EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease

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Background and purpose: Previous studies have indicated clinical benefits of a combination of cholinesterase inhibitors (ChEI) and memantine over ChEI monotherapy in Alzheimer's disease (AD). Our objective was the development of guidelines on the question of whether combined ChEI/memantine treatment rather than ChEI alone should be used in patients with moderate to severe AD to improve global clinical impression (GCI), cognition, behaviour and activities of daily living (ADL).

Methods: A systematic review and meta-analysis of randomized controlled trials based on a literature search in ALOIS, the register of the Cochrane Dementia and Cognitive Improvement Group, was carried out with subsequent guideline development according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: Pooled data from four trials including 1549 AD patients in the moderate to severe disease stage demonstrated significant beneficial effects of combination therapy compared to ChEI monotherapy for GCI [standardized mean difference (SMD) −0.20; 95% confidence interval (CI) −0.31; −0.09], cognitive functioning (SMD −0.27, 95% CI −0.37; −0.17) and behaviour (SMD −0.19; 95% CI −0.31; −0.07). The quality of evidence was high for behaviour, moderate for cognitive function and GCI and low for ADL. Agreement of panellists was reached after the second round of the consensus finding procedure. The desirable effects of combined ChEI and memantine treatment were considered to outweigh undesirable effects. The evidence was weak for cognition, GCI and ADL so that the general recommendation for using combination therapy was weak.

Conclusions: We suggest the use of a combination of ChEI plus memantine rather than ChEI alone in patients with moderate to severe AD. The strength of this recommendation is weak.

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Introduction

Cholinesterase inhibitors (ChEIs) and memantine, an uncompetitive *N*-methyl-D-aspartate receptor antagonist which was reported to normalize dysfunctional glutamatergic neurotransmission [1], have demonstrated symptomatic efficacy in the treatment of Alzheimer's disease (AD) [2,3]. Treatment for 6 months with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to AD produced improvements in cognitive function, on average 2.7 points on the 70-point ADAS-Cog scale. Benefits were also seen on the global clinical state and on measures of activities of daily living (ADL) and behaviour [2]. Pooled 6 months' memantine data indicate a beneficial effect on cognition of 2.97 points on the 100-point severe impairment battery, and positive effects on clinical impression, ADL and behaviour [3]. In Europe, ChEIs are approved for mild to moderate AD and memantine for moderate to severe AD [4]. Since ChEI and memantine have different and probably complementary modes of action, combination of the two classes of drugs may offer additive beneficial effects to patients with AD [1]. Clinical benefits of a combination of ChEI and memantine have been described in AD patients [5], and the original study that led to registration of memantine was actually designed as add on to ChEI [6]. Previous studies assessed various outcomes including cognitive functioning [6–13], behavioural disturbances [6,7,11–14], ADL [6–10,12,15] and nursing home placement [10]. Three of these studies were open-label investigations [6,10,11] and eight studies reported data from double-blind randomized trials [6,7,9,12–15] with three of them [7,14,15] providing *post hoc* analysis of the original MEM-MD-02 study [6]. All but one study conducted in mild to moderate AD cases [9] described combination therapy as slowing cognitive and functional decline in AD beyond that seen with ChEI monotherapy. Nonetheless the reported benefits of combination therapy were modest and the UK National Institute for Health and Care Excellence (NICE) did not consider the evidence sufficient to recommend the use of dual therapy in AD [16]. The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012 [17] also stated that there is insufficient evidence to recommend for or against the combination of a ChEI and memantine in AD. Nonetheless, there has been only one systematic review on combination therapy for AD [18]. The data of this review suggested a small benefit at 6 months, but the authors found no evidence for sustained effects over longer observational periods [18]. A large controlled clinical trial with 1-year follow-up was published thereafter [12]. Importantly, at this point there exist no clinical recommendations on the use of combination therapy in AD for different clinical outcomes based on systematic assessment of quality of evidence. This led the European Federation of Neurological Societies (EFNS) Scientific Panel on Dementia and Cognitive Neurology and the European Neurological Society (ENS) Subcommittee on Cognitive Neurology which merged in the setting of the European Academy of Neurology to develop guidelines for the concomitant use of ChEI and memantine in AD.

