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Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review.

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Abstract

Background – Memantine is licensed for moderate-to-severe AD. NICE guidance does not recommend the use of memantine in combination with cholinesterase inhibitors (AChEI). The underpinning meta-analysis was disputed by the manufacturer.

Objectives – To compare the efficacy of AChEI monotherapy with combination memantine and AChEI therapy in patients with moderate-to-severe AD and to examine the impact of including unpublished data on the results

Design – Systematic review and meta-analysis of randomised controlled trials.

Data sources – The Cochrane Dementia Group trial register, ALOIS, searched for the last time on 3rd May 2011.

Data synthesis – Data from four domains (clinical global, cognition, function, behaviour and mood) were pooled. Sensitivity analyses examined the impact on the NICE-commissioned meta-analysis of restricting data to patients with moderate-to-severe AD and of including an unpublished trial of an extended release (ER) preparation of memantine.

Results – Pooled data from the trials which were included in the NICE-commissioned meta-analysis but which were restricted to moderate-severe AD only, showed a small effect of combination therapy on cognition (SMD = -0.29 [-0.45 to -0.14]). Adding data from an unpublished trial of ER memantine (total 3 trials, 1317 participants) showed a small benefit of combination therapy on global scores (SMD = -0.20 [-0.31 to -0.09]), cognition (SMD = -0.25 [-0.36 to -0.14]) and behaviour and mood (SMD -0.17 [-0.32 to -0.03]) but not function (SMD = -0.04 [-0.21 to 0.13]) at 6 months. No clinical data have been reported from a 1 year trial, although this found 'no significant benefit' on any clinical measures at 1 year.

Conclusions – These results suggest there may be a small benefit of adding memantine to AChEIs at 6 months. However, the impact on clinical global impression depends on exactly which studies are included, and there is no benefit on function, so its clinical relevance is not robustly demonstrated. Currently available information from RCTs indicates no benefit at 1 year. Legislation on the form and content of registry posted results is needed in Europe.

Introduction

Two classes of drugs are licensed by the European Medicines Agency (EMA) for the treatment of Alzheimer's Disease (AD): acetylcholinesterase inhibitors (AChEIs) for mild-to-moderate disease and memantine for moderate (MMSE 10-19) and severe disease (MMSE < 10)[1]. Memantine is a moderate affinity non-competitive NMDA receptor antagonist, which blocks the effects of tonic pathologically elevated levels of glutamate that may lead to neuronal dysfunction. It has a small but consistent effect, but its place in therapy has been controversial in Europe.

Both NICE and IQWiG (the German Institute for Quality and Efficiency in Healthcare) have revised their original conclusions that there was insufficient evidence to recommend memantine as a monotherapy for AD [2,3,4]. Following the release of IQWiQ's original report in 2009[3], the manufacturer of 'Axura' memantine, Merz, submitted a responder analysis, presenting data from two previously excluded, unpublished trials, IE2101 and MD-22. Despite initially stating that this analysis could not be utilized[5], IQWiG revised their conclusion and in 2011 reported that the new data provided proof of a benefit of memantine on cognition in AD[4].

NICE currently recommends the use of memantine in severe disease, or as a 2nd line treatment in moderate disease for patients who are intolerant or have a contraindication to AChEIs. However, it does not recommend the use of memantine in combination with AChEIs, stating that there is 'a lack of evidence of additional clinical efficacy compared with monotherapy'[2]. This contrasts with the conclusions of a recent company-sponsored non-systematic review[6] which asserts that it is 'safe, well-tolerated, and may represent the current gold standard for treatment of moderate-severe AD and possibly mild-to-moderate AD as well'. Memantine does not have a license for mild AD and evidence is lacking for a clinical benefit in this group[7].

In the meta-analysis which informed the guidance (TA217)[8], two trials are included in the analysis of combination therapy[9,10]. Data for cognitive and activities of daily living (ADL)/function outcomes were controversially not pooled on the grounds that different scoring systems were used by the included trials. Pooled analyses in the other domains (global and behavioural) showed no benefit. A further source of dispute was that data from patients with mild AD in one of the trials (MD-12)[10] were included despite the separate availability of data (in Winblad et al 2007 [11]) for just the subgroup of patients with moderate AD, which falls within the licensed indication.

As part of a Cochrane review, we conducted a systematic review, meta-analysis, and sensitivity analyses to examine the impact of these issues and of the inclusion of unpublished data on the efficacy of combination memantine and AChEI therapy in moderate-to-severe AD.

Method

Search methods – ALOIS, the Cochrane Dementia and Cognitive Improvement Group's comprehensive, free access, register of trials[12] which contains records from all relevant sources was searched for the final time on 3rd May 2011. The search terms used were: memantine, D-145, DMAA, DRG-0267, ebixa, abixa, axura, akatinol, memox and namenda. ALOIS is maintained by the Trials Search Co-ordinator and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS
2. Monthly searches of a number of national and international trial registers: ISRCTN; UMIN (Japan's Trial Registry); ICTRP/WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, from Cochrane CENTRAL and from conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information section of the Dementia and Cognitive Improvement Group's website[13].

Additionally, the clinical trials registries of Lundbeck, Forest, and the Japanese registry the Japanese Pharmaceutical Information Centre (JAPIC), the websites of the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), NICE and press releases of manufacturers (Lundbeck, Merz, Forest, Suntori, Asubio, Daiichi), and all conference posters of studies sponsored by Merz, Lundbeck and Forest presented in 2004-2009 were studied in detail. Authors and companies were contacted directly with requests for missing information. A full account of the search strategy is available in the full Cochrane review from which this paper is drawn.

Trial inclusion criteria – Trials were included if they were (1) double-blind, parallel group, placebo-controlled, randomized trials of memantine in which AChEIs were permitted in patients with moderate to severe AD, (2) sample selection criteria were specified and diagnosis used established criteria (e.g. DSM or ICD criteria) and (3) outcome instruments were specified.

Data extraction – We extracted clinical and demographic characteristics and outcome data relating to patients with moderate and severe AD from the trial reports and, where not available from primary reports, from a published meta-analysis[11]. The data were extracted independently by at least two people and discrepancies were resolved by discussion. The outcomes of interest were clinical global impression, cognitive function, functional performance in activities of daily living (ADL) and mood and behavioural disturbance. These were assessed using instruments including the Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC-plus), the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) and Severe Impairment Battery (SIB), the Alzheimer Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale (19 and 23-item) and the Neuropsychiatric Inventory (NPI), respectively.

