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

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Swiss Medical Board
Stampfenbachstrasse 30
Postfach, 8090 Zürich

Geschäftsstelle
Susanna Marti C.

Telefon +41 43 259 24 79
info@medical-board.ch
www.medical-board.ch
Appraisal Committee of the Swiss Medical Board

- Nikola Biller-Andorno, Prof. Dr. med. Dr. phil., Direktorin des Instituts für Biomedizinische Ethik und Medizin-geschichte, Universität Zürich
- Stefan Felder, Prof. Dr. rer. pol., Ordinarius für Health Economics, Universität Basel
- Stephan Harbarth, Prof. Dr. méd., Service Prévention et Contrôle de l'Infection, Hôpitaux Universitaires de Genève
- Maria C. Katapodi, Prof. Dr. PhD, RN, FAAN Pflegewissenschaft, Medizinische Fakultät Universität Basel
- Christoph A. Meier, Prof. Dr. med., CMO - Ärztlicher Direktor, Universitätsspital Basel
- Urs Metzger, Prof. Dr. med. Dr. h.c., em. Chefarzt Chirurgie, Stadtspital Triemli, Zürich
- Brigitte Tag, Prof. Dr. iur. utr., ordentl. Professorin für Strafrecht, Strafprozessrecht und Medizinrecht, Universität Zürich
- Martin Tramèr, Prof. Dr. méd., Médecin chef du Service d'Anesthésiologie, Directeur Département APSI, Hôpitaux Universitaires de Genève

Scientific secretariat:
- Erik von Elm, Dr. med. MSc, Codirecteur Cochrane Suisse & Chef-de-clinique Unité d'évaluation des soins, Institut Universitaire de Médecine Sociale et Préventive (IUMSP), Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne
- Thomy Tonia, MSc, Collaboratrice scientifique, Cochrane Suisse & Unité d’évaluation des soins, Institut Universitaire de Médecine Sociale et Préventive (IUMSP), Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne
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Executive summary

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 assessment because their content was mostly based 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 a conditional recommendation not to use combination therapy (as compared to monotherapy) in the pharmacological treatment of patients with moderate to severe Alzheimer’s disease.

The full recommendations can be found on pages 12 and 13 of this report.
1. Background

Dementia corresponds to a group of neurocognitive disorders that come with a marked decline of cognitive function, compared to an earlier level, in one or more domains such as attention, executive functions, learning and memory, speech, perceptual-motor ability and social cognition. The limitations can be serious enough to lead to a loss of independence and a need for admission to a nursing home.\textsuperscript{1, 2}

The World Health Organisation (WHO) considers dementia as a priority in public health.\textsuperscript{3} Alzheimer’s disease – either on its own or in combination with other diseases – is one of the most frequent forms of dementia. It is the most prevalent type of dementia in Switzerland and worldwide. It has been estimated that, in 2011, about 110’000 people living in Switzerland suffered from dementia. The Swiss Federal Office of Public Health (FOPH) has established the “National dementia strategy 2014-2019”, which aims to “support those affected by dementia and promote their quality of life while consistently taking their individual circumstances into account.”\textsuperscript{4}

Mild dementia corresponds to a Mini-Mental State Examination (MMSE) score of 26 to 21 (maximum 30); moderate dementia to a MMSE score of 20 to 10 and severe dementia to a MMSE score of less than 10. Of note, definitions of MMSE cut-off values for disease severity vary slightly between sources.\textsuperscript{5, 6} On average, the MMSE score of a person with Alzheimer’s disease declines about two to four points each year.\textsuperscript{6}

Cholinesterase inhibitors are a pharmacological treatment option for mild to moderate dementia and include donepezil, galantamine and rivastigmine. Memantine is given for moderate to severe dementia. Both substances are approved for the treatment of dementia of moderate severity. In clinical practice it appears that both medications are being prescribed in combination frequently. In an earlier study,\textsuperscript{7} prescription data from France were used because detailed prescription data for Switzerland were not available: about 19% of Alzheimer’s disease patients with pharmacotherapy had received combination therapy. Clinicians’ experience suggests that (i) the combination therapy is well tolerated, (ii) cholinesterase inhibitors may have less side effects when given in combination with memantine than given alone, and (iii) combination therapy improves symptoms and delays nursing home placement.

The Swiss statutory health insurance only covers monotherapy with either cholinesterase inhibitors or memantine but not the combination therapy. If combined, the more expensive of both drugs is being reimbursed by the health insurance and the cheaper one paid by the patient. In 2011 and 2012, one of the manufacturers of memantine applied twice to the FOPH for a change of this policy i.e. for the cheaper drug to be reimbursed also when given in combination. However, both these applications were rejected because the FOPH regarded the submitted research evidence as insufficient to establish the effectiveness and appropriateness of the combination therapy (for details see supplementary material online).

This report aims to assess the efficacy, safety and cost-utility of combination therapy versus monotherapy for moderate to severe Alzheimer’s disease. Other factors, such as health equity, accessibility and feasibility were also taken into account. Importantly, an assessment of the benefits and harms of monotherapy as compared to no treatment or placebo was not within the scope of this report.

