IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Cholinesterase inhibitors in Alzheimer's disease: supplementary commission rivastigmine patches and galantamine[1]

Executive Summary

[1] Translation of the executive summary of the final report "Cholinesterasehemmer bei Alzheimer Demenz: Ergänzungsauftrag Rivastigmin-Pflaster und Galantamin" (Version 1.0; Status: 03.02.2012). 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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Executive summary

On 18.12.2009, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess rivastigmine patches and galantamine in Alzheimer's disease within the framework of a supplementary commission.

Background

The report A05-19A "Cholinesterase inhibitors in Alzheimer's disease" was published in early 2007. In summer 2009, the G-BA commissioned IQWiG to perform an update search in the form of a rapid report (Commission A09-03) to determine whether substantive new evidence on cholinesterase inhibitors had become available in the intervening period. The rapid report concluded that there was a need to update 2 research questions.

Because of a relevant amount of additional data for the comparison galantamine versus placebo or no treatment, it appeared possible that a re-assessment of this research question might change the corresponding conclusions reached in the final report A05-19A. It was also noted that after completion of this report, a new form of administration of rivastigmine (transdermal patches) had been approved. Consideration of this new research question would therefore lead to additional conclusions.

Research question

The aims of the present investigation were to update the assessment of the benefit of galantamine and to assess the benefit and added benefit of rivastigmine as a transdermal patch in patients with mild to moderate Alzheimer‘s disease with respect to patient-relevant outcomes.

Methods

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the above-named research question. All the studies, publications, study reports and trial registry information on galantamine as well as on rivastigmine patches identified as relevant for the final report A05-19A and the rapid report A09-03, which met the pre-defined inclusion criteria, were used for this commission and included in the assessment.

During the course of the project, an update search analogous to the search in the rapid report A09-03 was conducted in bibliographical databases, publicly accessible trial registries and publicly accessible documents of regulatory authorities for the period from September 2009. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). The search for relevant systematic reviews took place in the databases MEDLINE and EMBASE in parallel to the search for relevant primary literature. Searches were also conducted in the databases Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), and Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for

additional relevant studies. The literature search covered the period up to 14.07.2011. In addition, documents of the manufacturers (Janssen-Cilag GmbH and Novartis Pharma GmbH) were used to identify published and unpublished studies.

The literature screening was performed by 2 reviewers independently of each other. After assessing the risk of bias, the results of the individual studies were classified according to outcomes, compared and described. These were subdivided into patient-relevant outcomes, outcomes relevant to (caregiving) relatives, and supplementary outcomes.

Results

Overall, 9 placebo-controlled studies were identified as relevant for the benefit assessment of galantamine (study duration 4 to 24 months, study size between 130 and 978 patients). Six of these studies had already been assessed in A05-19A, 3 were identified in A09-03. One of these 3 studies (continuation of previous galantamine treatment) was evaluated separately because of its special design.

Two relevant studies (study duration 24 weeks, study size 859 and 892 patients, both found in A09-03) were identified for assessing the benefit and added benefit of rivastigmine patches. One was a four-arm active and placebo-controlled study (comparators: rivastigmine patches 10 cm^2 and 20 cm^2, rivastigmine for oral administration [12 mg] and placebo) and the other was a placebo-controlled study on rivastigmine patches 5 cm^2 and 10 cm^2.

The update search produced no new hits for either research question.

All the study information requested from the manufacturers was made available for this benefit assessment.

Galantamine versus placebo

The meta-analysis revealed statistically significant effects in favour of galantamine for each of the outcomes “activities of daily living” and “accompanying psychopathological symptoms”. The standardized effect sizes in favour of galantamine were 0.19 (95% CI [0.10; 0.27]) and 0.11 (95% CI [0.02; 0.20]) respectively. As no information was identified about the applied scales in order to assess the relevance of these effects and/or the observed effect sizes, a standardized effect size of 0.2 was used as threshold value for the assessment. In both cases the effect estimator as well as the lower limit of the confidence interval was below this value. Therefore, the relevance of the present effect could not be estimated with certainty and hence, in the areas of activities of daily living and accompanying psychopathological symptoms, there was no proof of added benefit.