Data synthesis and analysis - Data from the four clinical domains were pooled and a random effects model was used to estimate differences between groups. Effect sizes were presented as standardised mean differences (SMD) – the absolute mean difference divided by the standard deviation – with 95% confidence intervals (CIs) and P values, calculated using Revman 5.0 software[14]. This meant that data could be pooled when different rating scales (e.g. SIB and ADAS-Cog) were used to assess the same outcome. In the TA217

assessment report, all effect sizes were presented as weighted mean differences (WMD), and data was not pooled when included trials used different rating scales. In this review, we have replicated the findings of the TA217 report for comparison, presenting them first as WMDs (as in the original report) in Analysis 1a, and then as SMDs in Analysis 1b.

Sensitivity analyses were performed to examine the effect sizes in the NICE-commissioned Assessment Report[8] in comparison with those derived from all available data, as follows.

1a – Replication of TA217 Assessment Report analysis, presented as weighted mean differences (WMDs)

1b – Replication of TA217 Assessment Report analysis, presented as standardised mean differences (SMDs) for comparison

2 – Pooled data from trials included in the TA217 Assessment Report, presented as standardised mean differences (SMDs), excluding data from patients with mild disease

3 – As in 2, but from all trials meeting our inclusion criteria

Results

Description of studies – 5 trials were identified (MD-02[9], MD-12[10], MD-50[15], Lu10112[16], DOMINO-AD[17]) that met inclusion criteria, of which 3 (MD-02[9], MD-12[10] and MD-50[15]) were included in this meta-analysis. Two of these were included in the TA217 Assessment Report analysis of memantine combination therapy [9, 10]. Of these trials, one was of patients with moderate-severe disease (MMSE range 5-14, average score 10.0)[9], and one of mild-moderate disease (MMSE range 10-22, average score 16.9)[10]. Data for the subgroup of patients with moderate AD were available through a published company-sponsored meta-analysis[11]. MD-50[15] studied an extended release preparation of 28mg/day, which has recently been granted a license by the FDA[18] but is not currently marketed in the US, is not licensed in Europe, and would have been ineligible for inclusion in the NICE meta-analysis.

Two 12 month trials of combination therapy were also identified. First, a randomised controlled trial (Lu10112[16]), of 277 patients with moderate AD in which the primary was an imaging outcome, and in which 72% of patients were taking an AChEI, was completed in February 2009. A conference poster in September 2009 [19] and a registry posting in May 2010[16] did not report details of important clinical data (ADAS-Cog, NPI, time to institutionalisation) but reported that there was no significant benefit of memantine on these measures at 12 months. The cut-off point for inclusion in the TA217 meta-analysis was March 2010 [8]. Total brain atrophy rates were greater in those taking combination therapy than in those taking memantine alone[19]. Secondly, the DOMINO-AD trial[17], which includes comparison of mono- and combination therapy, is due to report shortly.

Participants – The total number of participants was 1317. All patients were diagnosed with Alzheimer's disease, classed as mild, moderate or severe disease based on their MMSE score. See Table 1 for the baseline characteristics of participants.

Interventions – MD-02 and MD-12 compared the efficacy and safety of 20mg/day memantine in patients receiving stable treatment with donepezil. MD-50 studied an extended release preparation of 28mg/day, equivalent to 20mg daily in patients receiving a stable dose of any cholinesterase inhibitor.

Outcome measures – The primary outcomes of interest were clinical global impression, cognitive function, functional performance in activities of daily living, and behavioural and mood disturbance. MD-02 assessed these using CIBIC-Plus, SIB, ADCS-ADL_{19}, and NPI respectively. MD-12 used CIBIC-Plus, ADAS-Cog, ADCS-ADL_{23} and NPI, and MD-50 used CIBIC-Plus, SIB, NPI and ADCS-ADL_{19}.

Quality of included studies – The commercially sponsored studies conducted after 1993 are likely to have conformed to GCP standard, and to have been at low risk of bias with regards their sequence generation, allocation concealment and methods of blinding. In the included studies, the characteristics of the treatment and placebo groups were well-balanced at baseline (see table). The risk of bias of the included studies was judged to be low as indicated in the 'risk of bias' tables in the main Cochrane Review from which this systematic review is derived.

Results of individual studies – Of the three included studies, MD-02[9] showed a significant benefit of combination therapy compared with AChEI monotherapy on cognition, activities of daily living, global outcome and behaviour. Combination therapy was well tolerated. MD-12[10] showed no advantage of combination therapy compared with AChEI monotherapy in any domain in the overall group of patients with mild as well as moderate disease. There were no significant differences in safety or tolerability between the two groups. Data from the subset of patients in MD-12[10] with moderate disease was taken from the Winblad et al 2007[11] meta-analysis. MD-50[15] showed a statistically significant improvement from combination therapy with memantine ER on cognition, global improvement and behaviour, but not function, after 6 months compared with AChEI alone. Memantine ER was well tolerated.

Results of synthesis of studies - The synthesis of data from trials of memantine combination therapy is summarised in Table 2. When data from the two trials[9, 10] which were included in the TA217 meta-analysis[8] were pooled, but data from patients with mild disease were excluded and data from the same domain but different instruments were pooled using SMDs, there was a small but significant benefit of memantine combination therapy on cognition, but not on any other outcome. When data from the memantine ER trial (MD-50[15]) was also pooled, the small benefit on cognition persisted (SMD = -0.25 [-0.36, -0.14]), and there were also small, significant benefits of combination therapy on the global improvement score (SMD = -0.20 [-0.32 to -0.09]) and on behaviour and mood (SMD = -0.17 [-0.32 to -0.03]) but not on function (SMD = -0.04 [-0.21 to 0.13]).

