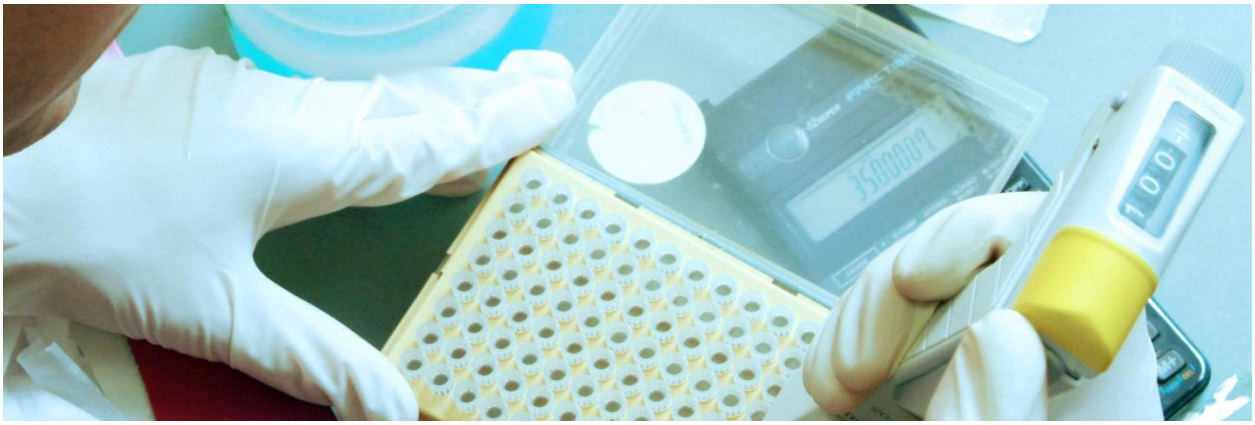
swiss medical board

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



Summary of the Appraisal Report

September 1st, 2017

Alzheimer's disease is one of the most prevalent forms of dementia and is characterised by a progressive decline in cognitive function that can lead to loss of independence and the need for admission to a nursing home. Disease stages range from mild (Mini-Mental State Examination score 26 -21) to moderate (20 - 10) and severe (<10). Cholinesterase inhibitors are approved for mild to moderate disease and memantine for moderate to severe disease. In clinical practice, both medications are being prescribed in combination frequently. The Swiss statutory health insurance currently only covers monotherapy with either a cholinesterase inhibitor or memantine. Two applications from a drug manufacturer to also cover combination therapy were rejected by the Federal Office of Public Health (FOPH) in 2012 due to insufficient evidence of effectiveness and appropriateness.

This Appraisal Report examined the evidence on effectiveness, safety and cost-utility of combination therapy compared to monotherapy for patients with moderate to severe Alzheimer's disease. It did not compare monotherapy with no therapy. In the preceding assessment randomised controlled trials were considered for effectiveness and safety while using the GRADE approach for summarizing and appraising the evidence. For the overall appraisal and to reach recommendations we used the Evidence to Decision framework to document all judgements and considerations. Stakeholder input was taken into account during scoping and appraisal.

Nine RCTs were included, seven comparing combination therapy with cholinesterase inhibitor monotherapy, one with memantine monotherapy and one including both comparisons. Most RCTs assessed outcomes during short–term follow-up (up to 9 months) only. Due to sparse data on the comparison between combination therapy and memantine monotherapy, we mainly focused on combination therapy versus cholinesterase inhibitor monotherapy. After short-term follow-up there was statistically significant improvement in cognition, activities of daily living, clinical global impression and caregiver burden or distress. Fewer outcomes were assessed during long-term follow up. Delay in nursing home placement was analysed in one study and for long-term follow-up only, with no difference found between groups. There were more adverse events reported with combination therapy during short-term but not during long-term follow-up. Withdrawal from study was more frequent with combination therapy in the long-term but not the short-term follow-up. Data on quality of life were not reported. The overall quality of the evidence was very low.

The cost-utility analyses favoured combination therapy, assuming that it leads to a deferral of nursing home placement. However, the Appraisal Committee regarded the evidence of resource requirements as inconclusive. In addition, the potential gains were very small. Other factors, such as health equity, feasibility and acceptability, were also considered. They did not greatly influence the appraisal because their content was based mostly on assumptions.

The close balance between benefits and harms and the limited confidence in the estimated effects and cost-utility led the Appraisal Committee to issue the following recommendations:

Recommendations

We recommend not to use combination therapy (as compared to monotherapy) in the pharmacological treatment of patients with moderate to severe Alzheimer's disease (Conditional recommendation against the intervention). This is in line with the current policy of the FOPH.

1. **Justification**: The benefits and harms of combination therapy are closely balanced and the confidence in the effect estimates is limited. The Appraisal Committee judged that the small short-term benefits observed with combination therapy do not outweigh the potential harms. If there are no gains from delayed nursing home placement combination therapy is more costly.

2. **Implementation considerations**: Physicians should discuss with patients or their caregivers, if the patient is incompetent, and weight the possible benefits and harms of pharmacological treatment options. Shared decision making of patients, their caregivers and health professionals should include communication about (i) the limited evidence supporting either combination therapy or monotherapy, (ii) the need to consider individual aspects such as adherence to daily medication and perceived importance of any gains in terms of overall quality of life, and (iii) information on costs. Some patients or their caregivers might be willing to try combination therapy in order to gain some beneficial effects, at least in the short term. They might choose to stop it if any undesirable effects become serious or frequent. If such undesirable effects are not serious, the case-by-case assessment might also take into account the patient's comorbidities and other medications. Patients may wish to continue combination therapy if they improve in important or critically important outcomes without major undesirable effects.

3. **Monitoring and evaluation**: When a patient with moderate to severe Alzheimer's disease receives combination therapy, the individual response should be monitored and evaluated regularly to determine whether it should be continued or stopped.

4. **Research priorities:** More long-term studies are needed, especially assessing any effect on delays in nursing home placement, as well as patient-important outcomes such as cognition and quality of life.