The meta-analysis of the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) non-responders showed a statistically significant difference in favour of galantamine (OR 0.48; 95% CI [0.39; 0.58], $p < 0.001$) for the outcome “cognitive performance”. The responder analyses reported in the studies were based on the established minimal important

difference (MID) of 4 points for an individual change on the ADAS-cog scale. The observed statistically significant effect was here regarded as a relevant effect because the response definition already included a threshold of relevance (namely the MID). In summary, there was proof of a benefit of galantamine in the higher dosage range for the outcome "cognitive performance".

No data were reported in the studies on the outcomes "health-related quality of life" and "need for full in-patient care (institutionalization)".

No proof of a change in the outcome "mortality" under galantamine treatment compared to placebo could be detected. However, only a few deaths were observed and no studies were designed to assess this outcome.

A statistically significant difference (OR 2.00; 95% CI [1.52; 2.65], $p < 0.001$) in favour of placebo was found for the outcome "study discontinuations due to adverse events". Hence there was proof of harm from galantamine for this outcome. In respect of the outcome "serious adverse events", there was no statistically significant difference (OR 1.05; 95% CI [0.83; 1.33], $p = 0.709$). There was thus no proof of harm from galantamine for this outcome. For "individual adverse events" (nausea, vomiting, loss of appetite and dizziness), there was a statistically significant difference in favour of placebo and hence proof of harm from galantamine for these adverse events. There was no statistically significant difference for the adverse event of diarrhoea and hence no proof of harm from galantamine for this adverse event.

The outcome "quality of life of caregiving relatives", which was recorded in 4 studies, showed a statistically significant difference in favour of galantamine (Hedges' g: 0.11; 95% CI [0.00; 0.21]). However, the difference could not be classed as clinically relevant because both the effect estimator and the lower limit of the confidence interval were below 0.2. In addition, the result was essentially based on 2 studies with a high risk of bias. Overall, there was no proof of an effect in favour of galantamine for this outcome.

No new data were available on the outcome relevant to caregiving relatives "degree of care provided by one or more caregiver(s) or institution(s)". The results were described and evaluated in the final report A05-19A, in which it was reported that the available data merely gave an indication of a favourable effect on the degree of care by galantamine.

No data were reported in the studies on the outcomes "time and effort invested in relation to the disease and intervention" or "patient satisfaction with the treatment".

The meta-analysis of the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) non-responders for the outcome "clinical global impression" showed a moderate heterogeneity ($I^2 = 47$ %, $p = 0.08$), so it was not meaningful to provide an overall effect estimator. The qualitative evaluation of the results on the proportions of CIBIC-plus

non-responders in the individual studies produced proof of an effect in favour of galantamine in the higher dosage range.

Continuation of previous galantamine treatment

The conclusions reached below with regard to continuation of galantamine treatment after 1 year of therapy with galantamine in treatment-responders are based exclusively on the data of a single, small, randomized, placebo-controlled study (GAL-ITA-2 study).

There was no statistically significant difference in the comparison of galantamine with placebo for the outcome "activities of daily living". Hence there was no proof of benefit of long-term treatment with galantamine for this outcome.

There was no statistically significant difference in the comparison of galantamine with placebo for the outcome "cognitive performance" as defined by changes on the ADAS-cog scale compared to baseline. Hence there was no proof of benefit of long-term treatment with galantamine for cognitive performance operationalized in this way. However, the further definition as "time to deterioration by ≥ 4 points on the ADAS-cog scale" produced a statistically significant difference in favour of galantamine (hazard ratio 1.78; 95% CI [1.07; 2.94]). Because of inconsistent results on the outcome "cognition", overall a hint of a benefit of continuation of previous galantamine treatment in responders is inferred.