Figure 1 – Clinical Global (CIBIC-plus)

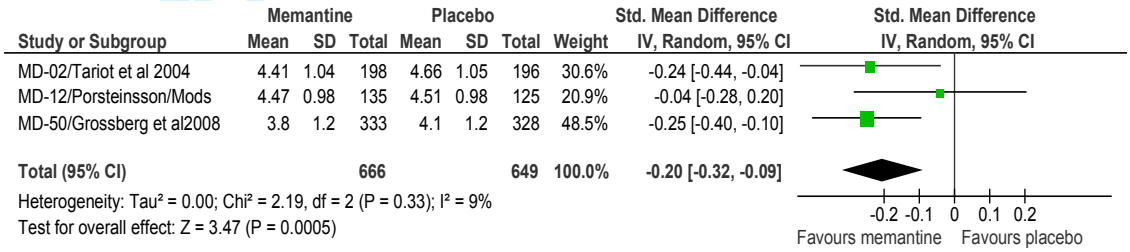

Figure 2 – Cognition (ADAS-Cog and SIB)

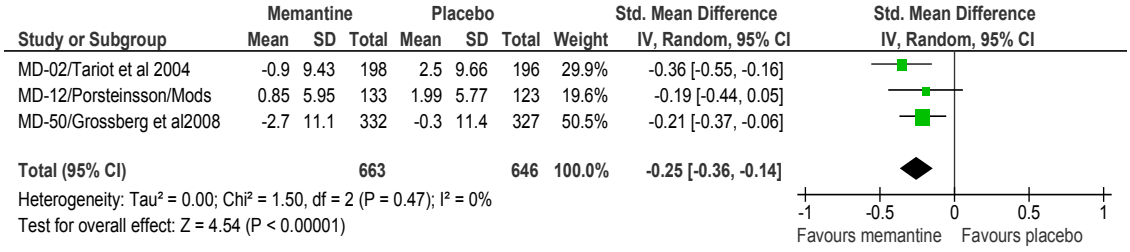

Figure 3 – Function (ACDS-ADL$_{19}$ and ADCS-ADL$_{23}$)

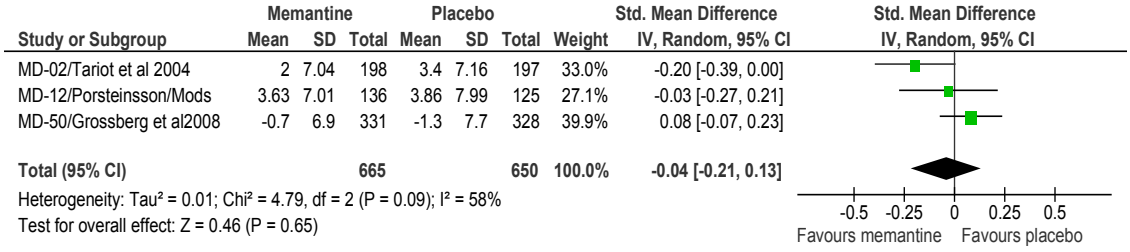

Figure 4 – Behaviour and mood (NPI)

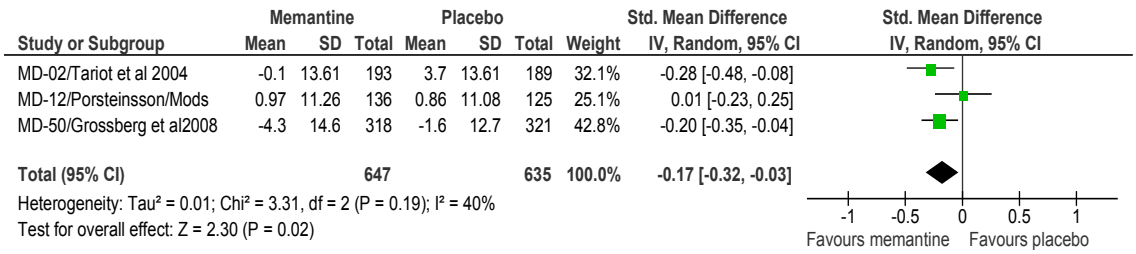

Table 1 – Characteristics of included studies (including baseline characteristics of participants)

Trial	MMSE inclusion range (mean score)	Trial Duration	Total no. of patients	No. of patients in Placebo + AChEI and Memantine + AChEI groups		Mean age	Mean cognitive score (score used)	Mean function score (score used)	Mean behaviour/mood score (NPI)
MD-02 /Tariot et al 2004 [9]	Moderate-severe AD 5-14 (10.0)	24 weeks	403	Placebo + AChEI	203	75.5	80.0 (SIB)	35.8 (ADCS-ADL_{19})	13.4
				Memantine + AChEI	201	75.5	78.0 (SIB)	35.5 (ADCS-ADL_{19})	13.4
MD-12 /Porsteinsson et al 2008 [10]	Mild-moderate AD 10-22 (16.9)	24 weeks	433	Placebo + AChEI	216	76.0	26.8 (ADAS-Cog)	54.8 (ADCS-ADL_{23})	12.3
				Memantine + AChEI	217	74.9	27.9 (ADAS-Cog)	54.7 (ADCS-ADL_{23})	11.8
MD-12 /Porsteinsson et al 2008[10] – Subgroup with moderate disease, from Winblad 2007[11]	Moderate AD	24 weeks	302	Placebo + AChEI	148	Not known*	Not known*	Not known*	Not known*
				Memantine + AChEI	154	Not known*	Not known*	Not known*	Not known*
MD-50 /Grossberg et al 2008[15]	Moderate-severe AD 3-14 (10.8)	24 weeks	697	Placebo + AChEI	355	Not known†	Not known†	Not known†	Not known†
				Memantine + AChEI	342	Not known†	Not known†	Not known†	Not known†

The global score, CIBIC-Plus, is a measure of change from baseline, so baseline scores are not given as they are not applicable.

*The data from the subgroup of patients with moderate disease is taken from the Winblad 2007 meta-analysis[11], which does not present the baseline characteristics for this subgroup.

