| | | Co-payments (€) | 5.95 | 5.98 | 6.01 | 5.89 | 2.61 | 3.93 | 2.65 | 3.93 |
| | Duloxetine (test drug) | Drug costs (€) | 142.07 | 142.79 | 143.50 | 140.63 | 22.24 | 42.31 | 22.58 | 42.31 |
| | | Co-payments (€) | 6.15 | 6.18 | 6.21 | 6.08 | 2.61 | 3.96 | 2.65 | 3.96 |
| SSRIs | SSRIs Leading compound | Drug costs (€) | 19.43 | 19.53 | 19.63 | 19.24 | 53.79 | 49.58 | 54.61 | 49.58 |
| | | Co-payments (€) | 3.01 | 3.03 | 3.04 | 2.98 | 3.17 | 4.59 | 3.22 | 4.59 |
| TCAs | TCAs Leading compound | Drug costs (€) | 22.86 | 22.97 | 23.09 | 22.62 | 35.80 | 40.14 | 36.35 | 40.14 |
| | | Co-payments (€) | 0.00 | 0.00 | 0.00 | 0.00 | 3.54 | 3.62 | 3.59 | 3.62 |
| Other | Trazodone | Drug costs (€) | 68.04 | 68.39 | 68.73 | 67.35 | 33.96 | 41.88 | 34.48 | 41.88 |
| | | Co-payments (€) | 0.00 | 0.00 | 0.00 | 0.00 | 3.07 | 3.48 | 3.12 | 3.48 |
| | Bupropion (test drug) | Drug costs (€) | 95.24 | 95.72 | 96.20 | 94.27 | 33.56 | 45.39 | 34.08 | 45.39 |
| | | Co-payments (€) | 10.04 | 10.09 | 10.14 | 9.94 | 3.01 | 4.85 | 3.06 | 4.85 |
| | Agomelatine | Drug costs (€) | 152.78 | 153.55 | 154.32 | 151.24 | 33.46 | 53.44 | 33.97 | 53.44 |
| | | Co-payments (€) | 9.22 | 9.26 | 9.31 | 9.13 | 3.03 | 4.76 | 3.08 | 4.76 |
| | Mirtazapine (test drug) | Drug costs (€) | 24.94 | 25.07 | 25.20 | 24.69 | 35.66 | 39.44 | 36.20 | 39.44 |
| | | Co-payments (€) | 3.04 | 3.05 | 3.07 | 3.01 | 3.07 | 4.37 | 3.12 | 4.37 |

cont.: continuous (continuation of state in following cycle), FT: first-line therapy, SNRIs: selective serotonin noradrenaline reuptake inhibitors, SSRIs: selective serotonin reuptake inhibitors, ST: second-line therapy, TCAs: tricyclic antidepressants (+ maprotiline)

Table 8: Model of health economic evaluation – Cost parameters of further health service sectors

| **Markov states →**<br><br>**Cost parameters ↓** | **Depression FT (acute)** | **Response FT (cont.)** | **Remission FT (cont.)** | **Depression FT (cont.) after relapse** | **Depression ST after discontin.** | **Depression ST – No response** | **Response / remission FT after discont.** | **Depression ST after relapse** |
|---|---|---|---|---|---|---|---|---|
| Outpatient costs (all strategies except TCAs and placebo) (€) | 76.00 | 34.71 | 25.43 | 55.96 | 56.09 | 57.55 | 56.95 | 57.55 |
| Outpatient costs (TCAs) (€) | 83.81 | 42.56 | 25.43 | 63.69 | 56.09 | 57.55 | 56.95 | 57.55 |
| Outpatient costs (placebo) (€) | 63.46 | 34.71 | 25.43 | 55.96 | 56.09 | 56.00 | 56.95 | 56.00 |
| Psychotherapy (all strategies) (€) | 43.91 | 36.17 | 0.00 | 83.13 | 83.13 | 83.13 | 36.17 | 83.13 |
| Inpatient costs (all strategies) (€) | 97.30 | 48.65 | 0.00 | 194.60 | 194.60 | 194.60 | 48.65 | 194.60 |
| Co-payments SHI insurants (outpatient, psychotherapy, inpatient; all strategies) (€) | 9.31 | 8.15 | 7.00 | 11.61 | 11.61 | 11.61 | 8.15 | 11.61 |
| One-time transition costs (outpatient; all strategies except placebo) (€) | 0.00 | 0.00 | 0.00 | 32.52 | 32.52 | 57.95 | 33.02 | 57.95 |
| One-time transition costs (outpatient; placebo) (€) | 0.00 | 0.00 | 0.00 | 32.52 | 32.52 | 32.52 | 33.02 | 32.52 |
| One-time transition costs (psychotherapy; all strategies) (€) | 0.00 | 0.00 | 0.00 | 18.28 | 18.28 | 18.28 | 0.00 | 18.28 |
| Indirect costs (all strategies) (€) | 200.64 | 140.45 | 0.00 | 200.64 | 200.64 | 200.64 | 140.45 | 200.64 |
| Rehabilitation (pension insurance) incl. co-payments (all strategies) (€) | 0.00 | 17.73 | 0.00 | 17.73 | 17.73 | 17.73 | 17.73 | 17.73 |