Methods

Guideline development followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [19] in line with the 2012 recommendations for preparation of neurological management guidelines by EFNS scientific task forces [20]. The GRADE approach is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between advantages and disadvantages, and finally judgement about the strength of recommendations [21].

The clinical question

As in any well-conducted research study, the GRADE guideline development addresses well-designed clinical questions. Each clinical question contains the four components known by the acronym 'PICO': patients; intervention; comparison; and the outcome(s) of interest, both beneficial and harmful [21]. Our PICO question was whether a combination of ChEI plus memantine rather than ChEI alone should be used in patients with moderate to severe AD in general and specifically to improve (i) global clinical impression (GCI), (ii) cognitive functioning, (iii) behaviour and (iv) ADL. In line with the GRADE recommendations, when several outcomes are possible for each clinical question the GRADE approach asks panellists to make explicit judgements about the importance of each outcome for making a recommendation [21]. Each panellist was asked to make an explicit judgement in writing using a nine-point scale [21] with scores in the range 7–9 identifying outcomes of critical importance for decision making. Ratings between 4 and 6 characterized important but not critical outcomes and those in the range between 1 and 3 were outcomes of limited importance. The rating of the importance of the different outcomes took place prior to systematic statistical outcome evaluation. Overall, all outcomes were considered to be of critical

importance with the mean of the ratings being 7.9 for ADL, 7.6 for behaviour, 7.3 for cognitive functioning, 6.3 for GCI. The importance of serious adverse events was also rated and obtained a mean score of 6.5.

Search strategy

Trials were identified from a search of ALOIS [22], the specialized register of the Cochrane Dementia and Cognitive Improvement Group, using the search terms 'Alzheimer's disease', 'donepezil', 'E2020', 'Aricept', 'galanthamin', 'galantamine', 'reminyl', 'rivastigmine', 'exelon', 'ENA 713' and 'ENA-713', 'memantine', 'combination therapy' and 'dual therapy'. This register consists of records from major healthcare databases including MEDLINE (Ovid SP), Embase (Ovid SP), PsycInfo (Ovid SP), Cinahl (EBSCOhost) and Lilacs (Bireme). It also searches major trial and pharmaceutical industry trials registers. ALOIS covers all randomized controlled trials of interventions for people with dementia, for people with cognitive impairment and for the improvement of, or prevention of decline in, cognitive function in healthy people. It was created in 2008 and represents a free open-access resource. We found 11 publications related to our PICO question [6–15,23].

Trial inclusion and data extraction

Other than in the study by Schneider *et al.* [24] which included patients with mild cognitive impairment and mild AD, we considered only trials if they included moderate to severe AD patients, assessed at least one of the outcomes defined in our PICO question and followed a randomized double-blind, parallel group design. Seven studies fulfilled these criteria [6,7,9,12,14,15,23]. To avoid duplications we excluded those studies [7,14,15] which represented *post hoc* analysis of the original MEM-MD-02 trial [6], leaving four trials to be included in the analysis [6,9,12,23]. The clinical and demographic characteristics and data on outcomes under investigation were extracted from primary reports. All data were independently extracted by two panellists (EH and RS) and discrepancies were resolved by discussion.

Assessment of the risk of study bias

Based on the description of methodology all included studies were evaluated for random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias that might have been detected during the review process.

Data synthesis and analysis

We performed a meta-analysis to estimate the difference between the group with ChEI and memantine treatment and the group with ChEI monotherapy. The data of each clinical domain (ADL, behaviour, cognitive functioning, GCI), as well as serious adverse events, were pooled separately. In order to be able to pool data from different rating scales within a domain, the standardized mean difference (SMD) was chosen as the effect size**.** The risk difference was calculated for serious adverse events. A random effects meta-analysis with an inverse-variance weighting approach was conducted using the RevMan 5.2 software [25] and yielded a combined SMD/risk difference with a 95% confidence interval (CI) and several measures of heterogeneity (e.g. I^2 index). A GRADE evidence profile [20,26] was created using the GRADEpro software [27] for each clinical domain and serious adverse events.