†The baseline characteristics of patients in this unpublished study are not given

Table 2 – Memantine Combination Therapy (Results of synthesis of data)

Analysis no. and description **Trials included - code (LOCF/OC data)**	**Efficacy Domain**							
	Clinical Global		**Cognition**		**Function**		**Behaviour + Mood**	
	SMD/WMD (95% CI)	**P-value**	**SMD (95% CI)**	**P-value**	**SMD/WMD (95% CI)**	**P-value**	**SMD/WMD (95% CI)**	**P-value**
Analysis 1 – Trials included in the TA217 Assessment Report, data presented as WMDs: MD-02[9] (LOCF data) MD-12[10] (LOCF data)	WMD = - 0.140 [-0.346, 0.066]	P = 0.182	Data not pooled		Data not pooled		WMD = -1.715 [-5.733, 2.302]	P = 0.403
Analysis 1b – Trials included in the TA217 Assessment Report, data presented as SMDs: MD-02[9] (LOCF data) MD-12[10] (LOCF data)	SMD = -0.14 [-0.33, 0.06]	P = 0.16	SMD = -0.16 [-0.54, 0.23]	P = 0.43	SMD = -0.10 [-0.28, 0.08]	P = 0.27	SMD = -0.13 [-0.42, 0.17]	P = 0.41
Analysis 2 – Trials included in the TA217 Assessment Report. Data from patients with mild AD excluded. Data pooled within domains (SMDs): MD-02[9] (LOCF data) MD-12 (OC data, from Winblad 2007 [11])	SMD = -0.15 [-0.35, 0.04]	P = 0.12	SMD = -0.29 [-0.45, -0.14]	P = 0.0002	SMD = -0.13 [-0.29, 0.03]	P = 0.11	SMD = -0.14 [-0.42, 0.14]	P = 0.32
Analysis 3 - All trials meeting our inclusion criteria, data from patients with mild disease excluded: MD-02[9] (LOCF data) MD-12 (OC data, from Winblad 2007 [11]) MD-50[15] (LOCF data)	SMD = -0.20 [-0.32, -0.09]	P = 0.0005	SMD = -0.25 [-0.36, -0.14]	P < 0.00001	SMD = -0.04 [-0.21, 0.13]	P = 0.65	SMD = -0.17 [-0.32, -0.03]	P = 0.02

Discussion

This systematic review and meta-analysis suggests a small but significant benefit of memantine combination therapy on cognitive, global and behaviour measures, but not on function/ADL, when data from all included trials, including one trial of ER memantine, were pooled. When data from the trials included in the TA217 meta-analysis, but from patients with moderate-severe disease only, were pooled there was a small, significant benefit of combination therapy on cognition (SMD = 0.29). This effect size is comparable to that seen for memantine monotherapy. However, since the impact on clinical global impression depends on exactly which studies are included, and there is no benefit on function, the clinical relevance of combination therapy is not robustly demonstrated.

Clinical data from a negative one year trial, which would have been available at the time of the NICE meta-analysis, remains unpublished. The DOMINO study[17] is due to report shortly. Whether pooling of these one year studies would show a robust effect on clinical global remains to be seen.

Data for moderate AD patients from one trial[10] were only available as observed case (OC) data[11] and it was necessary to pool these with the last observation carried forward (LOCF) data from the other trials[9, 15] which is not methodologically ideal. In the full Cochrane review, this strategy was shown to have no material effect on results. The LOCF treatment of missing data is a conservative approach because dropout rates are equivalent, or slightly favour memantine. Consideration of the cost-effectiveness of combination AChEI and memantine was outside the scope of this review.

To the extent that we found a significant benefit of combination therapy on cognition, our analyses of the available data contrast with the findings of the TA217 Report[8] which found no evidence of additional benefit of combination therapy. The explanations given by the Peninsula Technology Assessment Group (PenTAG) for not pooling data from the same clinical domain ('it is not valid to synthesize these data on their original scales'[8]) or for not restricting analyses to data from the licensed patient subgroup ('The upper range of the MMSE scores for the participants of this study was 20.37… …this was only minimally over the threshold of 20 (so we) include(d) this study…')[20] remain controversial.

The inclusion of unpublished registry data on the ER preparation extends the evidence of benefit of combination therapy at 6 months. The dose of 28mg memantine in this preparation was designed to be equivalent to 20mg daily of the currently marketed preparation[21]. However, the trend for an adverse effect on ADL may account for the fact that these data have not been published in peer review literature. Although there is biological plausibility to the possibility of dose-related adverse effects of memantine[22] and memantine is associated with more rapid neurological decline in cognitively impaired patients with multiple sclerosis [23, 24], memantine is well tolerated over 6 months, with slightly fewer dropouts in the memantine than placebo arms, and long term open label follow-up studies do not suggest an obvious safety signal [25, 26, 27]. There are no long term randomised placebo-controlled studies to address this issue directly.

Nevertheless, we find the benefit of combination therapy to be less convincing than other reviewers [6], primarily because important data are missing from registry posting of trial results. Posting of clinical data is not mandatory for trials sponsored by companies who are not the Marketing Authorisation Holder in the US. However, the fact that clinical data have not been released from the 12 month trial Lu10112[16] is disturbing for two reasons. First, cerebral atrophy rates were greater in those taking combination therapy than in those taking memantine alone[19]. Whilst the presented analysis suggests that this unexpected finding of increased atrophy was attributable to the AChEI rather than the memantine, there is no information about whether this is reflected in the clinical domains. Second, the reason given for not posting the clinical data is revealing: sponsors who are not marketing authorisation holders in the US are not obligated by US public Law 110-85. This law mandates the posting of defined clinical data items on registries within a year of study completion.

The greatest benefit of registries is ensuring the timeliness of the release of results. Without this, there are obvious incentives to delay the release of negative data until as close to the end of patent life as possible. However, registries are likely to become the preferred repository of incomplete or negative data. This makes it particularly important that harmonising legislation specifies in detail which clinical data must be posted. Furthermore, until there is harmonisation onto a single registry, such as clinicaltrials.gov, systematic reviews should routinely include comprehensive searches across all registries.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS -			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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BMJ open

Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review

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Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a Systematic Review.

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Competing Interest Declaration - All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that they have had no financial support or other relationships or activities that could appear to have influenced this work.

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Abstract

Background – Memantine is licensed for moderate-to-severe AD. NICE guidance does not recommend the use of memantine in combination with cholinesterase inhibitors (AChEI). The underpinning meta-analysis was disputed by the manufacturer.

Objectives – To compare the efficacy of AChEI monotherapy with combination memantine and AChEI therapy in patients with moderate-to-severe AD and to examine the impact of including unpublished data on the results

Design – Systematic review and meta-analysis of randomised controlled trials.

Data sources – The Cochrane Dementia Group trial register, ALOIS, searched for the last time on 3rd May 2011.