No data were reported in the study on the outcomes "accompanying psychopathological symptoms", "health-related quality of life" and "need for full in-patient care (institutionalization)".

No proof could be found of a change in the outcome "mortality" under long-term galantamine treatment compared to placebo. However, only a few deaths occurred and the study was not designed to assess this outcome.

In each case, there were numerically distinct differences for the outcomes "serious adverse events" and "discontinuations due to adverse events", but these differences between the treatment groups were not statistically significant ($p = 0.155$; $p = 0.247$). Hence there was no proof of harm from galantamine in long-term treatment for this outcome.

The reported event rates for the "individual adverse events" of nausea, vomiting, diarrhoea, dizziness and loss of appetite were very low and therefore no reliable conclusions could be derived for these adverse events from the available data.

No data were reported in the study on the outcomes "quality of life of caregiving relatives", "degree of care provided by one or more caregiver(s) or institution(s)", "time and effort invested in relation to the disease and intervention" and "patient satisfaction with the treatment".

Because it was not considered in a high proportion of cases, the outcome "clinical global impression" was not evaluated in the analysis.

Rivastigmine patches versus placebo

The conclusions drawn below on the comparison of rivastigmine patches (5 cm^2) with placebo are based exclusively on the data of a single, medium-sized RCT (D1301 study). Data from 2 studies were available for the comparison of rivastigmine patches (10 cm^2) with placebo.

The meta-analysis found a statistically significant effect in favour of rivastigmine patches (10 cm^2) for the outcome "activities of daily living". The standardized effect size in favour of these patches was 0.20 (95% CI [0.08; 0.31]). As no information was identified for the applied Alzheimer's Disease Cooperative Study group – Activities of Daily Living (ADCS-ADL) and Disability Assessment for Dementia (DAD) scales in order to assess the relevance of these effects and/or the observed effect sizes, a standardized effect size of 0.2 was used as threshold value for the assessment. Since the lower limit of the confidence interval was below this threshold, the relevance of the existing effect could not be reliably estimated. The comparison of rivastigmine patches (5 cm^2) with placebo showed no statistically significant difference ($p = 0.270$). There was therefore no proof of benefit of rivastigmine patches (5 cm^2 or 10 cm^2) compared to placebo for this outcome.

The meta-analysis regarding the outcome "cognitive performance" for the comparison of rivastigmine patches (10 cm^2) with placebo showed a statistically significant difference in favour of rivastigmine patches (10 cm^2) with respect to the proportion of ADAS-cog non-responders (OR 0.70; 95% CI [0.52; 0.95], $p = 0.023$), whereby neither of the two individual studies showed any statistically significant difference. The robustness of this result needed to be checked using sensitivity analyses because at 0.95, the upper limit of the 95% CI was almost 1 (i.e. group equality) and the IDEAL study, which was included in the meta-analysis with a weight of almost 60%, was subject to a high risk of bias for the outcome "cognitive performance".

In one of these sensitivity analyses, all patients who were not included in the primary ITT LOCF-RDO[2] analysis were defined as non-responders. This still resulted in a statistically significant difference in favour of rivastigmine patches (10 cm^2) (OR 0.73; 95% CI [0.54; 0.99], $p = 0.046$). Since the use of LOCF data as a replacement strategy for missing values can be problematic in Alzheimer's disease because of the progressive course of the disease, a further sensitivity analysis was carried out in which all patients in both groups who had not been fully followed-up until the end of the study were assessed as non-responders. This analysis was performed on the basis of the information in the study report of the IDEAL study with patients observed up to the end of the study ("Observed Cases"). In this second sensitivity analysis, no statistically significant difference was found between rivastigmine patches (10 cm^2) and placebo (OR 0.78; 95% CI [0.56; 1.07], $p = 0.124$). Therefore a