Determination of the direction and strength of recommendation and consensus finding

Determination of direction and strengths of recommendations was based on the balance between desirable and undesirable effects of combined ChEI and memantine treatment versus ChEI treatment alone, the quality of evidence, values and preferences and costs. For details we refer to the EFNS guidance for preparation of neurological management guidelines [20]. Direction was a recommendation 'for' or 'against' combined ChEI and memantine treatment, and the strength of recommendation had only two levels: 'strong' or 'weak'. Recommendations were given for each outcome. Consensus was reached by use of the Delphi method during which panellists answered a questionnaire, working independently without meeting in person. After each round, RS served as a facilitator and provided an anonymous summary of the panellists' opinions from the previous round, and participants were encouraged to revise their earlier answers in light of the replies from other members of the group.

Results

Study descriptives

Table 1 displays the characteristics of trials that met the criteria for inclusion in the meta-analysis. Three of

Table 1 Baseline characteristics and frequency of serious adverse events of included studies

Trial	Severity of AD	MMSE inclusion range (mean score)	Trial duration (weeks)	Total no. of patients	Treatment groups	No. of patients	No. of SAEs	Mean age	Mean ADL score (score used)	Mean behaviour score (score used)	Mean cognitive score (score used)	Outcomes measured	Scores used
Tariot [6]	Moderate to severe	5–14 (10.1)	24	403	Placebo + AChEI Memantine + AChEI	201 202	25 15	75.5 75.5	35.8 ($ADCS\text{-}ADL_{19}$) 35.5 ($ADCS\text{-}ADL_{19}$)	13.4 (NPI) 13.4 (NPI)	80.0 (SIB) 78.0 (SIB)	ADL Behaviour Cognitive functioning Global clinical impression	$ADCS\text{-}ADL_{19}$ NPI SIB CIBIC-Plus
Porsteinsson[a] [9]	Moderate	Not known[a]	24	302	Placebo + AChEI Memantine + AChEI	148 154	15 11	Not known[a]	Not known[a]	Not known[a]	Not known[a]	ADL Behaviour Cognitive functioning Global clinical impression	$ADCS\text{-}ADL_{23}$ NPI ADAS-Cog CIBIC-Plus
Howard [12]	Moderate to severe	5–13 (9.1)	30	146	Placebo + AChEI Memantine + AChEI	73 73	46 40	77.2 77.5	28.2 (BADLS) 26.9 (BADLS)	22.3 (NPI) 20.3 (NPI)	9.0 (SMMSE) 9.1 (SMMSE)	ADL Behaviour Cognitive functioning	BADLS NPI SMMSE
Grossberg [23]	Moderate to severe	3–17 (10.8)	24	676	Placebo + AChEI Memantine + AChEI	335 341	23 28	76.8 76.2	32.8 ($ADCS\text{-}ADL_{19}$) 33.1 ($ADCS\text{-}ADL_{19}$)	16.5 (NPI) 17.2 (NPI)	75.2 (SIB) 76.8 (SIB)	ADL Behaviour Cognitive functioning Global clinical impression	$ADCS\text{-}ADL_{19}$ NPI SIB CIBIC-Plus

AD, Alzheimer's disease; MMSE, Mini Mental State Examination; SAE, serious adverse event; AChEI, acetylcholinesterase inhibitor; ADL, activities of daily living; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; BADLS, Bristol Activities of Daily Living Scale; NPI, neuropsychiatric inventory; SIB, severe impairment battery; SMMSE, Standardized MMSE; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale. The global clinical impression score CIBIC-Plus (Clinician's Interview-Based Impression of Change Plus Caregiver Input) is a measure of change from baseline, so baseline scores are not given as they are not applicable. [a]The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al*. [28] which does not present the baseline characteristics for this subgroup.