Data synthesis – Data from four domains (clinical global, cognition, function, behaviour and mood) were pooled. Sensitivity analyses examined the impact on the NICE-commissioned meta-analysis of restricting data to patients with moderate-to-severe AD and of including an unpublished trial of an extended release (ER) preparation of memantine.

Results – Pooled data from the trials which were included in the NICE-commissioned meta-analysis but which were restricted to moderate-severe AD only, showed a small effect of combination therapy on cognition (SMD = -0.29 [-0.45 to -0.14]). Adding data from an unpublished trial of ER memantine (total 3 trials, 1317 participants) showed a small benefit of combination therapy on global scores (SMD = -0.20 [-0.31 to -0.09]), cognition (SMD = -0.25 [-0.36 to -0.14]) and behaviour and mood (SMD -0.17 [-0.32 to -0.03]) but not function (SMD = -0.04 [-0.21 to 0.13]) at 6 months. No clinical data have been reported from a 1 year trial, although this found 'no significant benefit' on any clinical measures at 1 year.

Conclusions – These results suggest there may be a small benefit at 6 months of adding memantine to AChEIs. However, the impact on clinical global impression depends on exactly which studies are included, and there is no benefit on function, so its clinical relevance is not robustly demonstrated. Currently available information from RCTs indicates no benefit of combination therapy over monotherapy at 1 year. Legislation on the form and content of registry posted results is needed in Europe.

Introduction

Two classes of drugs are licensed by the European Medicines Agency (EMA) for the treatment of Alzheimer's Disease (AD): acetylcholinesterase inhibitors (AChEIs) for mild-to-moderate disease and memantine for moderate (MMSE 10-19) and severe disease (MMSE < 10)[1]. Memantine is a moderate affinity non-competitive NMDA receptor antagonist, which blocks the effects of tonic pathologically elevated levels of glutamate that may lead to neuronal dysfunction. It has a small but consistent effect, but its place in therapy has been controversial in Europe.

Both NICE and IQWiG (the German Institute for Quality and Efficiency in Healthcare) have revised their original conclusions that there was insufficient evidence to recommend memantine as a monotherapy for AD [2,3,4]. Following the release of IQWiQ's original report in 2009[3], the manufacturer of 'Axura' memantine, Merz, submitted a responder analysis, presenting data from two previously excluded, unpublished trials, IE2101 and MD-22. Despite initially stating that this analysis could not be utilized[5], IQWiG revised their conclusion and in 2011 reported that the new data provided proof of a benefit of memantine on cognition in AD[4].

NICE currently recommends the use of memantine in severe disease, or as a 2nd line treatment in moderate disease for patients who are intolerant or have a contraindication to AChEIs. However, it does not recommend the use of memantine in combination with AChEIs, stating that there is 'a lack of evidence of additional clinical efficacy compared with monotherapy'[2]. This contrasts with the conclusions of a recent company-sponsored non-systematic review[6] which asserts that it is 'safe, well-tolerated, and may represent the current gold standard for treatment of moderate-severe AD and possibly mild-to-moderate AD as well'. Memantine does not have a license for mild AD and evidence is lacking for a clinical benefit in this group[7].

In the meta-analysis which informed the guidance (TA217)[8], two trials are included in the analysis of combination therapy[9,10]. Data for cognitive and activities of daily living (ADL)/function outcomes were controversially not pooled on the grounds that different scoring systems were used by the included trials. Pooled analyses in the other domains (global and behavioural) showed no benefit. A further source of dispute was that data from patients with mild AD in one of the trials (MD-12)[10] were included despite the separate availability of data (in Winblad et al 2007 [11]) for just the subgroup of patients with moderate AD, which falls within the licensed indication.

As part of a Cochrane review, we conducted a systematic review, meta-analysis, and sensitivity analyses to examine the impact of these issues and of the inclusion of unpublished data on the efficacy of combination memantine and AChEI therapy in moderate-to-severe AD.

Method

Search methods – ALOIS, the Cochrane Dementia and Cognitive Improvement Group's comprehensive, free access, register of trials[12] which contains records from all relevant sources was searched for the final time on 3rd May 2011. The search terms used were: memantine, D-145, DMAA, DRG-0267, ebixa, abixa, axura, akatinol, memox and namenda. ALOIS is maintained by the Trials Search Co-ordinator and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS
2. Monthly searches of a number of national and international trial registers: ISRCTN; UMIN (Japan's Trial Registry); ICTRP/WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL)
4. Six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, from Cochrane CENTRAL and from conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information section of the Dementia and Cognitive Improvement Group's website[13].

Additionally, the clinical trials registries of Lundbeck, Forest, and the Japanese registry the Japanese Pharmaceutical Information Centre (JAPIC), the websites of the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), NICE and press releases of manufacturers (Lundbeck, Merz, Forest, Suntori, Asubio, Daiichi), and all conference posters of studies sponsored by Merz, Lundbeck and Forest presented in 2004-2009 were studied in detail. Authors and companies were contacted directly with requests for missing information. A full account of the search strategy is available in the full Cochrane review from which this paper is drawn.

Trial inclusion criteria – Trials were included if they were (1) double-blind, parallel group, placebo-controlled, randomized trials of memantine in patients with moderate to severe AD who were taking AChEIs , (2) sample selection criteria were specified and diagnosis used established criteria (e.g. DSM or ICD criteria) and (3) outcome instruments were specified.

Data extraction – We extracted clinical and demographic characteristics and outcome data relating to patients with moderate and severe AD from the trial reports and, where not available from primary reports, from a company-sponsored meta-analysis which was conducted during the European regulatory review process [11]. The data were extracted independently by at least two people and discrepancies were resolved by discussion. The outcomes of interest were clinical global impression, cognitive function, functional performance in activities of daily living (ADL) and mood and behavioural disturbance. These were assessed using instruments including the Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC-plus), the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog) and Severe Impairment Battery (SIB), the Alzheimer Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale (19 and 23-item) and the Neuropsychiatric Inventory (NPI), respectively.