cont.: continuous (continuation of state in following cycle), discontin.: discontinuation, FT: first-line therapy, SHI: statutory health insurance, ST: second-line therapy, TCAs: tricyclic antidepressants (+ maprotiline)

**Results of the health economic evaluation**

On the basis of the available data, in the short-term horizon of 2 months from the SHI insurants‘ perspective, all test drugs and largely all comparators for the outcomes “response”, “remission” and “treatment discontinuation due to adverse events” could be considered in the base case analysis. This analysis considered estimates from the consistent network of MTC meta-analyses or direct estimates (if no MTC meta-analysis could be calculated). For the outcome “health-related quality of life”, only 2 of the 4 test drugs (venlafaxine, duloxetine) and the SSRIs (represented by paroxetine) could be considered. In the scenarios of the long-term horizon (both from the SHI insurants‘ perspective and the societal perspective in the narrower sense), only data on the 3 test drugs duloxetine, mirtazapine and venlafaxine were available for the outcomes “remission”, “relapse”, and “treatment discontinuation due to adverse events”.

No efficiency frontiers could be generated for any outcomes in the long-term horizon of one year or only an added-benefit-adjusted reimbursement price for duloxetine could have been calculated based on an efficiency frontier including mirtazapine and venlafaxine. Efficiency frontiers could be determined for the outcomes “response”, “remission” and “health-related quality of life” in the short-term horizon. As in the long-term horizon (12 months), no efficiency frontier could be determined for the outcome “treatment discontinuation due to adverse events” in the short-time horizon. For the outcomes “remission” and “treatment discontinuation due to adverse events”, a comparison of the modelling results over the time horizon covered by the studies (2 months) with modelling results over the 12-month period showed cost savings in the outpatient, inpatient and psychotherapy sectors to the advantage of venlafaxine, mirtazapine and duloxetine. However, in the long-time horizon of 12 months, except for placebo, comparators of the therapeutic area are lacking and thus a robust interpretation related to the added-benefit-adjusted reference prices is impossible.

In the short-term horizon of 2 months from the SHI-insurants’ perspective, all test drugs lay below the efficiency frontier (= negative NHB) for the outcomes “remission” and “response”. On the basis of the efficiency frontiers, for these 2 outcomes, factors could be calculated via the NHB approach from which an added-benefit-adjusted reimbursement price could be calculated from the basic price of the test drugs set in this health economic evaluation. For the outcomes “remission” and “response”, reimbursement prices were yielded of €42.99 and €40.91 for venlafaxine, €31.66 and €24.28 for mirtazapine, €30.66 and €9.30 für duloxetine, and €2.93 and €1.48 for bupropion (see Table 10 in the conclusion).

For the outcome “health-related quality of life” venlafaxine lay above the efficiency frontier and had a positive NHB, duloxetine lay below the efficiency frontier and had a negative NHB. No data were available for other test drugs or other comparators than the SSRIs (paroxetine) or placebo. A conclusion on the added-benefit-adjusted reimbursement prices is therefore regarded to be problematical and is not drawn against the background that exactly those comparators are missing that form the efficiency frontier for the other outcomes (TCAs for

the outcomes “remission” and “response” and additionally agomelatine for the outcome “remission”).