2. Methods

Following the process for HTA reports established by the Swiss Medical Board, its governing body (Trägerverein/ Association responsible) decided to assess the subject of this report after a broad
consultation with stakeholders. This was followed by a scoping process, which led to the refinement of the questions to be answered. Medical societies and other stakeholders were invited to comment on the drafted questions and changes were made accordingly. For each question, potentially relevant outcomes were assessed for their importance from the patient’s perspective (i.e. not important, important or critically important) taking into account the views of clinicians. Only important and critically important outcomes were assessed further. Important outcomes were: withdrawal from the study, adverse events, caregiver burden or distress and general quality of life. Critically important outcomes were: delay in nursing home placement, cognition, activities of daily living, clinical global impression and behavioural and psychological symptoms of dementia.

The Assessment Team conducted systematic searches to identify from the literature the relevant evidence on (i) clinical effectiveness and safety based on randomised controlled trials (RCTs) only and (ii) on health economic data. The retrieved studies were then analysed and evaluated following the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework for the clinical effectiveness and safety domains. For the health economics part, a budget impact analysis for Switzerland was performed. Summary of findings tables were created and included in the final Assessment Report.

The Assessment Report was made publicly available in January 2017, and stakeholders were invited to comment in writing or by attending a hearing in March 2017, at which both the Assessment Team and the Appraisal Committee were present. Next, the Appraisal Committee appraised the synthesized evidence in further face-to-face meetings, taking into account the preceding scoping document, the Assessment Report and the feedback received from stakeholders. The appraisal was done using the Evidence-to-Decision (EtD) framework and included the development of recommendations (see supplementary material). The EtD framework considers several domains such as the balance between desirable and undesirable effects, the quality of the evidence, patients’ and caregivers’ values and preferences, resource requirements, cost-effectiveness, health equity, acceptability and feasibility. The recommendations derived in this framework are formulated as strong or conditional in favour of or against a given intervention or in favour of either the intervention or the comparison.

The present Appraisal Report was prepared between March and August 2017 and is complemented by the following documents, which are available online as supplementary material (www.medical-board.ch):
1. Scoping document,
2. Assessment Report,
3. Stakeholder document,
4. EtD document,
5. Copy of prior topic-related decisions by FOPH,
6. Overview of frequency of adverse events in included studies.

3. Evidence on clinical effectiveness and harm

Overall nine RCTs were included: seven compared combination therapy with cholinesterase inhibitor monotherapy, one with memantine monotherapy and one with both cholinesterase inhibitor and memantine monotherapy. During the scoping process it was decided to regard all outcomes measured up to 9 months as short-term outcomes and those beyond 9 months as long-term outcomes. Seven RCTs assessed outcomes only for the short-term follow-up. One RCT reported outcomes only for the long-term follow-up, while another reported outcomes for both the long- and short-term follow-up. Four studies included patients with moderate Alzheimer’s
disease, while the remaining five\textsuperscript{9, 11, 12, 14, 17} included patients with Alzheimer’s disease ranging from moderate to severe. For more detailed quantitative results, please see the Summary of Findings (SoF) tables in the Appendix 1 and the Assessment Report.

When compared to memantine monotherapy, combination therapy had no significant effect on cognition, activities of daily living and adverse events for either short- or long-term follow-up (see Table 2 in Appendix 1). Delay in nursing home placement was reported in one RCT and for long-term follow-up only; there was no statistically significant benefit with combination therapy. No study reported extractable data on clinical global impression, behavioural and psychological symptoms, caregiver burden, distress or quality of life. Because of the sparse data on the comparison with memantine monotherapy, we focused the appraisal on the evidence for the comparison of combination therapy with cholinesterase inhibitor monotherapy.

3.1 Desirable effects

Evidence

With short-term follow-up, there was a statistically significant improvement in the critically important outcomes of cognition, activities of daily living, clinical global impression, and in the important outcome of caregiver burden or distress. There was no difference in behavioural and psychological symptoms.

For long-term follow-up periods, only the critically important outcomes of cognition, activities of daily living and delay in nursing home placement were reported. There was no difference between both treatment options for these outcomes.

Delay in nursing home placement (critically important outcome) was not reported for short-term follow-up; clinical global impression and behavioural and psychological symptoms (critically important outcomes) were not reported for the long-term follow-up. Quality of life (important outcome) was reported for neither the short-term nor the long-term follow-up.

Additional considerations

Some caution is warranted when interpreting the outcome data for delay in nursing home placement. In the one study that reported this outcome,\textsuperscript{17} there was no difference after a follow-up of up to 48 months. Of note, patients and physicians were unblinded and free to choose the treatment after the first 12 months. The difference in the probability of nursing home placement between combination therapy and cholinesterase inhibitor monotherapy after these first 12 months was not significant (mean difference -0.01, 95% CI -0.15 to 0.13). One of the included studies\textsuperscript{12} reported that 1.1% of patients with combination therapy and 4.8% of patients with monotherapy discontinued the trial due to nursing home placement at 24 weeks. However, there was no information reported about whether the patients who completed the trial were placed in a nursing home.