Data synthesis and analysis - Data from each of the four clinical domains were pooled separately and a random effects model (DerSimonian-Laird) was used to estimate differences between groups. Effect sizes were presented as standardised mean differences (SMD) – the absolute mean difference divided by the standard deviation – with 95% confidence intervals (CIs) and P values, calculated using Revman 5.0 software[14]. This

meant that data could be pooled when different rating scales (e.g. SIB and ADAS-Cog) were used to assess the same outcome. In the TA217 assessment report, all effect sizes were presented as weighted mean differences (WMD), and data was not pooled when included trials used different rating scales. In this review, we have replicated the findings of the TA217 report for comparison, presenting them first as WMDs (as in the original report) in Analysis 1a, and then as SMDs in Analysis 1b.

Sensitivity analyses were performed to examine the effect sizes in the NICE-commissioned Assessment Report[8] in comparison with those derived from all available data, as follows.

1a – Replication of TA217 Assessment Report analysis, presented as weighted mean differences (WMDs)

1b – Replication of TA217 Assessment Report analysis, presented as standardised mean differences (SMDs) for comparison

2 – Pooled data from trials included in the TA217 Assessment Report, presented as standardised mean differences (SMDs), excluding data from patients with mild disease

3 – As in 2, but from all trials meeting our inclusion criteria

Results

Description of studies – 5 trials were identified (MD-02[9], MD-12[10], MD-50[15], Lu10112[16], DOMINO-AD[17]) that met inclusion criteria, of which 3 (MD-02[9], MD-12[10] and MD-50[15]) were included in this meta-analysis. Of these, MD-02 and MD-12 were included in the TA217 Assessment Report analysis of memantine combination therapy [9, 10]. One trial (MD-02[9]) was of patients with moderate-severe disease (MMSE range 5-14, average score 10.0), and one (MD-12[10]) was of mild-moderate disease (MMSE range 10-22, average score 16.9). Data for the subgroup of patients in MD-12 with moderate AD were available through a published company-sponsored meta-analysis[11]. MD-50[15] studied an extended release preparation of 28mg/day, which has recently been granted a license by the FDA[18] but is not currently marketed in the US, is not licensed in Europe, and would have been ineligible for inclusion in the NICE meta-analysis.

Two 12 month trials (Lu10112[16], DOMINO-AD[17]) of combination therapy that met trial inclusion criteria were excluded from this review. First, a randomised controlled trial (Lu10112[16]), of 277 patients with moderate AD in which the primary was an imaging outcome, and in which 72% of patients were taking an AChEI, was completed in February 2009. A conference poster in September 2009 [19] and a registry posting in May 2010[16] did not report details of important clinical data (ADAS-Cog, NPI, time to institutionalisation) but reported that there was no significant benefit of memantine on these measures at 12 months. The cut-off point for inclusion in the TA217 meta-analysis was March 2010 [8]. Total brain atrophy rates were greater in those taking combination therapy than in those taking memantine alone[19]. Secondly, data were not yet available from the DOMINO-AD trial[17], which includes comparison of mono- and combination therapy and is due to report shortly.

Participants – The total number of participants was 1317. All patients were diagnosed with Alzheimer's disease, classed as mild, moderate or severe disease based on their MMSE score. See Table 1 for the baseline characteristics of participants.

Interventions – MD-02 and MD-12 compared the efficacy and safety of adding 20mg/day memantine with placebo in patients receiving stable treatment with donepezil (an AChEI). MD-50 compared the efficacy and safety of adding an extended release preparation of 28mg/day memantine, equivalent to 20mg daily, with placebo in patients receiving a stable dose of any cholinesterase inhibitor.

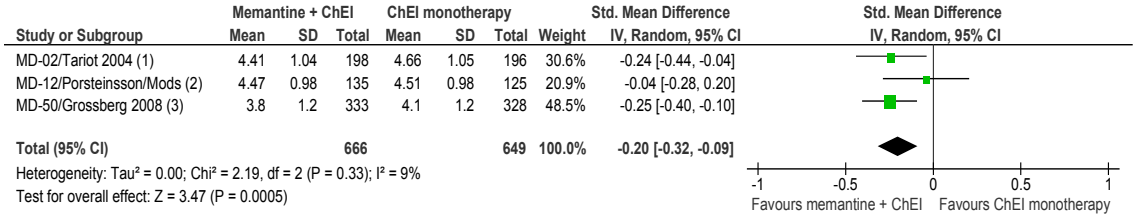
Outcome measures – The primary outcomes of interest were clinical global impression, cognitive function, functional performance in activities of daily living, and behavioural and mood disturbance.

Quality of included studies – The commercially sponsored studies conducted after 1993 are likely to have conformed to GCP standard, and to have been at low risk of bias with regards their sequence generation, allocation concealment and methods of blinding. In the included studies, the characteristics of the treatment and placebo groups were well-balanced at baseline (see table). The risk of bias of the included studies was judged to be low as indicated in the 'risk of bias' tables in the main Cochrane Review from which this systematic review is derived.

Results of individual studies – Of the three included studies, MD-02[9] showed a significant benefit of combination therapy (memantine plus AChEI) compared with AChEI monotherapy on cognition, activities of daily living, global outcome and behaviour. Combination therapy was well tolerated. MD-12[10] showed no advantage of combination therapy compared with AChEI monotherapy in any domain in the overall group of patients with mild as well as moderate disease. There were no significant differences in safety or tolerability between the two groups. Data from the subset of patients in MD-12[10] with moderate disease was taken from the Winblad et al 2007[11] meta-analysis. MD-50[15] showed a statistically significant improvement from combination memantine ER plus AChEI therapy compared with AChEI monotherapy ER on cognition, global improvement and behaviour, but not function, after 6 months. Memantine ER was well tolerated.

