swiss medical board

Combination therapy compared to monotherapy for moderate to severe Alzheimer's Disease

Summary

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Background

Alzheimer's disease is a serious neurocognitive disorder which is characterized by a progressive decline of cognitive functions and memory. The resulting disabilities are severe enough to limit independent daily living. Most patients suffer from Alzheimer's disease due to a variety of genetic factors (sporadic form). The onset of the sporadic form of the disease occurs mostly beyond the age of 60.

The WHO considers dementia as a priority in public health. It has been estimated that about 110'000 people living in Switzerland in 2011 suffered from dementia. Alzheimer's disease is one of the most frequent causes of dementia and thus plays a large role in Switzerland.

Cholinesterase inhibitors are given for mild to moderate dementia (Mini-Mental State Examination score of a maximum of 30 to 10), while memantine is given for moderate to severe dementia. Both substances can be co-administered in dementia of intermediate severity (Mini-Mental State Examination score 19 to 10). In contrast to the practice in most other European countries, the Swiss mandatory basic health insurance only covers either a cholinesterase inhibitor or memantine but not the combination therapy.

In clinical practice in Switzerland both substances are being given in combination, most of the time with the more expensive drug being reimbursed by the basic health insurance and the cheaper one being paid by the patient. Clinicians' perception is that the combination therapy is well tolerated, that cholinesterase inhibitors may even have less adverse events in combination with memantine than given alone, that the symptoms are improved, and that nursing home placement is delayed.

Aim

The aim of this HTA report is to assess

- the effectiveness and safety,
- the cost-effectiveness and budget impact,
- legal as well as ethical implications

of the combination therapy with memantine and a cholinesterase inhibitor compared to monotherapy with a cholinesterase inhibitor or memantine in patients with moderate to severe Alzheimer's Disease and Mini-Mental State Examination score (MMSE) of 19 or less.

Clinical effectiveness and safety

For this HTA report, the clinical effectiveness and safety of combination therapy compared to monotherapy were assessed. The search was conducted in June 2016 and filters for randomised controlled studies (RCT) were used. Study characteristics and results of the included studies were presented per RCT in tables and summarized descriptively. The main focus of the analysis was the combined results either at short-term (closest to 6 months, but <9 months) or long-term follow-up (longest available time point). Risk of bias was assessed according to the Cochrane Handbook and the quality of evidence was assessed according to GRADE for short- and long-

term follow-up. Where possible, outcome results were summarized quantitatively in a meta-analysis by using inverse variance models assuming random effects. Effect estimates (summary and single for each trial) with corresponding 95% confidence interval were presented as forest plots. Relative risks were calculated for binary outcomes. Continuous outcomes were presented as mean differences. In case of considerable heterogeneity, methodological and clinical factors that might explain the heterogeneity were explored in subgroup and sensitivity analyses when possible. Some of the pre-specified subgroup/sensitivity analyses were the familial form of Alzheimer's disease versus the sporadic form of Alzheimer's disease, moderate versus severe Alzheimer's disease, or patients treated in care facilities (i.e. living in a hospital, nursing home facility) versus patients treated in ambulatory care (i.e. living in the community). Further subgroup/sensitivity analyses addressed combination therapy with a dose of memantine of ≤10 mg versus a combination therapy with a dose of memantine of >10 mg, or oral versus transdermal application (transdermal patch) of cholinesterase inhibitors

Nine RCTs fulfilled the inclusion criteria. Seven RCTs compared combination therapy with cholinesterase inhibitor monotherapy, one RCT (Shao 2015) compared combination therapy with memantine, and one RCT (DOMINO-AD) compared combination therapy with both, cholinesterase inhibitor and memantine monotherapy. For all but one RCT (Wilkinson 2012), data were extracted for the short-term follow-up. Only one study (DOMINO-AD) reported outcomes at short- and long-term follow-up. Five studies (Araki 2014, DOMINO-AD, Grossberg 2013, Herrmann 2013, Tariot 2004) included a mix of patients with moderate to severe Alzheimer's disease and four studies (EXPECT, Porsteinsson 2008, Shao 2015, Wilkinson 2012) included patients with moderate Alzheimer's disease.