Judgment

The Appraisal Committee considered that, even if there were some desirable effects with combination therapy as compared to monotherapy, these were relatively small and mostly after short-term follow-up only. For the critically important outcomes, the largest positive effect was an SMD of 0.19 (95% CI 0.03 to 0.35) for cognition (see Table 1 in Appendix 1). In general, a standardized mean difference (SMD) of less than 0.2 is considered a small effect and between 0.2 and 0.5 a moderate effect.\textsuperscript{18} The upper 95% CI limit is 0.35 i.e. closer to moderate while the lower limit is close
to zero. The observed effects are even smaller with the other critically important outcomes such as activities of daily living and clinical global impression.

The biggest effect for important outcomes was on caregiver burden or distress, where there was an improvement in the short term for combination therapy in one RCT (Table 1 in Appendix 1). However, the quality of the evidence was low, partly due to the small sample size. The instrument used was the Zarit Burden Interview. Based on the available information we assumed that there is no established minimal clinically important difference and regarded this as problematic. Consequently, it was difficult to judge whether any reduction of caregiver burden or distress in the study was meaningful. One of the included studies used a different scale (General Health Questionnaire) and reported only estimated average differences across all time points (-0.5, 99% CI -1.3 to 0.3), which were again not statistically significant. In the assessment, these data could not be used for meta-analysis.

3.2 Undesirable effects

Evidence

There were significantly more adverse events reported with combination therapy during short-term follow-up but no difference during long-term follow-up. Withdrawal from study was significantly more frequent with combination therapy in the long term but not in the short term.

Additional considerations

Only scarce information on the nature and severity of adverse events is available from the studies included in the Assessment Report. The reporting of adverse events was inconsistent. For instance, the reported definitions included “all adverse events”, “treatment emergent adverse events” and “serious adverse events”. In order to facilitate the appraisal of the evidence on undesirable effects, the available information was extracted from the publications of the included studies after completion of the Assessment Report and considered by the Appraisal Committee (see supplementary material online). Of five studies reporting the frequency of serious adverse events, three had a higher proportion with monotherapy; however, we refrained from pooling these data. Most adverse events were similar in both groups. With monotherapy, adverse events mentioned in most studies included falls and dizziness and with combination therapy falls and agitation. Adverse events with combination therapy reported in at least two studies were falls, agitation, nausea, weight decrease, dizziness and urinary tract infections. Adverse events with monotherapy reported in at least two studies were falls, agitation, dizziness, urinary tract infection and accidental injury.

It is likely that the incidence and kind of adverse events reported from the included studies differ from what is to be expected in routine clinical practice. According to clinicians who participated in the stakeholder consultation, memantine is generally well tolerated. However, this information was anecdotal rather than based on systematic observation.

Some undesirable effects may become apparent only after the follow-up of RCTs was completed or they are under-reported in general. It is thus possible that they have not been reported in the included studies. In most studies, patients assigned to combination therapy received memantine when they were already on a regimen with a stable dose of a cholinesterase inhibitor. In this case, undesirable effects that may have occurred while patients were titrated to the stable dose of a cholinesterase inhibitor were not accounted for in the analyses. Consequently, the absolute number and diversity of adverse events reported from the included studies might be lower than in clinical routine and likely cover only those resulting from adding memantine. Studies looking at combination
therapy versus memantine alone found significant differences in adverse events neither at short-term nor at long-term follow-up, which strengthens this assumption.

Importantly, withdrawal from a given study cannot necessarily be considered an undesirable effect if the exact reasons are not reported. One should be careful to distinguish withdrawal from a study and withdrawal from an allocated treatment. Both might be due to increased side effects or non-response to the treatment. In addition, any early withdrawal from a study prevents collection of long-term outcome data such as delay in nursing home placement.

Adherence to treatment is another issue that needs to be considered, especially in patients who already take several other drugs. Although an additional medication might be easy to include in the established daily or weekly medication schedule, adherence might become more challenging with progressing dementia, especially outside the care setting of a nursing home.

Judgement

The Appraisal Committee judged that the relative clinical importance of the undesirable effects of combination therapy as compared to monotherapy was small. The relative risk of adverse events during short-term follow-up was 1.09 (95% CI 1.01 to 1.17), but this estimate was irrespective of their severity. The Appraisal Committee’s confidence in this effect was reduced due to risk of bias and indirectness of the included studies.

4. Considerations about the evidence

4.1 Overall quality of the evidence

The overall quality of the evidence was very low for both the comparison of combination therapy with cholinesterase inhibitor monotherapy and with memantine monotherapy. This is because, following the logic of the GRADE approach, the overall quality of the evidence for a given comparison is defined by the lowest quality of evidence for any critically important outcome. For comparison of combination therapy versus cholinesterase monotherapy, this lowest level was “very low” for the outcome “delay in nursing home placement” (see Table 1 in Appendix 1). According to the GRADE approach,20 very low quality of evidence means that the true effect is likely to be substantially different from the estimated effect (i.e. the latter might change substantially if new evidence from high-quality research is added in the future).

