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Non-drug therapies in Alzheimer's disease¹

Executive Summary

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Research question

The aim of this research was the assessment of the long-term benefit of non-drug therapies in Alzheimer's disease compared with (a) no therapy, (b) non-drug sham therapy, (c) a different non-drug therapy, or (d) therapy with a drug approved and available in Germany for the treatment of Alzheimer's disease. The focus of the assessment was on patient-relevant therapy goals.

Methods

The benefit assessment considered studies of patients with the diagnosis "Alzheimer's disease", including patients with mixed-type dementia (e.g., Alzheimer's disease and vascular dementia). Assuming that Alzheimer's disease is the underlying cause of about 70% of dementia cases, studies were also considered in which no explicit information on the dementia type was provided. Studies were also included in which the disease definition was based on test results from the 2 symptom areas "cognition" and "activities of daily living". Studies were excluded that mainly or solely investigated patients with other specific dementia types, for example, dementia due to vascular disease, frontotemporal degeneration, Lewy body disease, Parkinson's disease, and other rare causes.

Studies on the interventions and training provided to relatives or nursing staff were excluded if changes in patients were not assessed. The interventions had to be performed either according to a treatment scheme or described in a comprehensible manner.

The following patient-relevant outcomes were considered: activities of daily living; cognitive function; health-related quality of life; other disease-related symptoms (e.g., depression, sleep-wake reversal, mania, agitation); nursing home placement (institutionalization); mortality; and treatment-related adverse events. In addition, the following outcomes that were important to caregiving relatives (hereafter referred to as "caregivers") were assessed: quality of life of caregivers, and degree of care provided by one or several caregiver(s) or caregiving services/institution(s). Results were also reported that refer to the "clinical disease stage according to clinical impression". Results on caregiver-relevant outcomes and on the "clinical disease stage according to clinical impression" were reported only as supplementary information. The actual benefit assessment was conducted on the basis of outcomes directly relevant to patients.

The benefit assessment only considered randomized controlled trials (RCTs).

When drugs for dementia therapy are administered for the first time, the Drug Commission of the German Medical Profession recommends a check-up after 12 weeks in order to assess treatment success [1]. EMEA recommends a minimum study duration of 6 months for the evaluation of the short-term effects of antidementia drugs [2,3]. In order to meet both recommendations, a minimum observation period of 16 weeks was specified for the 4 IQWiG reports investigating the benefit assessment of different treatments for Alzheimer's disease (cholinesterase inhibitors, ginkgo compounds, memantine, non-drug therapy). It was

assumed that a response to therapy can be expected within this period and a longer term effect can be observed.

A systematic literature search was conducted in 6 electronic databases (BIOSIS Previews, CINAHL, EMBASE, MEDLINE, PsycINFO and Cochrane Central Register of Controlled Trials [Clinical Trials]), and covered the period up to June/July 2008. In addition, reference lists were screened of relevant primary publications and secondary publications (systematic reviews, HTA reports). If required, authors of (potentially) relevant primary publications were contacted.

The literature screening was conducted by at least 2 reviewers independently of one another. The prespecified methodological procedure (report plan) and IQWiG's preliminary benefit assessment (preliminary report) were published on the Internet and interested parties were invited to submit written comments. Relevant unclear aspects concerning the comments on the preliminary report were discussed in a scientific debate. If changes were made on the basis of aspects presented in the comments, this was noted in the final report subsequently produced.

Results

A total of 33 studies were included in this benefit assessment. The studies were classified according to 4 main treatment approaches: caregiver training, emotion-orientated interventions (validation and reminiscence therapy), cognitive training procedures, and activity-based interventions. The additional category "further procedures" included one study on sleep therapy and one on orientation training for persons relocating to a new environment; these studies could not be allocated to a conventional therapy approach. (Results of these individual studies are presented in the long version of the final report).

Most studies (n=17) investigated the effects of caregiver training. The comparator interventions were procedures without treatment (AENEAS 2005, Belle 2006, Gitlin 2005, Hébert 2003, McCallion 1999a, Mittelman 2006, Ostwald 1999, Teri 2005, Teri 2003, Ulstein 2007); inactive or non-specific treatment (Burgio 2003, Chien 2008, Davis 2004); a different type of caregiver training (Bourgeois 2002, Farran 2004); a cognitive training procedure (Perren 2006); and drug therapy with haloperidol or placebo (Teri 2000). In the studies included, the components of the caregiver training, as well as the frequency and duration of the interventions, were very heterogeneous.

The second most common studies (n=7) investigated cognitive training procedures. The comparator interventions were procedures without treatment (Bottino 2005, Onder 2005, Quayhagen 1995, Tárraga 2006); an inactive or non-specific intervention (Quayhagen 1995, Ousset 2002); a different cognitive procedure (Loewenstein 2004); and psychosocial activation (Heiss 1994).

Three studies on emotion-orientated interventions were identified. Comparator interventions were a procedure without treatment (Tadaka 2004, Thorgrimsen 2002, Toseland 1997) and psychosocial activation (Toseland 1997 [3-arm study]).

In 5 studies, the effect of activity-based interventions was compared with a procedure without treatment (Chapman 2004, Gitlin 2008, Onor 2007, Rolland 2007, Toseland 1997).

A total of about 3800 patients were investigated in the studies. However, most studies had small sample sizes that ranged from 11 to 406 patients (median: 88). Most studies had a 2-arm design. No studies were identified that compared a non-drug intervention with a drug assessed by IQWiG (cholinesterase inhibitors, ginkgo compounds, memantine). In studies including treatment with a cholinesterase inhibitor, this drug was used as concomitant therapy for patients in *all* intervention groups.

