Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer's disease and other dementias

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CRD summary
This review concluded that combination therapy with memantine and a cholinesterase inhibitor appeared superior to monotherapy in patients with moderate to severe Alzheimer's Disease. They advised a cautious interpretation due to variation in outcome scales and patient characteristics and said it was unclear whether improvements were clinically significant. The authors' cautious conclusions and recommendations for practice seem appropriate.

Authors' objectives
To assess the safety and efficacy of combination therapy with memantine and a cholinesterase inhibitor to treat dementia.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from inception to March 2012 for publications in English. Search terms were reported. Conference proceedings, abstracts, theses, grey literature journals, ClinicalTrials.gov and the Current Controlled Trials databases were searched. Reference lists of relevant reviews and articles were screened manually. Experts in the field were contacted.

Study selection
Eligible studies compared the safety and efficacy of combined therapy (memantine plus a cholinesterase inhibitor) versus monotherapy (memantine or a cholinesterase inhibitor) in the treatment of patients with cognitive impairment or dementia of degenerative or vascular origin (as diagnosed by the authors). Eligible patients were community living adults (>18 years old). Primary outcomes of interest were changes in cognitive and functional ability (measured using various scales). Eligible secondary outcomes and adverse events were stated. Case series and reports were excluded.

Included patients had Alzheimer's Disease of varying severity. Some patients had comorbidities (as reported in the review). Mean ages of patients ranged from 71.5 to 78.4 years. Most patients were female. Cholinesterase inhibitors included donepezil, rivastigmine and galantamine at varying doses.

Two reviewers screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Randomised controlled trials (RCTs) were assessed using the Cochrane risk of bias tool. Other studies were assessed using the Newcastle-Ottawa scale.

It was unclear how many reviewers assessed study quality.

Data extraction
Outcome data were extracted to calculate mean differences or odds ratios; standard errors or confidence intervals were converted to standard deviations where necessary.

One reviewer extracted outcome data and a second reviewer checked; disagreements were resolved by consensus.

Methods of synthesis
Data from blinded RCTs were pooled. Otherwise a narrative synthesis was presented. A fixed-effect or random-effects model was used to pool mean differences to calculate standardised or weighted mean differences and 95% confidence intervals. Odds ratios and their 95% CIs were also pooled.

Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic ($I^2=50\%$ indicated heterogeneity). Sensitivity analyses were performed (as reported in the review). Subgroup analyses were conducted for different dementing disorders or different types of cholinesterase inhibitors.
Publication bias was to be assessed using funnel plots if there were sufficient numbers of studies.

**Results of the review**

Thirteen studies were included in the review; five RCTs (three blinded (1,059 patients), two open label (433 patients)), four open-label non-RCTs (314 patients), and four cohort studies (1,082 patients). One blinded RCT was at low risk of bias, the remaining two blinded RCTs had undetermined risk. The six open label studies were all at high risk of bias.

Completion rates in the blinded RCTs ranged between 74% and 89.4%. Completion rates in the open label studies ranged between 64% and 95.3%. Drop-out rates were reported in two of four cohort studies and ranged from 21% to 34%.

**Cognitive function (three blinded RCTs):** Only subgroup analyses in moderate to severe patients showed statistically significant improvements in cognitive function when combination therapy was used compared to both memantine (SMD 0.52, 95% CI 0.35 to 0.69; two RCTs; I²=0%) and donepezil (SMD 0.45, 95% CI 0.27 to 0.63; two RCTs; I²=5%).

**Functional outcomes (three blinded RCTs):** Combination therapy statistically significantly improved functional outcomes in mild to severe patients when compared to donepezil monotherapy (SMD 1.07, 95% CI 0.26 to 1.89; three RCTs; I²=0%).

**Behavioural outcomes (three blinded RCTs):** The authors stated that there were no statistically significant differences between treatment groups across mild to severe patients. However, forest plots suggested that combination therapy compared to donepezil showed a small but statistically significant improvement (SMD 3.00, 95% CI 0.22 to 5.78; three RCTs; I²=79%). Subgroup analyses showed that combination therapy statistically significantly improved behavioural outcomes in patients with moderate to severe Alzheimer's Disease compared to monotherapy with memantine (SMD 3.7, 95% CI 1.98 to 5.43; two RCTs; I²=0%) or donepezil (SMD 4.40, 95% CI 3.01 to 5.79; two RCTs; I²=0%).

There were no statistically significant differences between treatment groups for global outcomes (two blinded RCTs), quality of life (one blinded RCT) or adverse events.

Three of six open-label studies and four cohort studies suggested benefit with combined therapy.

**Authors' conclusions**

Combination therapy appeared to be safe and well tolerated compared to monotherapy in patients with moderate to severe Alzheimer's Disease. A cautious interpretation was advised due to variation in outcome scales and patient characteristics. Whether the noted improvements were clinically significant was unclear.

**CRD commentary**

The review question and inclusion criteria were clearly stated. There was a comprehensive search of the literature. The restriction to studies in English may have introduced language bias. The authors acknowledged potential for publication bias. Study quality was assessed and indicated that there was only one RCT at low risk of bias. It was unclear whether quality assessment was performed in duplicate so reviewer error and bias could not be ruled out.

There was variation across studies in terms of study and patient characteristics; the authors went some way to account for this in the statistical analyses. Statistical heterogeneity was assessed and indicated evidence of heterogeneity for some outcomes. The evidence was based on a small number of studies and benefits were generally small. As such, the authors' cautious conclusions and recommendations for practice seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that more studies were required before a recommendation could be made for combination therapy to reduce deterioration in cognition or function in patients with any type of dementia.

**Research:** The authors stated that further blinded RCTs were needed to explore combination therapy in patients with all types of dementia. The authors suggested that future research should assess behavioural measures as the primary outcome and explore responses in patients with various comorbidities.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.