Combination therapy vs. cholinesterase inhibitors monotherapy

Eight RCTs compared combination therapy vs. cholinesterase inhibitor monotherapy. One RCT reported on the critical outcome of time to nursing home placement and found no statistically significant effect for this outcome at long-term follow-up. Time to nursing home placement was not reported at short-term follow-up, but the probability of nursing home placement, which was not significantly different, was reported. Combination therapy had statistically significantly better effects on the critical outcomes of cognition and activities of daily living at short-term follow-up, but not at long-term follow-up. There were also statistically significantly better effects of combination therapy on the critical outcomes of clinical global impression and behavioural and psychological symptoms of dementia at short-term follow-up. No study reported on these outcomes at long-term follow-up. There was no significant difference in the important outcome of withdrawal from study at short-term follow-up, whereas at long-term follow-up statistically significantly more patients withdrew from combination therapy. The risk of adverse events was statistically significantly higher with combination therapy at short-term follow-up, whereas at long-term follow-up there was no significant difference. Combination therapy had statistically significantly better effects on the important outcome of caregiver burden or distress at short-term follow-up; no study reported on caregiver burden or distress at long-term follow-up. No study was included in the meta-analysis on the important outcome of quality of life.

The **overall quality of evidence** was judged to be very low because of the very low quality of evidence for the critical outcome of delay in nursing home placement at long-term follow-up.

Combination therapy vs. memantine monotherapy

Two RCTs compared combination therapy vs. memantine monotherapy. One study reported on the critical outcome of time to nursing home placement. This outcome was not reported at short-term follow-up and combination therapy had no statistically significant effect on this outcome at long-term follow-up. Combination therapy had no statistically significant effect on the critical outcomes of cognition and activities of daily living at short-term or long-term follow-up. Also, the critical outcomes of clinical global impression, and behavioural and psychological symptoms of dementia were not reported. There was no statistically significantly difference in the important outcome of withdrawal from study at long-term follow-up; no study reported on withdrawal at short-term follow-up. There was no statistically significantly difference in adverse event occurrence at short- and long-term follow-up. No study reported extractable data on caregiver burden or distress and quality of life.

The **overall quality of evidence** was judged to be very low because of the very low quality of evidence for the critical outcome of delay in nursing home placement at long-term follow-up and the absence of RCT data at short-term follow-up.

Significant uncertainties remain regarding critical outcomes at short- and long-term, especially nursing home placement, because little or no data were available

Cost-effectiveness and budget impact analyses

Relevant databases including Medline, Embase, the Cochrane Library, the Centre for Review and Dissemination (CRD) database, and the UK National Health Service's Economic Evaluation Database (NHS EED) were systematically searched for relevant articles on the costs and cost-effectiveness of combination therapy of cholinesterase inhibitor and memantine, compared to cholinesterase inhibitor or memantine monotherapy, for patients with Alzheimer's disease. Quality of reporting was assessed against the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist. For international studies, qualitative transferability to Switzerland was assessed as described in the methods. In the case of studies classified as qualitatively transferable to Switzerland, direct medical costs data were adapted to improve comparability in three distinct steps: correction for different levels of resource utilisation, for different prices of healthcare services, and for change in level of resource utilisation and prices over time. Subsequently, adapted incremental cost-effectiveness ratios (ICERs) were calculated.

Budget impact was addressed by updating a previous Swiss study published by Pfeil et al. Total drug costs were estimated for 2016.

Five cost-effectiveness analyses published between 2007 and 2015 were finally eligible for inclusion in this report and were assessed using the CHEERS checklist. Two studies were performed in the US, one in Canada, one in France and one in Switzerland. All studies compared combination therapy of memantine and cholinesterase inhibitor with cholinesterase inhibitor monotherapy, i.e. there were no comparisons with memantine monotherapy. Three studies included patients with mild-to-moderate Alzheimer’s disease, whereas the US studies included moderate-to-severe Alzheimer’s disease patients. The cost-effectiveness was assessed as cost per quality-adjusted life year (QALY) gained, over time horizons ranging from three years to

lifelong. All studies reported results from the societal perspective. Four of five studies also reported results from a healthcare payer perspective.

All studies modelled treatment effects in terms of institutionalization rates and impact on quality of life (utility). The impact of complications, adverse events and treatment discontinuation on costs and QALYs was not explicitly included in the analyses. The same mortality rates were applied with both treatment strategies, which implies an assumption of no difference in mortality.