4.2 Considerations about patient/caregiver\(^1\) values

Evidence

The Assessment Report did not include a separate literature review focusing on patient or caregiver values. The utility values and estimates for quality-adjusted life years (QALY) and calculation of differences between treatment options from the economic values may be used as indirect evidence. In brief, the lowest estimated QALY difference in the included studies was 0.02752 and the highest 0.26. For details, please see the Assessment Report, sections 4.2.9 and 4.3.

\(^1\) The term “caregiver” is used throughout this report for family members who provide care for the patient and not for healthcare professionals.
Additional considerations

The Appraisal Committee noted that the decisive studies assume mean utility scores of 0.60 for patients not living in nursing homes and of 0.34 for patients in nursing homes. This difference drove the QALY difference between combination therapy and monotherapy. For patients who could avoid or delay nursing home placement due to the combination therapy, the utility difference of 0.26 was heavily biased. Two of the included studies \(^7,21\) used the same probabilities of nursing home placement. After five years, the probability of nursing home placement was estimated at 5.85% with combination therapy and 36.94% with monotherapy, i.e., 6.34 times as high. In the three first of the five years, the probability of nursing home placement was assumed to be zero for the combination therapy and 20% for the monotherapy. These differences could explain the relative high gain in utility with combination therapy. The Appraisal Committee deemed that the magnitude of both the utility and probability estimates do not correspond to the current situation in the Swiss context. It also considered values and preferences of patients and caregiver based on the feedback received from stakeholders. However, there was only little feedback from patient representatives and the Committee had to make their own assumptions. Another point to consider is that in the case of Alzheimer’s disease, the choice of drug treatment is mostly made by the physician in charge; consequently the physicians’ views should also be taken into account.

Uncertainty about and variability in how much people value the outcomes

The Appraisal Committee was quite confident that the outcomes reported in the included studies, such as improvements in cognition, behavioural and psychological symptoms, clinical global impression or quality of life are of great importance for patients and caregivers and more or less valued to the same degree. Furthermore, preventing or reducing undesirable effects is most probably also of great importance for them. It is less certain how much people value the outcome “withdrawal from study”. If it is due to side effects, most people will probably value it to the same extent.

Some variability might exist in how patients and caregivers value any delay in nursing home placement. Whether delaying nursing home placement is perceived as a benefit might depend considerably on the patient’s individual context: aspects such as the financial resources available, the support by and burden of caregivers and the severity of the disease weigh in differently depending on the context. Some outcomes such as the suffering associated with the loss of self might be important to patients but are difficult to capture.\(^22\) Wherever possible they should be taken into consideration in individual decisions about treatment. The Appraisal Committee did not dispose of any information on how much such aspects are valued by the people affected and therefore had to make their own assumptions.

Another uncertainty is whether patients (or caregivers) and health professionals in charge rank the importance of outcomes differently. This needs to be considered when physicians decide on the treatment on behalf of patients or caregivers because they are likely to make their own assumptions about what is best for a patient with dementia. Further, taxpayers might have different values about outcome importance than patients and caregivers.

Judgement

The Appraisal Committee judged that there is some uncertainty and possible variability on how different people value the different outcomes. This uncertainty, however, is not important enough to affect the overall decision.
4.3 Balance between desirable and undesirable effects

Taking into account all the desirable and undesirable effects, the Appraisal Committee deemed that the balance does not favour combination therapy over monotherapy. There are statistically significant differences reported for some desirable effects; however, the Appraisal Committee regarded them as small. In addition, there is very little information on the critically important outcome of delay in nursing home placement. Moreover, with combination therapy there were more undesirable effects reported from several studies with short-term follow-up.

When benefits are marginal, different people might use different thresholds about how much benefit is sufficient to accept the undesirable effects. In Alzheimer’s disease this is further complicated by the fact that most affected patients will not be able to make this judgment for themselves and their family or other caregivers will often need to make it on their behalf.

Judgement

Given the fact that (i) most of the desirable effects were not large; (ii) they were observed mostly during short-term follow-up; and (iii) there was uncertainty about the nature of undesirable effects, the question still remains about whether people would be willing to take the risk of an additional medication which may yield some small improvements in the short term. In addition, given the limited duration of the observed effects and the progressive nature of the disease, physicians might consider from when on further slowing of the disease course may no longer be in the patient’s best interest. This is a standard difficulty associated with care for patients with Alzheimer’s disease.

The reported difference in QALY as reported in the Assessment Report (0.12 to 0.26) was considerable but was based on a strong assumption regarding the probability to be admitted to a nursing home with combination therapy versus monotherapy. The Appraisal Committee suggests that the potential gain in QALY with combination therapy has been over-estimated.

4.4 Considerations about resource requirements

Evidence and additional considerations

The budget impact analysis for Switzerland showed that the total drug cost of cholinesterase inhibitor monotherapy was estimated at CHF 14.6 million in 2016. If combination therapy was included, the total drug costs would be CHF 18.8 million. Due to the reduction in drug prices in the last few years, there was a 13% decrease in total drug costs compared to the previous cost estimates for 2010. It has been suggested that the overall healthcare costs for Alzheimer’s disease including medical treatment and nursing care might reach CHF 5.87 billion. However, the Appraisal Committee doubted that this was a reliable estimate. If true, the share of drug costs would account for less than 0.5%. The updated drug cost estimation for 2016 shows a cost reduction of about CHF 3 million, as compared to 2010. In the context of the overall healthcare costs for Alzheimer’s disease this has been considered a rather negligible benefit.

