

## **Cholinesterase inhibitors in Alzheimer's disease**

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### **Background**

The Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]) was commissioned by the Federal Joint Committee to evaluate the benefits and harms of cholinesterase inhibitors (ChEIs) in Alzheimer's disease.

### **Research questions**

The aims of this evaluation were:

- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with placebo
- the evaluation of long-term treatment with a ChEI in Alzheimer's disease compared with treatment with a different drug or non-drug intervention.

The focus of this evaluation was on patient-relevant therapy goals.

### **Methods**

This evaluation was conducted on the basis of randomised controlled trials (RCTs) on the research questions outlined above. For this purpose, a systematic literature search was conducted in the bibliographic databases MEDLINE, EMBASE, and CENTRAL (in each case, coverage up to June 2006), as well as in CHID. In addition, reference lists of relevant secondary publications (systematic reviews, HTA reports, meta-analyses) were searched, and manufacturers of ChEIs were asked to provide information on relevant published or unpublished trials.

The evaluation included RCTs that investigated ChEIs (donepezil, galantamine and rivastigmine) in patients with Alzheimer's disease. The literature screening was conducted by 2 reviewers independently of one another.

After an evaluation of study quality, the results of the individual trials were collated according to therapy comparisons and therapy goals. IQWiG's preliminary evaluation, the preliminary report, was published on the Internet ([www.iqwig.de](http://www.iqwig.de)). Interested parties could submit written comments. Unclear aspects of these written comments were discussed in a scientific debate before production of the final report.

### **Results**

Of all citations viewed, 54 publications on 33 trials were assessed as relevant. Of these publications, 48 publications on 27 trials were included in the evaluation. 22 trials were placebo-controlled (donepezil: 12, galantamine: 6, rivastigmine: 4). Five trials were direct comparisons of different ChEIs. A total of 9883 patients were investigated. Eleven of the relevant publications contained pooled analyses of several trials. Trials comparing ChEIs with other drug or non-drug interventions approved and available in Germany were not identified. Of the trials included, 16 showed minor and 11 showed major deficiencies in respect of study and publication quality.

Except for 2 trials (both on donepezil, duration approx. 1 year), all comparisons with placebo only involved a treatment or observation period of a maximum of 26 weeks. Even though the longer trials did not show fundamentally different results, robust conclusions can essentially only be made for a 6-month period. In

contrast, 3 of the 5 trials comparing different ChEIs with each other lasted one year or longer. However, except for one trial on donepezil and rivastigmine, validity was restricted due to an unblinded design, while the sample sizes were too small to detect differences or demonstrate equivalence.

Comparison with placebo: In all trials, a dose-dependent effect was shown. In low-dose interventions, galantamine and rivastigmine showed no or uncertain efficacy (in contrast to donepezil). For galantamine, no noticeable difference was shown between doses of 16 mg and 24 mg. With regard to the reported adverse event rates, a dose-effect association was confirmed.

For the therapy goal “improvement in or prevention of restriction in activities of daily living”, indications of a beneficial effect of all 3 drugs in the medium- and/or high-dose range were shown. The average effects determined by means of meta-analyses were about 3 score points on the Disability Assessment for Dementia (DAD) and Progressive Deterioration Scale (PDS) for galantamine and rivastigmine respectively. The corresponding estimates for donepezil cannot be inferred with sufficient certainty, as one must assume an over-estimation of the treatment effect in the corresponding meta-analysis. Nevertheless, indications of a beneficial effect can also be assumed for donepezil.

In respect of the accompanying psychopathology, no indications of a beneficial or detrimental effect of donepezil or rivastigmine can be inferred (for donepezil, due to unconvincing data; for rivastigmine, due to lack of data). There was an indication of a positive effect for galantamine. However, this effect was minor (1-2 score points on the Neuropsychiatric Inventory [NPI] scale).

For all 3 drugs, a beneficial effect on cognition was shown compared with placebo. This effect was about 2 (for donepezil 5 mg or flexible dose) to 3 score points (for donepezil 10 mg, galantamine, rivastigmine) on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog).

For the therapy goal “improvement or maintenance of health-related quality of life”, only data on donepezil were available from 2 trials, which did not show clear indications of either a beneficial or a detrimental effect. No data were available for galantamine or rivastigmine.

No (interpretable) data were available for the therapy goal “prevention of placement in a nursing home” (institutionalisation). Very few deaths were reported in the trials, and no indications of a beneficial or detrimental effect of ChEIs on mortality can be inferred from these data.