[2] Intention-to-Treat Last Observation Carried Forward-Retrieved Drop-Outs

substantial influence on the overall conclusion by the differing proportions of patients not considered in the analysis cannot be completely ruled out. In addition, a subgroup analysis for the characteristic of age produced an indication of an effect modification (interaction test: p = 0.142) for the outcome "cognitive performance". This showed a statistically significant difference in favour of rivastigmine patches (10 cm^2) for patients < 75 years, but not for patients ≥ 75 years. On the basis of the overall analysis, there was still an indication of a benefit of rivastigmine patches (10 cm^2) on cognitive performance in patients < 75 years. Since there was only an indication of an effect modification, an effect also in the group of patients ≥ 75 years cannot be completely denied. Due to the uncertain data, there was nevertheless only a hint of a benefit of rivastigmine patches (10 cm^2) for the latter age group.

The comparison between rivastigmine patches (5 cm^2) and placebo produced no statistical significance (p = 0.329).

Overall, there was an indication - but no proof - of a benefit of rivastigmine patches (10 cm^2) with regard to cognitive performance. This indication applied to patients < 75 years. The data for patients ≥ 75 years were less reliable, so that there was only a hint of a benefit of rivastigmine patches (10 cm^2). For rivastigmine patches (5 cm^2), there was no proof of a benefit.

No data were reported in the studies on the outcomes "health-related quality of life" and "need for full in-patient care (institutionalization)".

The meta-analysis of the standardized mean differences for the comparison of rivastigmine patches (10 cm^2) with placebo showed no statistically significant difference (Hedges' g: 0.03; 95% CI [-0.09; 0.15], p = 0.656) for the outcome "accompanying psychopathological symptoms". There was also no statistically significant difference (p = 0.911) for the comparison of rivastigmine patches (5 cm^2) with placebo. There was therefore no proof of a benefit of rivastigmine patches (5 cm^2 or 10 cm^2) compared to placebo for this outcome.

There was no proof of change in the outcome "mortality" under rivastigmine patches therapy (5 cm^2 or 10 cm^2) compared to placebo. However, only a few deaths occurred and the study was not designed to assess this outcome.

The comparison of rivastigmine patches (5 cm^2 or 10 cm^2) with placebo showed a statistically significant difference in favour of placebo treatment for the outcome "study discontinuations due to adverse events" (5 cm^2: p = 0.019; 10 cm^2: OR 1.73; 95% CI [1.15; 2.62], p = 0.009). There was therefore proof of harm from rivastigmine patches (10 cm^2) and an indication of harm from rivastigmine patches (5 cm^2) for this outcome. In the case of "serious adverse events", comparison of rivastigmine patches (5 cm^2 or 10 cm^2) with placebo showed no statistically significant difference in the number of patients with at least one serious adverse event (5 cm^2: p = 0.377; 10 cm^2: OR 0.90; 95% CI [0.58; 1.40], p = 0.643). There was thus no proof of harm from rivastigmine patches (5 cm^2 or 10 cm^2) for this outcome.

For "individual adverse events" (nausea, vomiting), the meta-analyses on the comparison of rivastigmine patches (10 cm^2) with placebo found statistically significant differences in favour of placebo and hence proof of harm from rivastigmine patches (10 cm^2) for these adverse events. For the comparison of rivastigmine patches (5 cm^2) with placebo, there was no proof of harm from the former for the adverse events of nausea and vomiting. Likewise, no significant difference for the comparison of rivastigmine patches (5 cm^2 or 10 cm^2) with placebo could be demonstrated for the adverse events of diarrhoea, loss of appetite and dizziness. There was thus no proof of harm from rivastigmine patches (5 cm^2 or 10 cm^2) for these adverse events.

Comparison of rivastigmine patches (5 cm^2 or 10 cm^2) with placebo showed statistically significant differences in favour of placebo for individual skin irritations (erythema, oedema and pruritus [only 10 cm^2] [in each case, moderate or severe reaction]). For these adverse events, there was therefore proof (10 cm^2) and indications (5 cm^2) of harm from rivastigmine patches. There was no proof of harm from rivastigmine patches for other forms of skin irritation (scaling, fissures, pain, stinging and burning).