Quality of the evidence about resource requirements

Most of the data used for cost-utility analyses were not based on RCTs and the sources of effectiveness estimates used in these analyses were limited. In addition, all studies assumed that mortality was identical in both the combination therapy and cholinesterase inhibitor monotherapy groups. We cannot exclude the possibility that patients with a more rapid cognitive decline and early
nursing home placement may have different mortality rates compared to patients who are not placed in a nursing home. Moreover, all the assessed cost-utility studies were funded by drug manufacturers.

Delay in nursing home placement and quality of life were considered key drivers of cost-utility in the economic analyses. However, data on these outcomes was sparse and mostly not based on RCTs. Some studies included in economic analyses were on populations with mild Alzheimer’s disease and varying levels of comorbidities. Furthermore, some of the included studies had methodological limitations. The modelling of QALY differed between the included studies. The included cost-utility analyses did not consider complications, adverse events and treatment discontinuation in the modelling of QALY and costs. This may have favoured combination therapy over cholinesterase inhibitor monotherapy.

Due to the above, the Assessment Committee regarded the quality of the evidence of cost-utility analyses as very low. We cannot be certain that they accurately represent the real resource requirements.

**Does the cost-utility favour the intervention or the comparison?**

The cost-utility analyses favoured combination therapy. However, this was driven by the claimed delay in nursing home entry. The probability of nursing home placement was calculated as 6.3 times smaller with combination therapy. Any real delay of nursing home placement would clearly reduce the overall costs considerably. From the nine studies included in the Assessment Report for clinical effectiveness and safety there was no convincing evidence that combination therapy delays placement in nursing homes. Consequently, the Appraisal Committee was not confident that the dominancy of combination therapy in the cost-utility analyses corresponded to a real effect. It regarded the evidence from the budget impact analysis as inconclusive because the cost share of the combination remained unclear. A hypothetical reimbursement of the combination therapy would most likely increase its use and, so far, this has not been taken into account. In addition, possible effects on costs of other therapies (including non-pharmacological) were not accounted for.

**Judgement**

The Appraisal Committee considered that the evidence for resource requirements does favour neither the combination therapy nor the monotherapy. As the quality of the evidence about the resource requirements is very low, it remained uncertain what savings would be possible in the Swiss context.

**5. Other considerations**

**5.1 Health equity**

**Evidence and additional considerations**

There were no reasons to believe that the relative effectiveness of combination therapy (as compared to any monotherapy) would be different for any disadvantaged patient groups. However, some other factors might cause inequalities between groups: Currently, combination therapy is not reimbursed by the statutory health insurance in Switzerland. Patients who cannot afford to pay out-of-pocket for one drug might be disadvantaged if combination therapy is not given despite their physician regarding it as beneficial. The extra costs might put some of the caregivers in an ethical dilemma. Further, the costs of nursing home placement or support at home might cause inequalities.
between people who can cover them and those who cannot. If a proposed treatment approach (such as combination therapy) can delay the admission to a nursing home even for a short period of time, this could make a big difference to people facing financial challenges.

Patients with comorbidities and related medications might be disadvantaged with combination therapy, as another drug will be added to an already heavy medication schedule. These patients might find it more difficult to adhere to combination therapy and the burden for their caregivers might increase as well.

According to the clinicians that were consulted as stakeholders, the combination therapy sometimes is discontinued soon after nursing home placement - either because of the additional costs or the perception of the physicians in charge that they are not worthwhile and that poly-medications should be avoided.

Judgement

The Appraisal Committee judged that the effect on health equity might vary depending on the context and the individual situation of each patient.

5.2 Acceptability

Evidence and additional considerations

The Assessment did not comprise any analysis of current prescription practice in Switzerland or of the overall prevalence of combination therapy. Based on anecdotal evidence from the consulted physicians and previous estimations, a combination of cholinesterase inhibitor and memantine is prescribed to at least 19% of Alzheimer’s disease patients.

Given the short-term nature and small clinical significance of the observed effects, payers might not be willing to accept the increased drug costs with combination therapy. In addition, patients who are already taking several drugs on a daily basis and their caregivers might not be willing to add yet another one to their routine. Whether potential non-adherence to treatment differs between combination and monotherapy remains unclear.

Judgement

The Appraisal Committee deemed that the combination therapy would probably be acceptable to key stakeholders.

5.3 Feasibility

Evidence and additional considerations

It is not uncommon to prescribe combination therapy to patients with Alzheimer’s disease in Switzerland. This is the case although it is not covered by the statutory health insurance and one drug has to be paid out-of-pocket. The Appraisal Committee was not aware of any reported misuse of combination therapy or any fundamental barriers in accessing the drugs in question.

The legal framework poses some challenges if combination therapy was to be reimbursed through basic health insurance. The current regulatory practice only considers drug prices. This means that postponing the admission to a nursing home (e.g. as a consequence of effective combination therapy) could not be taken into account in the cost-utility evaluation.
Judgement

The Appraisal Committee considers that the implementation of combination therapy is feasible from a practical point of view.