the four trials included patients in the moderate to severe disease stage with Mini Mental State Examination (MMSE) ranges between 5 and 14 [6], 5–13 [12] and 3–14 [23]. One trial included mild to moderate cases in the MMSE range between 10 and 22 [9]. Of this study [9] only those 302 of a total of 433 study participants who were in the moderate stage of AD with MMSE scores between 10 and 20 were included in the current meta-analysis [28]. The DOMINO study [12] included a total of 295 patients but only 146 continued the ChEI treatment. Seventy-three of them received the ChEI plus placebo memantine and another 73 the ChEI plus active memantine. Only these two subgroups were used in our meta-analysis. The total number of participants in the analysis was 1549. Three studies [6,9,12] compared the efficacy and safety of 20 mg memantine per day with placebo in patients on a stable dose of ChEI. One study [23] added a daily dose of 28 mg memantine in its extended release form which is equivalent to a dosage of 20 mg. All included studies used random sequence generation and allocation concealment; participants and personnel concerned with the studies were blinded and there was no evidence for incomplete outcome data and selective reporting. Therefore the risk of study bias was low according to GRADE definitions [20].

Meta-analyses

The results of meta-analyses for pooled pre-defined clinical outcomes across different instruments of assessment using standardization are shown in Figs 1–4. Significant overall benefits of combination therapy over ChEI therapy alone was seen for behaviour (SMD −0.19; 95% CI −0.31; −0.07), cognitive function (SMD −0.27, 95% CI −0.37; −0.17) and GCI (SMD −0.20, 95% CI −0.31; −0.09). There were no overall significant differences between combination and monotherapy in terms of ADL (SMD −0.08, 95% CI −0.18; 0.02). The frequency of serious adverse events was not significantly different between the comparative treatment groups (Fig. 5). As can be seen from the figures I^2 for all outcomes was below 30% indicating consistency of data. However, imprecision of data was indicated for GCI, ADL, cognitive function and serious adverse events because the confidence intervals of some of the included studies were wide (Figs 1, 3 and 5). Additionally, the confidence interval of the overall effect of ADL and serious adverse events contained positive and negative values. The funnel plots for each outcome indicated no publication bias because the study estimates were spread symmetrically around the overall effect estimate (data not shown).

GRADE evidence profile

Figure 6 provides the GRADE evidence profile. Based on the study design and the results of the meta-analysis this evidence profile classifies the quality of evidence in one of four levels ranging from very low to high for the overall underlying literature for each important outcome. The starting level of quality for each outcome was high but for ADL and adverse events it was downgraded to low because the meta-analysis confidence intervals contained positive and negative values and the confidence intervals were wide (Figs 1 and 5). For cognitive functions and GCI downgrading to moderate had to be done due to serious imprecision with wide confidence intervals for effect estimates. No downgrading was needed for behaviour.

Direction and strength of recommendation

Agreement of panellists was reached after the second round of the consensus finding procedure. All panellists agreed already in the first round that, compared to ChEI monotherapy, the desirable effects of combined ChEI and memantine treatment outweigh undesirable effects in patients with moder-

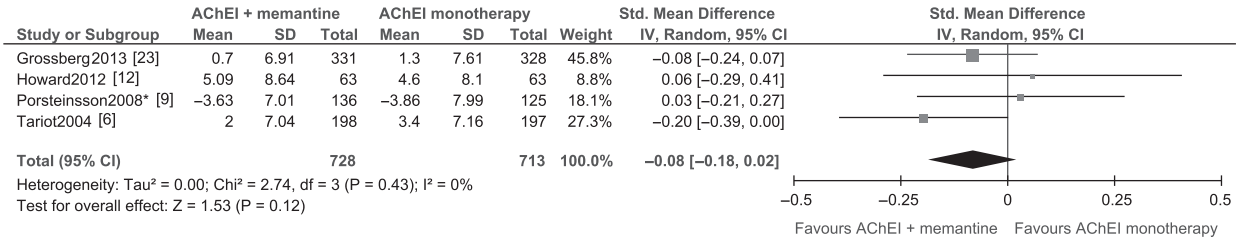

Figure 1 Results of meta-analysis on the effect of combined cholinesterase inhibitor plus memantine treatment versus cholinesterase inhibitor treatment alone on activities of daily living (ADCS-ADL and BADLS). *The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al.* [28]. AChEI, acetylcholinesterase inhibitor; ADCS-ADL, Alzheimer's Disease Cooperative Study - Activities of Daily Living; BADLS, Bristol Activities of Daily Living Scale; Std, standardized.