***Sensitivity analyses***

It could be seen in the deterministic sensitivity analyses that in all analyses, the respective effect estimates of the test drugs in comparison with placebo had a crucial influence on the NHB value for the respective outcome. Moreover, an influence was shown regarding the effect estimates of the comparators forming the efficiency frontier of the respective outcome. For instance, for the outcome “remission” and the outcome “response”, the effect estimate in the comparison of TCAs with placebo had a crucial influence on the NHB of the test drugs. Furthermore, for the outcomes “remission” and “response”, the effect estimate of agomelatine had a crucial influence on the NHB of venlafaxine, bupropion and duloxetine. For the outcome “health-related quality of life” (QLDS), the effect estimate of SSRIs and placebo had a crucial influence on the NHB of 2 of the test drugs, namely venlafaxine and duloxetine. Overall, it was shown that the change in costs (except for drug costs, which were not varied) had little influence on the NHB.

As no data on the basic probability of a natural course of disease is available for the German population, i.e. achievement of a response without drug treatment, this basic probability was modified over the full range of possible response under placebo, based on the basic probabilities of 12.8 to 63.2% (minimum and maximum value) recorded in the studies included. The ratio of the NHB values of the test drugs to each other remained about the same, even if the absolute values for response under placebo changed and were markedly lower or higher than for the median of 37.2% recorded in the studies. If the actual natural course of depression, measured as response under placebo, is different in Germany than assumed, the added-benefit-adjusted reimbursement price for the test drugs would change compared to the base case analysis. The reduction of the basic prices for the outcomes “response” and “remission” could be more or less pronounced.

No change in this scenario analysis was shown for the outcome “health-related quality of life”.

The scenario analyses with effect estimates from MTC meta-analyses with deviating a priori distributions in the MTC meta-analyses showed only minor differences compared to the results of the base case analysis. The same applies to scenario analyses based on the effect estimates from the MTC analyses including all studies. However, in the latter case, for the outcome “response” there is a change in the same direction of the NHB values to less negative values, i.e., the added-benefit-adjusted reimbursement price would be higher for this outcome in this scenario analysis than in the base case analysis.

The scenario analysis with effect estimates from the direct comparisons yielded different efficiency frontiers due to the deviating effect estimates of the TCA and agomelatine comparators that formed the efficiency frontier for the outcomes “response” and “remission”

in the basis case analysis. These deviations could be explained by the fact that only few studies were available for the calculation of the effect estimates of some of the comparators from direct comparisons and that therefore these estimates were based on less information than the estimates from the indirect comparisons. For this reason, the results from the MTC meta-analysis of the consistent study pool are regarded to be an adequate data basis for the health economic evaluation. Further analyses on the basis of direct comparisons, for example, the calculation of added-benefit-adjusted reimbursement prices, are thus not meaningful.

The results of the probabilistic sensitivity analyses for the added-benefit-adjusted reimbursement prices of venlafaxine and mirtazapine for the outcomes “remission” and “response”, including the interquartile regions, can be found in Table 10 in the conclusion.

**Results of the budget impact analysis**

The present results concerning the budget impact analysis reflect the status of the data for the year 2010.

A target population of 315 252 SHI insurants was calculated for patients with moderate to severe depression investigated in the health economic evaluation. The corresponding indication-related expenditure for drugs, outpatient care, inpatient care, as well as sickness benefits, amounted to €560.3 million in the reference year 2010.

The results of the budget impact analysis are reported here for the scenarios where 25% and 75% of the dominated drugs were substituted with venlafaxine and mirtazapine, using the added-benefit-adjusted reimbursement prices for the outcomes “remission” and “response” on the basis of the short-time horizon.