6. Other HTA reports and guidelines

The Institute of Quality and Efficiency in Health Care (IQWIG) in Germany assessed the evidence on treatment with memantine in 2009 and concluded that there is no proof of benefit from memantine therapy for patients with either moderate or severe Alzheimer’s disease, either as a monotherapy or in combination with other drugs.24

In 2011, the National Institute for Health and Care Excellence (NICE) in the UK did not recommend combination treatment with memantine and cholinesterase inhibitors due to a lack of evidence of additional clinical efficacy compared with monotherapy.5

In 2011, a Swedish-American author group recommended that combination therapy should be considered in patients with moderate to severe Alzheimer’s disease. This recommendation, however, was based on inconsistent or low quality evidence.25

The American Psychiatric Association concluded in 2014 that “on the basis of the available evidence, one could justify using both memantine and a cholinesterase inhibitor, using memantine alone, or using a cholinesterase inhibitor alone in treating an individual with Alzheimer’s disease”.26

In a guideline published in 2015 and based on a systematic review and meta-analysis, the European Academy of Neurology made a weak recommendation for the use of a combination therapy in patients with moderate to severe Alzheimer’s disease.27

A current guideline published in 2016 by the German Society of Neurology does not recommend combination therapy.28

A consensus statement from the British Association of Pharmacology published in 2017 states that there is some evidence in support of combination therapy. This statement was mostly based on previously published guidelines.29

7. 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. In addition, combination therapy might be 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.
8. References

Note: References 9-17 are the main papers of the studies included in the Assessment Report.

## 9. Appendix 1 - Summary of Findings tables

### Table 1. Summary of findings - Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer's disease

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Nº of participants (studies) Follow-up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with monotherapy with cholinesterase inhibitors</th>
<th>Difference with combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in nursing home placement - Short-term follow-up (&lt; 9 months) - not reported</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Delay in nursing home placement - Long-term follow-up (≥ 9 months) (NHP)</td>
<td>146 (1 RCT)</td>
<td>📆◯◯◯ VERY LOW a,b</td>
<td>-</td>
<td>-</td>
<td>MD 1.2 lower (16.28 lower to 13.88 higher)</td>
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</tr>
<tr>
<td>Cognition - Short-term follow-up (&lt; 9 months)</td>
<td>2132 (7 RCTs)</td>
<td>📆◯◯◯ LOW cd</td>
<td>-</td>
<td>-</td>
<td>SMD 0.19 higher (0.03 higher to 0.35 higher)</td>
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<tr>
<td>Cognition - Long-term follow-up (≥ 9 months)</td>
<td>343 (2 RCTs)</td>
<td>📆◯◯◯ LOW a,e</td>
<td>-</td>
<td>-</td>
<td>SMD 0.08 higher (0.13 lower to 0.29 higher)</td>
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<tr>
<td>Activities of daily living - Short-term follow-up (&lt; 9 months)</td>
<td>1784 (5 RCTs)</td>
<td>📆◯◯◯ MODERATE f</td>
<td>-</td>
<td>-</td>
<td>SMD 0.1 SD higher (0 to 0.19 higher)</td>
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<tr>
<td>Outcomes</td>
<td>Nº of participants (studies) Follow-up</td>
<td>Quality of the evidence (GRADE)</td>
<td>Relative effect (95% CI)</td>
<td>Anticipated absolute effects</td>
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<tr>
<td><strong>Activities of daily living - Long-term follow-up (≥ 9 months)</strong></td>
<td>145 (1 RCT)</td>
<td>☭✭✭✭ LOW g,h</td>
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<tr>
<td><strong>Clinical Global Impression - Short-term follow-up (&lt; 9 months)</strong></td>
<td>1665 (4 RCTs)</td>
<td>☭✭✭✭ MODERATE i</td>
<td>-</td>
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<tr>
<td><strong>Clinical Global Impression - Long-term follow-up (≥ 9 months) - not reported</strong></td>
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<tr>
<td><strong>Behavioural and psychological symptoms of dementia - Short-term follow-up (&lt; 9 months)</strong></td>
<td>1949 (6 RCTs)</td>
<td>☭✭✭✭ LOW d,j</td>
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<tr>
<td><strong>Behavioural and psychological symptoms of dementia - Long-term follow-up (≥ 9 months) - not reported</strong></td>
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<tr>
<td><strong>Withdrawal - Short-term follow-up (&lt; 9 months)</strong></td>
<td>2092 (6 RCTs)</td>
<td>☭✭✭✭ LOW k,l</td>
<td>RR 0.89 (0.72 to 1.11)</td>
<td>183 per 1.000</td>
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<td></td>
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<td>20 fewer per 1.000</td>
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<td></td>
<td>(51 fewer to 20 more)</td>
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<tr>
<td><strong>Withdrawal - Long-term follow-up (≥ 9 months)</strong></td>
<td>146 (1 RCT)</td>
<td>☭✭✭✭ VERY LOW ab</td>
<td>RR 1.33 (1.14 to 1.55)</td>
<td>712 per 1.000</td>
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<td>235 more per 1.000</td>
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<td></td>
<td>(100 more to 392 more)</td>
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<tr>
<td>Outcomes</td>
<td>Nº of participants (studies) Follow-up</td>
<td>Quality of the evidence (GRADE)</td>
<td>Relative effect (95% CI)</td>
<td>Anticipated absolute effects</td>
<td>Risk with monotherapy with cholinesterase inhibitors</td>
<td>Difference with combination therapy</td>
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<tr>
<td>Adverse events - Short-term follow-up (&lt; 9 months)</td>
<td>2053 (5 RCTs)</td>
<td>★★★★ LOW m,n</td>
<td>RR 1.09 (1.01 to 1.17)</td>
<td>661 per 1.000</td>
<td>59 more per 1.000</td>
<td>(7 more to 112 more)</td>
</tr>
<tr>
<td>Adverse events - Long-term follow-up (≥ 9 months)</td>
<td>146 (1 RCT)</td>
<td>★★★★★ VERY LOW g,o,p</td>
<td>RR 0.87 (0.67 to 1.14)</td>
<td>644 per 1.000</td>
<td>84 fewer per 1.000</td>
<td>(212 fewer to 90 more)</td>
</tr>
<tr>
<td>Care giver burden or distress - Short-term follow-up (&lt; 9 months)</td>
<td>25 (1 RCT)</td>
<td>★★★★ LOW b,q</td>
<td>-</td>
<td>-</td>
<td>MD 18.56 lower</td>
<td>(26.06 lower to 11.06)</td>
</tr>
<tr>
<td>Care giver burden or distress - Long-term follow-up (≥ 9 months) - not reported</td>
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<tr>
<td>Quality of life - Short-term follow-up - not reported</td>
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<tr>
<td>Quality of life - Long-term follow-up - not reported</td>
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</tbody>
</table>