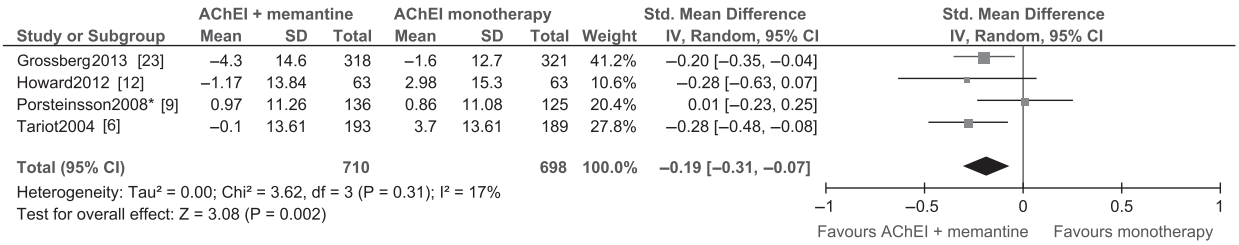

Figure 2 Results of meta-analysis on the effect of combined cholinesterase inhibitor plus memantine treatment versus cholinesterase inhibitor treatment alone on behaviour and mood (NPI). *The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al*. [28]. AChEI, acetylcholinesterase inhibitor; NPI, neuropsychiatric inventory; Std, standardized.

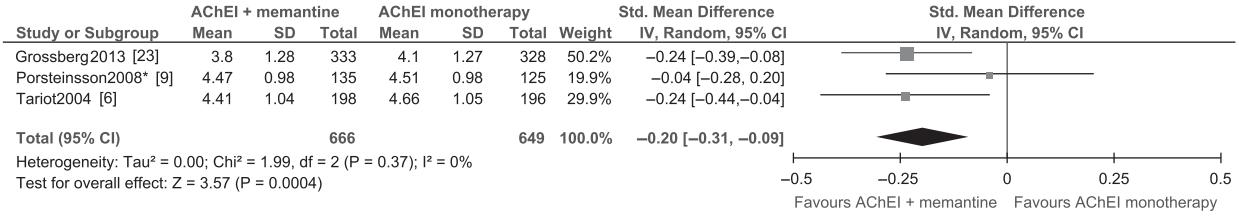

Figure 3 Results of meta-analysis on the effect of combined cholinesterase inhibitor plus memantine treatment versus cholinesterase inhibitor treatment alone on global clinical impression (CIBIC-Plus). *The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al*. [28]. AChEI, acetylcholinesterase inhibitor; CIBIC-Plus, Clinician's Interview – Based Impression of Change plus caregiver input; Std, standardized.

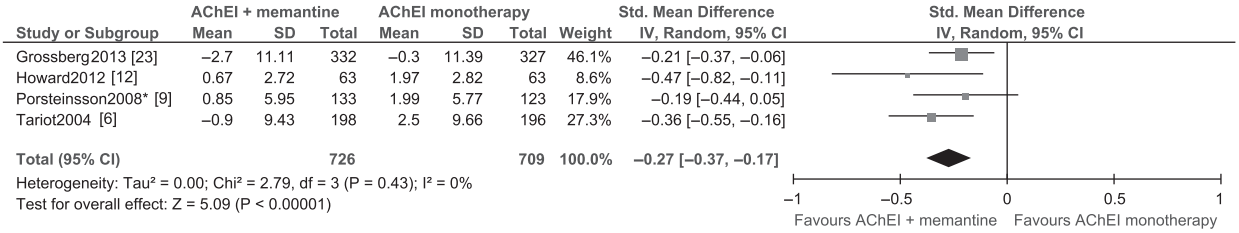

Figure 4 Results of meta-analysis on the effect of combined cholinesterase inhibitor plus memantine treatment versus cholinesterase inhibitor treatment alone on cognitive functioning (ADAS-Cog and SIB). *The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al*. [28]. AChEI, acetylcholinesterase inhibitor; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; SIB, severe impairment battery; Std, standardized.