For the outcome "quality of life of caregiving relatives", comparison of rivastigmine patches (10 cm^2) with placebo showed no statistically significant difference ($p = 0.886$). In summary, there was no proof of a benefit of rivastigmine patches (10 cm^2) over placebo for this outcome. No data were available for the comparison of rivastigmine patches (5 cm^2) with placebo.

Neither of the two studies reported data on the outcomes "degree of care provided by one or more caregiver(s) or institution(s)", "time and effort invested in relation to the disease and intervention" or for "patient satisfaction with the treatment".

As regards the outcome "clinical global impression", meta-analysis of the comparison of rivastigmine patches (10 cm^2) with placebo regarding the proportion of CIBIC-plus and/or ADCS-CGIC non-responders showed a statistically significant difference in favour of rivastigmine patches (10 cm^2) (OR 0.71; 95% CI [0.54; 0.92], $p = 0.009$). Comparison of rivastigmine patches (5 cm^2) with placebo showed no statistically significant difference for the outcome "clinical global impression" ($p = 0.063$). In summary, there was proof of an effect in favour of rivastigmine patches (10 cm^2), but not for rivastigmine patches (5 cm^2) as regards this outcome.

Rivastigmine patches (10 cm^2) versus rivastigmine p.o. (12 mg)

The conclusions drawn below on the comparison of rivastigmine patches (10 cm^2) with rivastigmine p. o. (12 mg) are based exclusively on the data from a single, medium-sized, RCT (IDEAL study). When interpreting the results of this study, it should be borne in mind that it was not designed to demonstrate the equivalence of the two forms of administration.

For the comparison of rivastigmine patches (10 cm^2) with rivastigmine p.o., there were no statistically significant differences for the outcomes "activities of daily living" (p = 0.691), **"**cognitive performance" (p = 0.447) and **"**accompanying psychopathological symptoms" (p = 0.804). Hence there was no proof of an added benefit of rivastigmine patches (10 cm^2) over rivastigmine p.o. for these outcomes.

No data on the outcomes "health-related quality of life" and "need for full in-patient care (institutionalization)" were reported in the study.

There was no proof of a change in the outcome "mortality" under rivastigmine patch therapy compared to rivastigmine p.o. However, only a few deaths were observed and the study was not designed to assess this outcome.

There were no statistically significant differences for the outcomes "serious adverse events" and "study discontinuations due to adverse events" for the comparison of rivastigmine patches (10 cm^2) with rivastigmine p.o. (p = 0.804; p = 0.399). Hence there was no proof of greater or lesser harm from rivastigmine patches (10 cm^2) over rivastigmine p.o. for these outcomes.

Statistically significant differences in favour of rivastigmine patches (10 cm^2) were found for "individual adverse events" (nausea, vomiting and dizziness) and therefore there was an indication of lesser harm from rivastigmine patches (10 cm^2) compared to rivastigmine p.o. for these adverse events. However, there were no statistically significant differences for the adverse events of diarrhoea and loss of appetite or for skin irritation in the form of oedema, scaling, fissures and pain, stinging, burning (in each case moderate or severe skin reaction) and hence no proof of greater or lesser harm from rivastigmine patches (10 cm^2) compared to rivastigmine p.o. In contrast, there were statistically significant differences in favour of rivastigmine p.o. for the adverse events of erythema and pruritus (in each case moderate or severe skin reaction) and hence an indication of greater harm from rivastigmine patches (10 cm^2) than from rivastigmine p.o. for these adverse events.

There was no statistically significant difference (p = 0.742) for the outcome "quality of life of caregiving relatives" for the comparison between rivastigmine patches (10 cm^2) and rivastigmine p.o. There was therefore no proof of a different effect of rivastigmine patches and rivastigmine p.o. for this outcome.