Table 9: Changes in depression-related healthcare expenditure in the target population in the case of substitution with mirtazapine or venlafaxine and introduction of the respective added-benefit-adjusted reimbursement price after a 3-year linear extrapolation

| | **Remission Scenario 75%[a]** | **Remission Scenario 25%[b]** | **Response Scenario 75%[c]** | **Response Scenario 25%[d]** |
|---|---|---|---|---|
| **Δ Mirtazapine (%)** | -0.52 | -0.25 | -0.86 | -0.40 |
| **Δ Mirtazapine (€)** | -2 935 489 | -1 420 315 | -4 812 088 | -2 251 444 |
| **Δ Venlafaxine (%)** | -0.80 | -0.37 | -1.02 | -0.45 |
| **Δ Venlafaxine (€)** | -4 465 107 | -2 068 401 | -5 694 753 | -2 514 535 |

a: Prognosis scenario based on the added-benefit-adjusted reimbursement prices for the outcome "remission", time horizon covered by studies, substitution of 75% of the dominant drugs.

b: Prognosis scenario based on the added-benefit-adjusted reimbursement prices for the outcome "remission", time horizon covered by studies, substitution of 25% of the dominant drugs.

c: Prognosis scenario based on the added-benefit-adjusted reimbursement prices for the outcome "response", time horizon covered by studies, substitution of 75% of the dominant drugs.

d: Prognosis scenario based on the added-benefit-adjusted reimbursement prices for the outcome "response", time horizon covered by studies, substitution of 25% of the dominant drugs.

Δ: Change in depression-related healthcare expenditure after 3 years in the case of substitution with mirtazapine or venlafaxine

According to the Pharmaceuticals Prescription Report 2011, the sum of all drug expenditure in the SHI in the year 2010 for the investigated drugs without restriction to the target population of the health economic evaluation and to the indication of depression, evaluated at economical net prices, amounted to €436.3 million. The introduction of the added-benefit-adjusted reimbursement price of mirtazapine based on the outcome "remission" (based on the outcome "response") yields a reduction in expenditure by 4.65% or €20.3 million (6.97% or €30.4 million). The introduction of the added-benefit-adjusted reimbursement price of venlafaxine based on the outcome "remission" (based on the outcome "response") reduces overall expenditure for the test drugs and comparators by 7.77% or €33.9 million (8.09% or €35.3 million).

### Need for updating

The need for updating from the year 2010 (benefit data and health economic evaluations) and 2011 (cost data) up to the completion date of the final report in the year 2013 was estimated on the basis of the available studies for the benefit data, the model concept, as well as changes in costs. A focussed literature search showed that the data basis for the benefit assessment had been extended since the last search, so that an update of the analyses would be required to ensure the robustness of the results of the assessment.

On the cost side, marked changes arise from the fact that venlafaxine and mirtazapine have been grouped into a reference price group, leading to a marked reduction in prices. The change in prices of the other drugs (including duloxetine and bupropion) is comparatively low (in the range of a few cents) and includes both lower and higher prices. In the cost sectors of

outpatient care, inpatient care, psychotherapy, rehabilitation, indirect costs, and co-payments, there were changes whose effects on the acute period can be estimated as being minor. In addition, the deterministic sensitivity analyses on the basis of data up to 2010/2011 showed that the NHB values were robust against the variation of further cost parameters.

On the basis of these developments, a renewed health economic evaluation using the present model would show different results.

**Conclusion**

The health economic evaluation provided efficiency frontiers for the outcomes "response" "remission" and "health-related quality of life" (QLDS) over the short-term horizon, which, with a cycle of 8 weeks, approximately corresponded to the study duration of the studies included from the preceding and updated benefit assessment. No efficiency frontiers could be determined in the long-term horizon, i.e. modelling over a year, as data were not available for all test drugs, and particularly not for the comparators.

From the efficiency frontiers for the outcomes "response" and "remission", it can be derived for all 4 test drugs based on the respective NHB how the current basic price would have to be changed (see Table 10) so that the test drugs lie on the efficiency frontier (i.e. an NHB = 0 is generated). In the present case, no efficiency frontier could be generated for the outcome "treatment discontinuation due to adverse events" and therefore no added-benefit-adjusted reimbursement price could be calculated for this outcome. A comprehensive weighing of benefit and harm is thus not reflected in the added-benefit-adjusted reimbursement prices.

The added-benefit-adjusted reimbursement prices are to be understood in connection with uncertainty, meaning they should not be interpreted independently of the interquartile regions reported in Table 10. The interquartile region covers those 50% of simulations in the probabilistic sensitivity analyses that lie above the 25% lowest results and below the 25% highest results for the reimbursement price. A further result of the probabilistic sensitivity analyses is that for both outcomes, more than 75% of the runs for venlafaxine and mirtazapine show an added-benefit-adjusted reimbursement price below the current basic price. For bupropion and duloxetine this even applies to more than 97.5% of the runs.