For all drugs, higher discontinuation rates due to adverse events were reported for high-dose therapy. Moreover, more adverse events occurred which are associated with the effects of ChEIs (e.g. nausea, vomiting, diarrhoea). There were no indications that more patients taking ChEIs experienced serious adverse events than those taking placebo. However, it should be noted that the reporting in this regard was in part insufficient. No statements on rare or long-term adverse events can be made, due to the study designs and reporting methods used.

For donepezil, no indications of a beneficial or detrimental effect on caregiver-related quality of life can be inferred from the available results. For galantamine, an indication of a positive effect was shown. However, this effect was minor, with a dimension of 1/10 of the standard deviation. No relevant data were found for rivastigmine.

There were indications that data on rivastigmine for the therapy goal “reduction in the degree of care provided by caregivers or institutions” were collected for all 4 larger phase-III trials. However, so far these data have not been published, so no conclusions can be made in this regard. The data on donepezil were insufficiently robust (mainly for methodological reasons). Therefore, no indications of a beneficial effect on the degree of care can be inferred from them. One trial on galantamine showed indications of a positive effect in this regard.

The global clinical impression was consistently improved by all 3 drugs. For galantamine and rivastigmine, there were indications that the treatment effect was larger in severely impaired patients than in those less severely impaired. No differentiated statements can be made with regard to age, gender, or concomitant diseases.

Comparison between cholinesterase inhibitors: A quantitative summary (meta-analysis) of comparative results on single outcomes was inappropriate, due to the limited number of trials available and the different study designs and methods used. Only 2 of the 5 trials had a sample size that was sufficiently large to detect moderate differences between treatment groups.

For donepezil vs. galantamine, neither trial included provided a clear indication of a superiority of either drug with regard to the effect on activities of daily living, accompanying psychopathology, cognition, and therapy-related adverse events. No comparative or clearly interpretable data were reported for health-related quality of life of patients, institutionalisation, and carer-relevant outcomes.

For donepezil vs. rivastigmine, data from one trial indicated a slight superiority of rivastigmine with regard to the effect on activities of daily living (effect estimate about 1/10 of the standard deviation); however, for methodological reasons the validity of these data is doubtful. There was no clear indication of a difference between these 2 drugs in respect of accompanying psychopathology, cognition, and mortality.

Substantially higher adverse event rates occurred under rivastigmine, in particular concerning nausea, vomiting, loss of appetite and weight. No comparative data were reported on health-related quality of life and carer-relevant outcomes.

For galantamine vs. rivastigmine, only results of a 3-arm comparison with very low sample sizes were available. In this comparison, no differences were noticeable with regard to the effect on psychopathological outcomes and the occurrence of adverse events. No data were available for other outcomes.

Overall, in the comparative trials, no evidence of the superiority of one drug over the other can be inferred from the non-existing or at most minor differences (which were of insufficient certainty) for efficacy parameters. However, nor can the results be interpreted as showing equivalence between drugs, as the trials were not recognisably designed as equivalence or non-inferiority trials with an a priori definition of "irrelevant differences".

## **Conclusion**

The ChEIs donepezil, galantamine, and rivastigmine have a benefit in patients with mild-to-moderate Alzheimer's disease with regard to the therapy goal "improvement in or maintenance of cognitive function". This applies to all administered doses of donepezil, and only to medium and high doses of galantamine and rivastigmine.

Moreover, for all 3 drugs, there are indications of a benefit in respect of the therapy goal "improvement in or prevention of restriction in activities of daily living".

Furthermore, for galantamine, there are indications of a benefit with regard to accompanying psychopathological symptoms. For donepezil, no corresponding benefit can be inferred from the available data, and for rivastigmine, no data were available.

No data were available (galantamine and rivastigmine) for the therapy goal "improvement in or maintenance of health-related quality of life", or they provided no indication of a benefit (donepezil).

No interpretable data were available on the therapy goal "prevention of placement in a nursing home" (institutionalisation). All 3 drugs triggered therapy-related adverse events in a dose-dependent manner. An

effect on mortality cannot be inferred from the available data; however, the trials were not designed to make conclusions in this regard.

Whereas the direct comparison between rivastigmine and donepezil showed indications of an additional benefit of rivastigmine for activities of daily living, rivastigmine also had a higher potential to cause harm. No conclusions can be made on the other two comparisons (galantamine vs. donepezil or galantamine vs. rivastigmine). Overall, no clear advantage of any of the 3 drugs investigated can be inferred from the available data.

The statements made above mainly refer to a study period of up to 6 months. For a further weighing of benefits and harms, direct comparative trials including other therapy options (other drug or non-drug treatment strategies) would be desirable.

The relevance of ChEIs vs. other drug or non-drug interventions is unclear, due to lack of data.

**The full version is available in German**

**under**

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