No data were reported in the study on the outcomes "degree of care provided by one or more caregiver(s) or institution(s)", "time and effort invested in relation to the disease and intervention" or "patient satisfaction with the treatment".

The comparison of rivastigmine patches (10 cm^2) with rivastigmine p.o. regarding the outcome "clinical global impression" showed no statistically significant difference (p = 0.520). There was therefore no proof of a different effect of rivastigmine patches and rivastigmine p.o. for this outcome.

Conclusions

Galantamine versus placebo

There is proof of a benefit of galantamine therapy (medium to high dose) in patients with mild to moderate Alzheimer's disease for the outcome "cognitive performance". This proof of benefit is opposed by proof of harm caused by the more frequent occurrence of gastrointestinal adverse effects and study discontinuations due to adverse events. There is no proof that serious adverse events or deaths occur more frequently under galantamine than under placebo.

Effects of galantamine therapy were shown in the areas of activities of daily living and accompanying psychopathological symptoms. However, due to the low intensity of these effects, their relevance for the patient has not been demonstrated, so that overall there was no proof of a benefit of galantamine in these areas.

These conclusions are restricted to a treatment period of up to 6 months.

Continuation of previous galantamine treatment

One long-term study of galantamine was available that investigated whether it is worth continuing galantamine treatment in patients who showed an improvement in cognition under this drug. From this study, there was a hint of a benefit of continued treatment after 12 months of previous treatment with galantamine for the outcome "cognitive performance".

Rivastigmine patches versus placebo

There is no proof of a benefit of rivastigmine patches in patients with mild to moderate Alzheimer's disease. This applies both to a patch size of 5 cm^2 applied once daily as well as to a size of 10 cm^2 applied once daily. In the area activities of daily living, there was admittedly an effect of rivastigmine patch therapy (10 cm^2). However, due to the low intensity of this effect, its relevance has not been demonstrated. In the area of cognition, although the effect was relevant, the result was dependent on the type of statistical analysis and therefore not sufficiently robust. Overall there is therefore an indication of a benefit of the treatment with rivastigmine patches (10 cm^2) in the area of cognition. This indication applies to patients < 75 years. For those ≥ 75 years, the data are less reliable, so there is only a hint of a benefit of rivastigmine patches (10 cm^2). There was also no proof of a benefit for rivastigmine patches (5 cm^2) in the area of cognition.

In addition, there is an indication (5 cm^2 patch) and/or proof (10 cm^2 patch) of greater harm, namely due to the more frequent occurrence of skin irritation of moderate to severe intensity, of gastrointestinal side effects (only 10 cm^2) and of study discontinuations due to adverse events. There is no proof that serious adverse events or deaths occur more frequently under rivastigmine patches than under placebo.

These conclusions are restricted to a treatment period of up to 24 weeks. To date, there are no long-term studies comparing rivastigmine patches with placebo.

Rivastigmine patches versus rivastigmine p.o. (12 mg)

There is no proof that treatment with rivastigmine patches (10 cm^2) in patients with mild to moderate Alzheimer's disease has added benefit compared to treatment with rivastigmine p.o. There is also no proof that the treatment with rivastigmine patches is of lesser benefit than treatment with rivastigmine p.o. However, there is only one study on the direct comparison and this was not designed to demonstrate the equivalence of the two treatment options.

The data on adverse events showed no proof of overall lesser or greater harm from rivastigmine patches (10 cm^2) than from rivastigmine p.o.. For individual adverse events, there was lesser harm (gastrointestinal side effects), and for other adverse events, greater harm (skin irritation) with the patch.

These conclusions are restricted to a treatment period of up to 24 weeks. To date, there are no long-term studies comparing rivastigmine patches with rivastigmine p.o..

Keywords: cholinesterase inhibitors, galantamine, rivastigmine, Alzheimer's disease, dementia, benefit assessment, systematic review

The full report (German version) is published under www.iqwig.de.