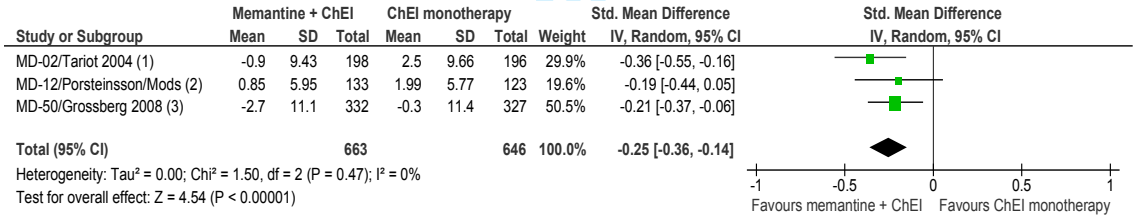
Results of synthesis of studies - The synthesis of data from trials of memantine combination therapy is summarised in Table 2. Analysis 1a shows the analysis conducted in TA127. Analysis 1b shows that had TA127 pooled cognitive and functional data across different instruments using standardisation, there would still have been no domains where combination therapy was significantly better than AChEI monotherapy. Analysis 2 shows the impact of excluding data from patients mild disease: there was a small (SMD=-0.29 [-0.45,-0.14], significant benefit of memantine combination therapy on cognition, but not on any other outcome. The most inclusive analysis, analysis 3, shows that when data from the memantine ER trial (MD-50[15]) was also pooled, the small benefit on cognition persisted (SMD = -0.25 [-0.36, -0.14]), and there were also small, significant benefits of combination therapy on the global improvement score (SMD = -0.20 [-0.32 to -0.09]) and on behaviour and mood (SMD = -0.17 [-0.32 to -0.03]) but not on function (SMD = -0.04 [-0.21 to 0.13]).

Figure 1 – Clinical Global (CIBIC-plus)



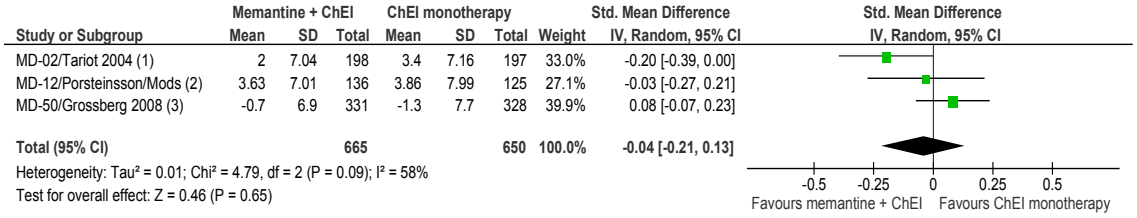
(1) LOCF; 20mg daily
(2) From Winblad 2007; OC; 20mg daily
(3) Unpublished registry data; LOCF; 28mg E/R preparation

Figure 2 – Cognition (ADAS-Cog and SIB)



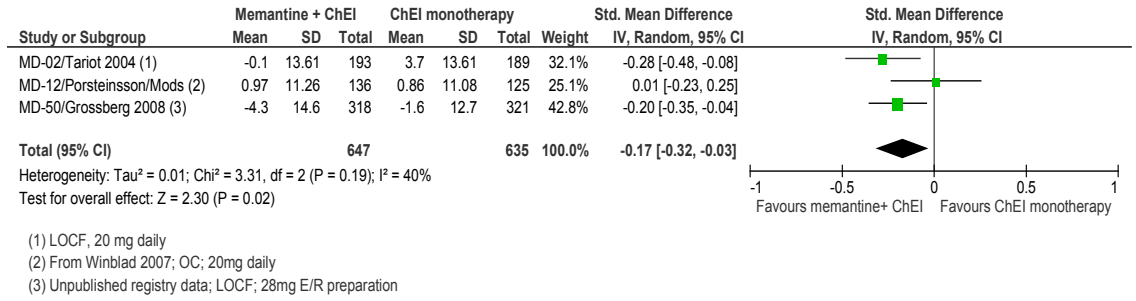
(1) SIB; LOCF; 20mg daily
(2) From Winblad 2007; ADAS-Cog; OC; 20mg daily
(3) Unpublished registry data; SIB; LOCF; 28mg E/R preparation

Figure 3 – Function (ACDS-ADL$_{19}$ and ADCS-ADL$_{23}$)



(1) LOCF; ADCS-ADL$_{19}$; 20mg daily
(2) From Winblad 2007; OC; ADCS-ADL$_{23}$; 20mg daily
(3) Unpublished registry data; ADCS-ADL$_{19}$; LOCF; 28mg E/R preparation

Figure 4 – Behaviour and mood (NPI)



(1) LOCF, 20 mg daily
(2) From Winblad 2007; OC; 20mg daily
(3) Unpublished registry data; LOCF; 28mg E/R preparation

Table 1 – Characteristics of included studies (including baseline characteristics of participants)

Trial	MMSE inclusion range (mean score)	Trial Dura-tion	Total no. of patients	No. of patients in Placebo + AChEI and Memantine + AChEI groups		Mean age	Mean cognitive score (score used)	Mean function score (score used)	Mean behaviour/ mood score (NPI)	Outcomes measured	Scores Used
MD-02 /Tariot et al 2004 [9]	Moderate-severe AD 5-14 (10.0)	24 weeks	403	Placebo + AChEI	203	75.5	80.0 (SIB)	35.8 (ADCS-ADL_{19})	13.4	Clinical global Cognition Function Behaviour/mood	CIBIC-Plus, SIB, ADCS-ADL_{19}, NPI
				Memantine + AChEI	201	75.5	78.0 (SIB)	35.5 (ADCS-ADL_{19})	13.4		
MD-12 /Porsteinsson et al 2008 [10]	Mild-moderate AD 10-22 (16.9)	24 weeks	433	Placebo + AChEI	216	76.0	26.8 (ADAS-Cog)	54.8 (ADCS-ADL_{23})	12.3	Clinical global Cognition Function Behaviour/mood	CIBIC-Plus, ADAS-Cog, ADCS-ADL_{23} NPI
				Memantine + AChEI	217	74.9	27.9 (ADAS-Cog)	54.7 (ADCS-ADL_{23})	11.8		
MD-12 /Porsteinsson et al 2008[10] – Subgroup with moderate disease, from Winblad 2007[11]	Moderate AD	24 weeks	302	Placebo + AChEI	148	Not known*	Not known*	Not known*	Not known*		
				Memantine + AChEI	154	Not known*	Not known*	Not known*	Not known*		
MD-50 /Grossberg et al 2008[15]	Moderate-severe AD 3-14 (10.8)	24 weeks	697	Placebo + AChEI	355	Not known†	Not known†	Not known†	Not known†	Clinical global Cognition Function Behaviour/mood	CIBIC-Plus, SIB, ADCS-ADL19 ,NPI
				Memantine + AChEI	342	Not known†	Not known†	Not known†	Not known†		

The global score, CIBIC-Plus, is a measure of change from baseline, so baseline scores are not given as they are not applicable.