The reporting quality of 29 of 33 included studies must be regarded as poor. Meaningful conclusions can therefore only be drawn with reservations. Study results mostly referred to considerably smaller sample sizes than initially included in the studies. In addition, in most studies, outcomes were assessed in an unblinded manner, which is also due to the type of assessment performed (mainly self-reported or assessment by caregivers). Most studies on cognitive procedures were evaluator-blinded. The randomization procedure was rarely reported appropriately.

In most studies, the observation period lay between the 4-month minimum required and 6 months. In individual studies, patients were also treated and/or followed up for longer periods of time. One study on caregiver training (Mittelman 2006) has followed up patients for a total period of up to 17 years.

The studies provide indications that *caregiver training* delays the institutionalization of patients. In contrast, the studies (Belle 2006, Teri 2005) also provide indications of harmful effects of caregiver training, for example, through an increase in hospital or emergency unit admissions. To what extent caregiver training also leads to a (negative) influence on mortality cannot be reliably assessed from the studies due to heterogeneous results.

For *cognitive procedures*, the studies provide indications of a benefit with regard to patients' cognitive function. The effect size (about 0.5 SD) and the estimated precision (95% CI: -0.80; -0.23) suggest that this also means a noticeable improvement for patients. The results are mainly based on studies in which patients received concomitant treatment with a cholinesterase inhibitor; however, positive effects were also observed in a study conducted before the introduction of these drugs (Quayhagen 1995). To what extent a combination therapy of cognitive training and cholinesterase inhibitors has a positive effect cannot be assessed on the basis of the studies included.

Due to heterogeneous study results, regarding *psychosocial activation* it remained unclear to what extent this procedure had a beneficial or harmful effect on accompanying psychopathological symptoms. The studies provide indications of a beneficial effect on the quality of life of caregivers and the degree of care given.

The results of one study (Rolland 2007) provide indications that measures of *physical activation* may possibly have a detrimental effect on physical health. Patients treated with this intervention experienced more hospital admissions than those not so treated. However, the fact that no increase in falls or fractures was reported makes it clear that this indication of a potential harm must be interpreted with caution.

Overall, however, in addition to the indications described above of beneficial, but also detrimental effects, in most studies statistically non-significant and mainly minor effects were observed.

Conclusion

For individual non-drug treatment strategies in Alzheimer's disease, the available studies provide indications of beneficial, but also of harmful effects for patients. Overall, the long-term benefit of the treatment strategies investigated has not been proven.

For the caregiver-training approaches investigated in the report, the studies provide indications that institutionalization of patients is delayed by caregiver training. This is opposed by indications of harm, suggested by more hospital and emergency unit admissions. Compared with the neuroleptic drug haloperidol, which is used to treat psychopathological symptoms such as restlessness and aggressiveness, the studies provide indications that a non-drug treatment approach has an additional benefit with regard to activities of daily living. This contrast probably results from the harm caused by haloperidol. Regarding other adverse events (gait disorders and slowness of movement), the studies also provide indications of a disadvantage of haloperidol compared with caregiver training.

Regarding cognitive function, the studies provide indications of a benefit of the cognitive training procedures investigated in the report. This conclusion refers to a patient population with mainly mild dementia, which received basic medication with antidementia drugs. It cannot be inferred from the studies to what extent this indication of a benefit can also be transferred to activities of daily living or to other untrained areas.

For the psychosocial activation procedures investigated in the report, the studies do not provide indications of a benefit with regard to patient-relevant outcomes. They provide indications of a positive effect on quality of life of caregivers and on the degree of care given.

For physical activation, either no (interpretable) data on patient-relevant outcomes are available or they provide no indications of a benefit. In contrast, indications of harm are provided by the increased occurrence of adverse events (hospital admissions).

Either no (interpretable) data are available or they provide no indications or proof of an effect regarding the benefit or harm of further non-drug treatment approaches (e.g., emotion-orientated interventions) and/or regarding further patient-relevant outcomes.

The benefit of non-drug therapy versus drug therapy with substances approved for Alzheimer's disease, such as cholinesterase inhibitors, memantine or ginkgo biloba, is unclear. No study was identified that investigated these treatment approaches in a direct comparison.

Additional randomized studies of appropriate quality would be desirable in order to draw ultimately more robust conclusions about the benefit or additional benefit of non-drug procedures in the treatment of Alzheimer's disease. On the one hand, in multi-arm studies the effects could be estimated of non-drug therapy alone and in fair comparison with drug therapy, or of combination therapy versus either non-drug therapy or drug therapy alone. On the other hand, it would be helpful to conduct studies in Germany in order to assess the

benefit of treatment procedures for which the national health care setting presumably plays a role.

Key words: non-drug therapy, Alzheimer's disease, dementia, benefit assessment, systematic review

References

1. Arzneimittelkommission der deutschen Ärzteschaft. Demenz: Therapieempfehlungen. [Commission of the German Medical Profession. Dementia. Therapy recommendations]. Köln: AkdÄ; 2004.
2. The European Agency for the Evaluation of Medicinal Products. Note for guidance in medicinal products in the treatment of Alzheimer's disease [Online]. 12.04.1997 [Accessed on 04.08.2008]. URL: <http://www.emea.europa.eu/pdfs/human/ewp/055395en.pdf>.
3. The European Agency for the Evaluation of Medicinal Products. Guideline on medicinal products for the treatment of Alzheimer's disease and other dementias [Online]. 24.07.2008 [Accessed on 22.10.2008]. URL: <http://www.emea.europa.eu/pdfs/human/ewp/055395en.pdf>.

The final report (including the full list of references) is available under www.iqwig.de