All study results adapted to Switzerland indicated combination therapy compared to cholinesterase inhibitor monotherapy to be cost-saving (dominant) from both the societal and healthcare payer perspectives. These very favourable results appeared to be inconsistent with the results reported in the clinical effectiveness domain. The clinical assessment reported only limited advantages of combination therapy over cholinesterase inhibitor monotherapy. One main driver of this inconsistency was the sources available to estimate the effectiveness of the interventions in the cost-effectiveness analyses. The clinical assessment was based exclusively on relatively recent randomized controlled trials. In these trials, information on the outcomes of nursing home placement and quality of life, which were of key relevance for the cost-effectiveness analyses, was extremely sparse. The inputs for the cost-effectiveness analyses were also extracted from other types of studies (i.e. cohort studies and cross-sectional studies). These studies were generally older and, where applicable, more in favour of combination therapy. In addition, the cost-effectiveness analyses involved, to a varying degree, indirect derivations of effect estimates. The validity of these approaches and of the available cost-effectiveness results remains difficult to judge in the presence of substantial uncertainties and against a background of sparse effectiveness data.

The budget impact analysis from the societal perspective indicated that total drug costs in Switzerland might have reached close to CHF 18.8 million in 2016 if combination therapy was consistently used. The total drug costs of cholinesterase inhibitor monotherapy would have reached CHF 14.6 million. In comparison with previous cost estimations for 2010 published by Pfeil et al., we identified a 13% decrease in total drug costs due to a significant reduction in drug prices in the last few years. Concerning overall healthcare costs, Pfeil et al. estimated the costs of Alzheimer's disease in 2009 in Switzerland to be CHF 4.18 billion. Assuming an annual increase in healthcare costs of 5% (as estimated by CSS insurance, which is based on the Pfeil et al.), Alzheimer's disease-related healthcare costs would have reached CHF 5.87 billion in 2016. Total medication costs of a magnitude of CHF 20 million would thus have accounted for less than 0.5% of the total healthcare costs of Alzheimer's disease.

Legal aspects

The starting point of the legal analysis was the pertinent provisions of the Federal Swiss Health Insurance Act (HIA). The HIA establishes a system of compulsory social health insurance for all Swiss residents.

Art. 1a (2) (a) HIA defines illness as any impairment of physical or mental health not caused by an accident that makes a medical examination or treatment necessary or results in an inability to work. It is generally recognized that Alzheimer's disease is an impairment of mental health not caused by an accident; therefore, it qualifies as an illness according to the official legal definition.

Art. 25 HIA regulates the benefits covered by the SHI in the case of illness. Alzheimer's disease treatments are usually medication-based. These costs are principally reimbursed by the social health insurance. However, there is a legally valid limitation on monotherapies because combination therapies are, according to the available clinical evidence, not sufficiently efficient, appropriate and economical (wirksam, zweckmässig und wirtschaftlich).

Therefore, the legal considerations lead to rather sobering conclusions. It is evident that the costs for medication-based Alzheimer's therapies are reimbursed by the social health insurance. However, there is a legally valid limitation on monotherapies which is difficult to overcome because the trials do not provide sufficiently conclusive evidence as to a therapeutic advantage of combination therapies over monotherapies. In addition, the applicable law is based on a rather narrow concept of cost-effectiveness which does not sufficiently take into consideration overall costs for the social insurance system or for society at large. Only clear evidence that the use of combination therapies delays costly placement in a nursing home or similar institution could result in the successful removal of the limitation on monotherapies.

Assessment of ethical issues

The evidence for the ethical assessment was reviewed based on:

- issues which became apparent during scoping and in subsequent discussions during assessment;
- a systematic analysis of possible ethical issues based on three grids;
- a literature search in PubMed and EBSCO for ethical issues associated with combination therapy for Alzheimer's disease using keywords associated with these terms, followed by screening of resulting titles, abstracts and papers. As recommended by EUnetHTA, this literature search was complemented by a reflective process of literature consultations on ethical issues associated with other, more studied, situations or technologies that pose similar issues.

The purpose of the ethics component of the assessment phase is to yield a series of questions, issues and comments to be integrated during ethical evaluation in the appraisal phase.

The main ethical issues identified in this assessment are difficulties associated with the integration of uncertain results, the value of affected outcomes and marginal clinical benefits, the distribution of benefits, decision making support, balancing values in coverage, and when to stop.

Based on the data identified in this report, the evaluated benefits of combined therapy are qualitatively limited, modest, and come with greater side effects. Combination therapy for Alzheimer's disease thus raises the issue of clinical meaningfulness and whether interventions with low added value should be covered or not.

In practice (whether or not combination therapy is reimbursed by health insurance), family members and caregivers will often need to decide on behalf of patients whether or not it should be implemented. Any recommendation to cover combination therapy should come with a recommendation as to how to support informed decision-making in individual cases. This support should include information on the direct and indirect costs.