CI: Confidence interval; MD: Mean difference; SMD: Standardised mean difference; RR: Risk ratio.

**Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer’s disease**
GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. The study limitation was very serious because risk of attrition bias was high in 1 study and because patients and physicians were unblinded after the first year of treatment and free to choose the subsequent treatment. No information on the treatments given in this second phase was collected.
b. Imprecision was serious because the total sample size was below the optimal information size (OIS).
c. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 7 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
d. Inconsistency was serious because heterogeneity was high and remained unexplained by sensitivity analysis.
e. The study limitations were serious because risk of attrition bias was unclear in 1 study and high in 1 study; risk of reporting bias was high in 1 study.
f. The study limitations were serious because risk of performance bias was unclear in 1 and high in 1 studies; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 5 studies; risk of reporting bias was unclear in 3 studies.
g. The study limitation was serious because risk of attrition bias was high in 1 study.
h. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and a medium effect (0.5 SD) in favour of combination therapy; in addition the total sample size did appear lower than the optimal information size (OIS).
i. The study limitations were serious because risk of performance bias was unclear in 1 and high in 1 studies; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 4 studies; risk of reporting bias was unclear in 3 studies.
j. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 and high in 1 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 6 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
k. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 2 studies; risk of performance bias was unclear in 2 and high in 1 studies; risk of detection bias was unclear in 3 and high in 1 studies; risk of attrition bias was high in 2 studies; risk of reporting bias was unclear in 4 and high in 1 studies.
l. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and appreciable benefit (relative risk increase greater than 25%) in favour of combination therapy.
m. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 and high in 1 study; risk of detection bias was unclear in 2 and high in 1 studies; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 3 and high in 1 studies.
n. Indirectness was serious because most studies did not report on total adverse events, but treatment emergent adverse events only.
o. Indirectness was serious because the single study (DOMINO-AD) did not report adverse events but reported on SAE including drug errors.
p. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and appreciable benefit (relative risk increase greater than 25%) in favour of combination therapy. the total sample size was lower than the optimal information size (OIS).
q. The study limitations were serious because risk of selection bias (allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 1 study.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>№ of participants (studies) Follow-up</th>
<th>Quality of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
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<tbody>
<tr>
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<td></td>
<td>Risk with monotherapy with memantine</td>
</tr>
<tr>
<td>Delay in nursing home placement - Short-term follow-up (&lt; 9 months) - not reported</td>
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</tr>
<tr>
<td>Delay in nursing home placement - Long-term follow-up (≥ 9 months)</td>
<td>149 (1 RCT)</td>
<td>★★★★★ VERY LOW</td>
<td>-</td>
<td>MD 4.1 months higher (4.73 lower to 12.93 higher)</td>
</tr>
<tr>
<td>Cognition - Short-term follow-up (&lt; 9 months)</td>
<td>234 (2 RCTs)</td>
<td>★★★★★ VERY LOW</td>
<td>-</td>
<td>MD 1.32 higher (0.44 lower to 3.08 higher)</td>
</tr>
<tr>
<td>Cognition - Long-term follow-up (≥ 9 months)</td>
<td>146 (1 RCT)</td>
<td>★★★★ LOW</td>
<td>-</td>
<td>MD 0.8 higher (1.01 lower to 2.61 higher)</td>
</tr>
<tr>
<td>Activities of daily living - Short-term follow-up (&lt; 9 months)</td>
<td>234 (2 RCTs)</td>
<td>★★★★★ VERY LOW</td>
<td>-</td>
<td>SMD 0.06 higher (0.55 lower to 0.68 higher)</td>
</tr>
<tr>
<td>Activities of daily living - Long-term follow-up (≥ 9 months)</td>
<td>146 (1 RCT)</td>
<td>★★★★ LOW</td>
<td>-</td>
<td>SMD 0.22 higher (0.1 lower to 0.55 higher)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Nº of participants (studies) Follow-up</td>
<td>Quality of the evidence (GRADE)</td>
<td>Relative effect (95% CI)</td>
<td>Anticipated absolute effects</td>
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<td>Risk with monotherapy with memantine</td>
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<tr>
<td>Clinical Global Impression - Short-term follow-up (&lt; 9 months) - not reported</td>
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<tr>
<td>Clinical Global Impression - Long-term follow-up (≥ 9 months) - not reported</td>
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<tr>
<td>Behavioural and psychological symptoms of dementia - Short - term follow-up (&lt; 9 months) - not reported</td>
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<tr>
<td>Behavioural and psychological symptoms of dementia - Long - term follow-up (≥ 9 months) - not reported</td>
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<tr>
<td>Withdrawal - Short-term follow-up (&lt; 9 months) - not reported</td>
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<tr>
<td>Withdrawal - Long-term follow-up (≥ 9 months)</td>
<td>149 (1 RCT)</td>
<td>★★★★★ VERY LOW ^ai</td>
<td>RR 0.62 (0.29 to 1.34)</td>
<td>197 per 1.000 75 fewer per 1.000 (140 fewer to 67 more)</td>
</tr>
<tr>
<td>Adverse events - Short-term follow-up (&lt; 9 months)</td>
<td>88 (1 RCT)</td>
<td>★★★★★ VERY LOW ^k,l</td>
<td>RR 1.40 (0.60 to 3.27)</td>
<td>227 per 1.000 91 more per 1.000 (91 fewer to 516 more)</td>
</tr>
<tr>
<td>Adverse events - Long-term follow-up (≥ 9 months)</td>
<td>149 (1 RCT)</td>
<td>★★★★★ VERY LOW ^l,m,n,s</td>
<td>RR 1.07 (0.80 to 1.43)</td>
<td>526 per 1.000 37 more per 1.000 (105 fewer to 226 more)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Nº of participants (studies) Follow-up</td>
<td>Quality of the evidence (GRADE)</td>
<td>Relative effect (95% CI)</td>
<td>Anticipated absolute effects</td>
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<tr>
<td>Care giver burden or distress - Short-term follow-up (&lt; 9 months) - not reported</td>
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</tr>
<tr>
<td>Care giver burden or distress - Long-term follow-up (≥ 9 months) - not reported</td>
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<tr>
<td>Quality of life - Short-term follow-up (&lt; 9 months) - not reported</td>
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<tr>
<td>Quality of life - Long-term follow-up (≥ 9 months) - not reported</td>
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</tbody>
</table>

