

## Alzheimer Disease: Monotherapy vs. Combination Therapy

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### Clinical Question

Is the combination of memantine with donepezil more effective in the treatment of Alzheimer disease than either drug alone?

### Evidence-Based Answer

Combination treatment with memantine and donepezil results in a small improvement in cognitive function that is of uncertain clinical significance in patients with moderate to severe Alzheimer disease, but no improvement in patients with mild to moderate disease. (Strength of Recommendation: B, based on a meta-analysis of randomized controlled trials.)

### Evidence Summary

A meta-analysis of three double-blind randomized controlled trials evaluated the use of combination therapy with memantine plus donepezil (two studies) or memantine plus donepezil, galantamine, or rivastigmine in patients with Alzheimer disease.<sup>1</sup> Data were analyzed for 1,043 patients diagnosed with likely Alzheimer disease based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria or Mini-Mental State Examination (MMSE). The two studies of memantine plus donepezil included patients with moderate to severe Alzheimer disease. One study included patients with mild to moderate dementia. Patients receiving monotherapy (cholinesterase inhibitor alone [two studies] or memantine alone [one study]) were compared with those using a combination of a cholinesterase inhibitor plus either memantine or placebo. Patients were followed for 24 to 52 weeks. Post-therapy cognitive outcomes were measured using the MMSE, the Alzheimer's Disease Assessment Scale–Cognitive Subscale, or the Severe Impairment Battery. Analysis of

pooled results of all three studies found no difference between combination and monotherapy. A subgroup analysis limited to patients with moderate to severe dementia found a small but significant cognitive improvement with combination therapy compared with donepezil alone (standard mean difference = 0.45; 95% confidence interval, 0.27 to 0.63). There was no significant benefit with combination therapy in the study of patients with mild to moderate dementia.

A retrospective cohort study investigated the combination of memantine and a cholinesterase inhibitor compared with a cholinesterase inhibitor alone.<sup>2</sup> The study included 240 patients with Alzheimer disease who were older than 60 years and had been treated with a cholinesterase inhibitor for at least six months. Initially, 117 patients received donepezil, 110 received rivastigmine, and 13 received galantamine. Memantine was then added to the regimen and titrated to a target of 20 mg per day at four weeks. Baseline MMSE scores were compared with scores at three and six months of combination therapy. There was a minimal yet significant improvement in MMSE scores between month 3 and month 6 (14.58 to 14.74; paired t-test;  $P < .02$ ).

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### REFERENCES

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