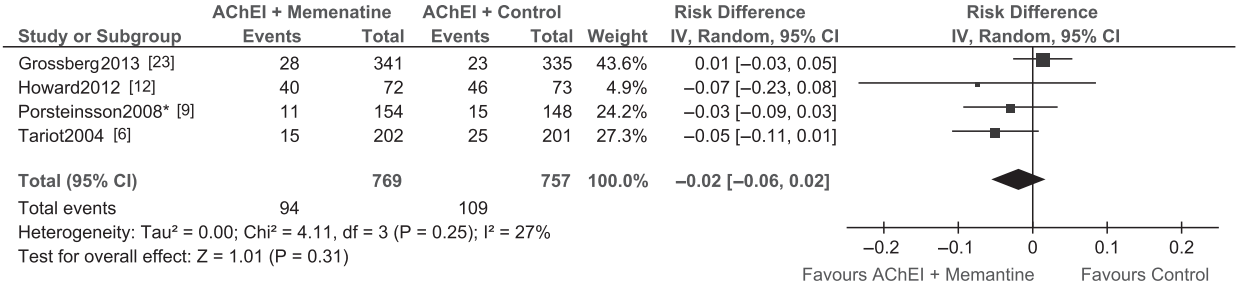

Figure 5 Results of meta-analysis on serious adverse events in patients under combined cholinesterase inhibitor plus memantine treatment versus cholinesterase inhibitor treatment alone. *The data from the subgroup of patients with moderate disease is taken from the meta-analysis by Winblad *et al*. [28]. AChEI, acetylcholinesterase inhibitor; Std, standardized.

ate to severe AD. With one exception there existed also agreement in the first round that the general recommendation in favour of combination therapy is weak. All panellists gave a weak recommendation for ADL, a strong recommendation for behaviour with two exceptions and a weak recommendation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AChEI + memantine	AChEI monotherapy	Relative (95% CI)	Absolute		
Activities of daily living (follow-up 24 -30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	728	713	-	SMD 0.08 lower (0.18 lower to 0.02 higher)	⊕⊕OO LOW	CRITICAL
Behaviour (follow-up 24-30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	710	698	-	SMD 0.19 lower (0.31 to 0.07 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Cognitive functioning (follow-up 24-30 weeks[1]; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	726	709	-	SMD 0.27 lower (0.37 to 0.17 lower)	⊕⊕⊕O MODERATE	CRITICAL
Frequency of serious adverse events (follow-up 24-30 weeks[1])												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	94/769 (12.2%)	109/757 (14.4%)	Risk Difference –0.02 (–0.06 to 0.02)	2 fewer per 100 (from 6 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Global clinical impression (follow-up 24 weeks; Better indicated by lower values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	666	649	-	SMD 0.20 lower (0.31 to 0.09 lower)	⊕⊕⊕O MODERATE	CRITICAL

[1] Tariot2004, Porsteinsson2008 and Grossberg2013: 24 weeks, Howard2012: 30 weeks
[2] Metaanalysis confidence interval contains positive and negative values
[3] Howard2012: wide confidence interval
[4] Wide confidence intervals in individual studies

Figure 6 GRADE evidence profile. Quality, Quality of evidence [20].

for cognition and GCI with three exceptions. In the second round all panellists agreed on recommendations in favour of combined ChEI plus memantine treatments as summarized in Table 2.

Discussion

This meta-analysis suggests a small but significant benefit of combined ChEI plus memantine treatment over ChEI treatment alone on behaviour, cognitive functions and GCI, with no evidence for major differences in the rate of serious adverse events with combination as opposed to monotherapy. These data are in line with a previous systematic review [18], but importantly the current meta-analysis extends previous work [18] by inclusion of recently published data of the DOMINO trial [12] and the data of a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate to severe AD on the effects of combined ChEI treatment and 28 mg memantine [23]. This is the first report on combined ChEI plus memantine treatment in which the GRADE system was used to come up with guidelines for the use of combination therapy in moderately severe cases of AD. Guideline development was based on the opinion of 17 researchers from 12 countries in the setting of the EFNS/ENS dementia panel, and it is thus likely

Table 2 Panellists' recommendations

PICO question	Panellists' unanimous recommendation
Do the desirable consequences of combined treatment in moderate to severe AD outweigh the undesirable ones?	Yes
Strength of recommendation	Weak
Activities of daily living	Weak
Behaviour	Strong
Cognitive functioning	Weak
Global clinical impression	Weak