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**Combination therapy compared to monotherapy with cholinesterase inhibitors for Alzheimer's disease**

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Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

*The study limitation was very serious because risk of attrition bias was high in 1 study and because patients and physicians were unblinded after the first year of treatment and free to choose the subsequent treatment. No information on the treatments given in this second phase was collected.*

*Imprecision was serious because the total sample size was lower than the optimal information size (OIS).
c. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of attrition bias was high in 1 study; risk of reporting bias was unclear in 1 study.

d. Inconsistency was serious because heterogeneity was high.

e. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and an MCID of 2.1 (MMSE) in favour of combination therapy; this is consistent with: the standardized effect estimate (0.38 [0.11, 0.65]) is sufficiently wide to include no effect and a medium effect (0.5 SD). In addition, the total sample size was lower than the optimal information size (OIS).

f. The study limitation was serious because risk of attrition bias was high in 1 study.

g. Inconsistency was serious because heterogeneity was high and the individual point estimates varied into different directions

h. Imprecision was very serious because the 95% CI of the effect estimate is sufficiently wide to include a 0.5 SD either in favour or against combination therapy.

i. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include no effect and a 0.5 SD in favour of memantine and because the total sample size was lower than the optimal information size (OIS).

j. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and an appreciable benefit (relative risk increase greater than 25%) of combination therapy. In addition the event rate was too low.

k. The study limitations were serious because risk of selection bias (random sequence generation and allocation concealment) was unclear in 1 study; risk of performance bias was unclear in 1 study; risk of detection bias was unclear in 1 study; risk of reporting bias was unclear in 1 study.

l. Imprecision was very serious because the 95% CI of the effect estimate is sufficiently wide to include appreciable harm or benefit (relative risk increase greater than 25%) of combination therapy.

m. Indirectness was serious because the single study (DOMINO-AD) did not report adverse events but reported on SAE including drug errors.

n. Imprecision was serious because the 95% CI of the effect estimate is sufficiently wide to include both no effect and an appreciable harm (relative risk increase greater than 25%) of combination therapy. In addition the event rate was too low.