*The data from the subgroup of patients with moderate disease is taken from the Winblad 2007 meta-analysis[11], which does not present the baseline characteristics for this subgroup.

†The baseline characteristics of patients in this unpublished study are not given

Table 2 – Memantine Combination Therapy (Results of synthesis of data)

Analysis no. and description **Trials included - code (LOCF/OC data)**	**Efficacy Domain**							
	Clinical Global		**Cognition**		**Function**		**Behaviour + Mood**	
	SMD/WMD (95% CI)	**P-value**	**SMD (95% CI)**	**P-value**	**SMD/WMD (95% CI)**	**P-value**	**SMD/WMD (95% CI)**	**P-value**
Analysis 1a – Trials included in the TA217 Assessment Report, data presented as WMDs: MD-02[9] (LOCF data) MD-12[10] (LOCF data)	WMD = - 0.140 [-0.346, 0.066]	P = 0.182	Data not pooled		Data not pooled		WMD = -1.715 [-5.733, 2.302]	P = 0.403
Analysis 1b – Trials included in the TA217 Assessment Report, data presented as SMDs: MD-02[9] (LOCF data) MD-12[10] (LOCF data)	SMD = -0.14 [-0.33, 0.06]	P = 0.16	SMD = -0.16 [-0.54, 0.23]	P = 0.43	SMD = -0.10 [-0.28, 0.08]	P = 0.27	SMD = -0.13 [-0.42, 0.17]	P = 0.41
Analysis 2 – Trials included in the TA217 Assessment Report. Data from patients with mild AD excluded. Data pooled within domains (SMDs): MD-02[9] (LOCF data) MD-12 (OC data, from Winblad 2007 [11])	SMD = -0.15 [-0.35, 0.04]	P = 0.12	SMD = -0.29 [-0.45, -0.14]	P = 0.0002	SMD = -0.13 [-0.29, 0.03]	P = 0.11	SMD = -0.14 [-0.42, 0.14]	P = 0.32
Analysis 3 - All trials meeting our inclusion criteria, data from patients with mild disease excluded: MD-02[9] (LOCF data) MD-12 (OC data, from Winblad 2007 [11]) MD-50[15] (LOCF data)	SMD = -0.20 [-0.32, -0.09]	P = 0.0005	SMD = -0.25 [-0.36, -0.14]	P < 0.00001	SMD = -0.04 [-0.21, 0.13]	P = 0.65	SMD = -0.17 [-0.32, -0.03]	P = 0.02

Discussion

This systematic review and meta-analysis suggests a small but significant benefit of memantine combination therapy on cognitive, global and behaviour measures, but not on function/ADL, when data from all included trials, including one trial of ER memantine, were pooled. When data from the trials included in the TA217 meta-analysis, but from patients with moderate-severe disease only, were pooled there was a small, significant benefit of combination therapy on cognition (SMD = 0.29). This effect size is comparable to that seen for memantine monotherapy. However, since the impact on clinical global impression depends on exactly which studies are included, and there is no benefit on function, the clinical relevance of combination therapy is not robustly demonstrated.

Clinical data from a negative one year trial, which would have been available at the time of the NICE meta-analysis, remains unpublished. The DOMINO study[17] is due to report shortly. Whether pooling of these one year studies would show a robust effect on clinical global remains to be seen.

Data for moderate AD patients from one trial[10] were only available as observed case (OC) data[11] and it was necessary to pool these with the last observation carried forward (LOCF) data from the other trials[9, 15] which is not methodologically ideal. In the full Cochrane review, this strategy was shown to have no material effect on results. The LOCF treatment of missing data is a conservative approach because dropout rates are equivalent, or slightly favour memantine. Consideration of the cost-effectiveness of combination AChEI and memantine was outside the scope of this review.

To the extent that we found a significant benefit of combination therapy on cognition, our analyses of the available data contrast with the findings of the TA217 Report[8] which found no evidence of additional benefit of combination therapy. The explanations given by the Peninsula Technology Assessment Group (PenTAG) for not pooling data from the same clinical domain ('it is not valid to synthesize these data on their original scales'[8]) or for not restricting analyses to data from the licensed patient subgroup ('The upper range of the MMSE scores for the participants of this study was 20.37… …this was only minimally over the threshold of 20 (so we) include(d) this study…')[20] remain controversial.

The inclusion of unpublished registry data on the ER preparation extends the evidence of benefit of combination therapy at 6 months. The dose of 28mg memantine in this preparation was designed to be equivalent to 20mg daily of the currently marketed preparation[21]. However, the trend for an adverse effect on ADL may account for the fact that these data have not been published in peer review literature. Although there is biological plausibility to the possibility of dose-related adverse effects of memantine[22] and memantine is associated with more rapid neurological decline in cognitively impaired patients with multiple sclerosis [23, 24], memantine is well tolerated over 6 months, with slightly fewer dropouts in the memantine than placebo arms, and long term open label follow-up studies do not suggest an obvious safety signal [25, 26, 27]. There are no long term randomised placebo-controlled studies to address this issue directly.

Nevertheless, we find the benefit of combination therapy to be less convincing than other reviewers [6], primarily because important data are missing from registry posting of trial results. Posting of clinical data is not mandatory for trials sponsored by companies who are not the Marketing Authorisation Holder in the US. However, the fact that clinical data have not been released from the 12 month trial Lu10112[16] is disturbing for two reasons. First, cerebral atrophy rates were greater in those taking combination therapy than in those taking memantine alone[19]. Whilst the presented analysis suggests that this unexpected finding of increased atrophy was attributable to the AChEI rather than the memantine, there is no information about whether this is reflected in the clinical domains. Second, the reason given for not posting the clinical data is revealing: sponsors who are not marketing authorisation holders in the US are not obligated by US public Law 110-85. This law mandates the posting of defined clinical data items on registries within a year of study completion.

The greatest benefit of registries is ensuring the timeliness of the release of results. Without this, there are obvious incentives to delay the release of negative data until as close to the end of patent life as possible. However, registries are likely to become the preferred repository of incomplete or negative data. This makes it particularly important that harmonising legislation specifies in detail which clinical data must be posted. Furthermore, until there is harmonisation onto a single registry, such as clinicaltrials.gov, systematic reviews should routinely include comprehensive searches across all registries.

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