PICO, population/patient intervention/indicator comparator/control outcome; AD, Alzheimer's disease.

that the opinions expressed represent a European view. All panellists agreed on the fact that the desirable consequences of combined treatment in moderate to severe AD outweigh the undesirable ones. Whilst the final overall recommendation was 'weak', this reflects the GRADE scoring rules [20] which mandate that the final grade reflects the outcome with the lowest quality of evidence. With respect to specific clinical outcomes there was some heterogeneity as to the strength of recommendations among panellists at the first round of consensus finding. Most discrepant views existed regarding cognition and GCI with three of 10 panellists giving a strong recommendation. Although all panellists accepted that the strength of a recommendation may be weak because the GRADE quality rating was poor, it was argued that in the case of cognition and GCI the only reason this was poor was really the imprecision of the estimate, not the quality of the studies. It was emphasized that the most important aim of a meta-analysis is to bring studies together to improve that precision, and the results of the current meta-analysis for cognition and GCI were fairly consistent, which suggests that this quality indicator may not be a particular problem. Despite these arguments all panellists finally agreed to follow the general GRADE approach and gave a weak recommendation for cognition and GCI during the second and final round of consensus finding. There was also general agreement that the recommendation for the use of combined ChEI plus memantine treatment to ameliorate behavioural symptoms in moderate to severe AD should be rated as strong. It is known that ChEIs reduce behavioural symptoms in AD [29]; however, in almost all trials in the current meta-analysis patients were on stable long-term ChEI dosages prior to memantine administration. The beneficial effect on behavioural symptoms occurred in those patients randomized to ChEI plus memantine treatment and not in those randomized to ChEI plus placebo suggesting that the behavioural benefits were attributable to memantine, although an interactive effect between ChEI and memantine on behavioural symptoms cannot be excluded. We were unable to meta-analyse specific Neuropsychiatric Inventory (NPI) domains, but it has been reported that combination therapy particularly affects frontally mediated behaviour including agitation, aggression, irritability, lability and eating [14]. The strong recommendation for behavioural symptoms was further emphasized by the fact that GRADE also includes costs as a determinant of the strength of recommendation. It is well established that behavioural symptoms in patients with AD are associated with higher care costs than in AD patients with no or little behavioural change. A 1-point increase on the NPI, which is a tool to assess dementia-related behavioural symptoms with a maximum score of 144 [30], increases the annual care costs by US$247–409 [31]. Therefore the approximately 3-point difference on NPI between ChEI monotherapy and combination therapy translates into substantial cost savings.

The mechanism(s) by which the combination of ChEI and memantine improves behaviour, cognition and GCI are unclear. The most obvious explanation is potentiation of the individual symptomatic improvements achieved by ChEIs and memantine alone. Views that combination therapy may even have disease-modifying effects have been expressed by several authors [5]; however, a brain magnetic resonance imaging study failed to demonstrate that the change in brain atrophy over time can be attenuated by combined ChEI and memantine treatment [13].

In conclusion, we suggest that the use of a combination of ChEI plus memantine rather than ChEI alone may provide useful benefits in patients with moderate to severe AD. Despite statistically significant differences, the observed treatment effects remain modest in terms of clinical management of individual patients. The strength of the evidence for use of the combination for moderate to severe AD varied between the four domains. It was strong for patients with behavioral symptoms. The overall strength of recommendation was weak

Author contributions

Reinhold Schmidt MD was involved in the planning of the guideline, in trial selection and data analysis, assessment of the risk of study bias, in the consensus finding process and in writing the manuscript. Edith Hofer did the data synthesis and analysis and was part of the consensus finding process. Femke H Bouwman, Katharina Buerger, Charlotte Cordonnier, Jan Laczó, Dorota Religa were involved in the literature search, trial selection and data extraction and participated in the consensus finding process. Tormod Fladby, Daniela Galimberti, Jean Georges, Michael T Heneka, Jakub Hort, José L Molinuevo, John T O'Brien, Philip Scheltens, Jonathan M Schott and Sandro Sorbi were involved in the planning of the guideline, were part of the consensus finding process and manuscript writing. All authors reviewed the manuscript prior to submission.

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