For venlafaxine an added-benefit-adjusted reimbursement price was determined of €42.99 (interquartile range [IQR]: €35.33 to €83.04) for the outcome "remission" and of €40.91 (IQR: €31.22 to €54.25) for the outcome "response". For mirtazapine an added-benefit-adjusted reimbursement price was determined of €31.66 (IQR: €20.68 to €44.90) for the outcome "remission" and of €24.28 (IQR: €14.29 to €35.96) for the outcome "response". For duloxetine an added-benefit-adjusted reimbursement price was determined of €30.66 (IQR: €22.94 to €69.66) for the outcome "remission" and of €9.30 (IQR: €0.35 to €21.95) for the outcome "response". For bupropion an added-benefit-adjusted reimbursement price was determined of €2.93 (IQR: €0 to €10.32) for the outcome "remission" and of €1.48 (IQR: €0 to €8.29) for the outcome "response".

Table 10: Overview of the added-benefit-adjusted reimbursement prices on the basis of base case analyses and probabilistic sensitivity analyses

| Test drug | Basic price (€) | RP Remission (€) | RP IQR PSA Remission (€) | RP Response (€) | RP IQR PSA Response (€) |
|---|---|---|---|---|---|
| **Bupropion** | 104.88 | 2.93 | 0–10.32 | 1.48 | 0–8.29 |
| **Duloxetine** | 241.18 | 30.66 | 22.94–69.66 | 9.30 | 0.35–21.95 |
| **Mirtazapine** | 46.46 | 31.66 | 20.68–44.90 | 24.28 | 14.29–35.96 |
| **Venlafaxine** | 92.57 | 42.99 | 35.33–83.04 | 40.91 | 31.22–54.25 |
| IQR: interquartile region, PSA: probabilistic sensitivity analysis, RP: reimbursement price | | | | | |

All added-benefit-adjusted reimbursement prices only refer to the indication of depression. If single drugs are also approved for other indications, no conclusion can be drawn from the present health economic evaluation with regard to the added-benefit-adjusted reimbursement price to be weighted across indications.

The budget impact analysis was calculated on the basis of these added-benefit-adjusted reimbursement prices. As the factor for bupropion and duloxetine would lead to a strong price reduction, in the following text only mirtazapine and venlafaxine are considered, using the added-benefit-adjusted reimbursement price on the basis of the outcomes “remission” and “response”. A target population of 315 252 SHI insurants was calculated for patients with moderate to severe depression investigated in the health economic evaluation. The corresponding indication-related expenditure for drugs, outpatient care, inpatient care, as well as sickness benefits, amounted to €560.3 million in the reference year 2010.

In the case that a maximum of 75% of the drugs that were dominated in the efficiency frontier analysis were substituted with mirtazapine, 3 years after introduction of the added-benefit-adjusted reimbursement price, this expenditure decreases by 0.52% or €2.9 million (calculation on the basis of the outcome “remission”) and 0.86% or €4.8 million (calculation on the basis of the outcome “response”). For venlafaxine, after 3 years the introduction of the added-benefit-adjusted reimbursement price leads to a reduction in the overall expenditure for the target population of 0.80% or €4.5 million (calculation on the basis of the outcome “remission”) and of 1.02% or €5.7 million (calculation on the basis of the outcome “response”).

If only drug expenditure based on all SHI prescriptions is considered, the resulting savings would be as follows: about 5% (calculation of the added-benefit-adjusted reimbursement price for the outcome “remission”) to 7% for mirtazapine (calculation of the added-benefit-adjusted reimbursement price for the outcome “response”), and about 8% for venlafaxine (calculation of the added-benefit-adjusted reimbursement price for the outcomes “remission” and “response”) relating to the annual prescriptions for antidepressants in the case of the introduction of the respective added-benefit-adjusted reimbursement prices, with consistent proportions of prescriptions.

Due to new data, there is a need to update the present health economic evaluation. This was not conducted due to a change in legal requirements for the Institute following the introduction of AMNOG. The concrete results reflect the status of the years 2010/2011.

**Keywords:** depression, depressive disorder, venlafaxine, duloxetine, bupropion, mirtazapine, systematic review, cost-effectiveness analysis

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