Benefit of memantine in the treatment of Alzheimer's disease not proven

October 28 2009

There is no scientific proof that patients with moderate or severe Alzheimer's disease benefit from drugs containing the agent memantine. This is the conclusion in the final report that the Institute for Quality and Efficiency in Health Care (IQWiG) published in September 2009.

The report is part of a broader commission awarded by the Federal Joint Committee (G-BA) to assess both drug and non-drug therapy options for Alzheimer's disease. In addition to memantine, IQWiG has investigated cholinesterase inhibitors, Ginkgo biloba and non-drug therapy alternatives.

Memantine is intended to regulate excess glutamate

Memantine is approved for moderate to severe Alzheimer's disease, but not for the mild stage of the disease. In Germany memantine is sold under the tradenames "Axura" (Merz) and "Ebixa" (Lundbeck).

Memantine is intended to prevent an excess of glutamate from damaging the brain. Glutamate is a neurotransmitter, in other words a substance that transmits neural signals. Animal experiments have shown that patients suffering from Alzheimer's disease might have a permanent excess of glutamate, which leads to neural cells dying. Memantine is intended to prevent this without affecting the normal transmission of neural signals.

The substance was developed several decades ago and prescribed for other diseases such as Parkinson's. Memantine has been used in the treatment of Alzheimer's disease since 2002.

Studies with nearly 2000 participants included in the assessment

The scientists searched for studies which investigated outcomes that were relevant to patients and their families: this includes cognitive function (e.g. memory capacity) and activities of daily living (e.g. personal hygiene) as well as mental concomitant symptoms (e.g. depression, agitation), quality of life and avoiding being put in a nursing home.

IQWiG was able to include in its assessment 7 studies, in which a total of 1913 patients suffering from Alzheimer's disease were treated with memantine over a period of 16 to 28 weeks. In 5 of these studies, the subjects received only memantine (monotherapy), in the remaining 2 the substance was administered as an add-on to an existing therapy with a cholinesterase inhibitor. Each study had a comparator control group, in which the patients took a placebo. Up till now, there have not been any usable studies comparing memantine with another dementia drug or with a non-drug therapy.

There are 2 other relevant manufacturer's studies, but they could not be included in the assessment as not all the necessary data were made available.

Only minimal differences in cognition and activities of daily living

Point scales were used in order to measure activities of daily living and

cognitive function. The values were determined on each scale, for example, by giving the patients observation tests or asking the patients and their families about changes in the disease symptoms and how they managed with activities of daily living. However, not every change on such a scale means that the patient's disease stage actually improves or deteriorates. As the analysis of the study results shows, there are differences between the groups for these 2 outcomes, but these are minimal. Moreover, they are debatable due to the incompleteness of the data. It is therefore doubtful whether patients and their families can in fact see these differences as an advantage.

However, the manufacturer could also have provided evidence of benefit by means of a responder analysis. This investigates whether more patients in the memantine group notice a perceptible improvement in their symptoms than in the placebo group. However, the manufacturer did not provide a reliable responder analysis. Consequently, IQWiG did not find any overall proof of benefit from memantine in the activities of daily living and in cognitive function.

No reliable data on quality of life and necessity of inpatient care

The included studies did not provide reliable information on all outcomes. There are no data on the health-related quality of life of patients because they were not collected in the studies. However, there have been very few suitable instruments for displaying quality of life with this disease.

Although some studies did record whether patients had to be institutionalized, the results are not reliable. Consequently, it remains unclear whether memantine has an influence on how long persons with dementia can be cared for at home.

Data on concomitant symptoms do not reveal any differences

Information on concomitant psychopathological symptoms, such as depression, sleep disorders or severe agitation, was collected and reported. However, the studies do not document any difference between those patients treated with memantine and those given a placebo.

Nor did the scientists find a difference with regard to mortality. However, there is not much information on this as the studies were not designed to address this research question.

Memantine does not have any noticeable drug risks

Participants in the memantine group did not withdraw from the trial on account of adverse effects any more frequently than those in the placebo group. Nor was there any difference in the number of patients with (severe) adverse effects. Thus, there were no noticeable drug risks associated with memantine. However, the longest study only ran for 28 weeks, so it is not possible to draw conclusions on long-term effects. In addition, the number of subjects was altogether too low for potential rare side effects to be recorded.

Other family members do not appear to benefit either

IQWiG did not only consider the patients but also their families. However, the study results did not provide any proof that taking memantine reduces their burden, for instance, by lessening the amount of care required or the emotional burden. None of the included studies defined quality of life of the family caregivers as an outcome. The amount of care required was collected in most of the studies, but the majority of the data was not made available by the manufacturers.

Consequently, the present results cannot be reliably interpreted.

Final report takes account of additional, previously unpublished data

IQWiG and its external experts had considerably more data available for the final report than for the preliminary report, in which only 4 studies with a total of 1263 patients could be included. In the course of the submission of comments procedure, the manufacturers submitted previously unpublished study analyses. For the final report, Merz provided subgroup analyses of participants with moderate and severe Alzheimer's disease because in some studies memantine had also been given to patients with mild severity, which was not in compliance with approval when viewed from today's perspective.

Nevertheless, the data pool for the final report is still incomplete. Relevant information is still lacking on 2 more clinical trials with a total of 580 participants. In contrast to the preliminary report, IQWiG has not placed a caveat on the final report because the small amount of information published on these 2 studies, including that disseminated at conferences, suggests that the minimal effects on cognition and activities of daily living would be even less if the missing data were included. There would be no change to the overall result - the lack of proof of benefit.

More research is needed

According to the scientists, the study pool for memantine is still insufficient overall. There is a lack of studies of longer duration that enable the long-term effects of therapy with memantine to be estimated. There is also a lack of research on patients living in nursing homes who suffer from the concomitant diseases typical in this age group. It cannot

be excluded that memantine has a better effect in some patient groups.

"As long as it is not proven that therapies give patients or caregivers a perceptible advantage, it is very difficult to justify continuing to prescribe them when their costs are carried by the general public," comments Peter Sawicki, Director of IQWiG. "The number of elderly people is growing and so are the medical and social problems associated with Alzheimer's disease. I don't think that we will find a simple solution to this problem in the near future. That's why it is important at this stage to provide better social and medical care to patients and to relieve the burden for family caregivers. And it is surely better to 'invest' in this rather than in drugs, where we don't know whether they actually provide a benefit."

Report preparation procedure

IQWiG published the preliminary results in the form of the preliminary report in August 2008 and interested parties were invited to submit comments. When the comments stage ended, the preliminary report was revised and sent as a final report to the contracting agency, the Federal Joint Committee, in July 2009. Documentation of the written comments and minutes of the oral debate are published in a separate document simultaneously with the final report. The report was produced in collaboration with external experts.

Source: Institute for Quality and Efficiency in Health Care