Memantine was better than placebo in Alzheimer disease already being treated with donepezil

Tariot PN, Farlow MR, Grossberg GT, et al. **Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial.** JAMA. 2004;291:317-24.

QUESTION

In patients with Alzheimer disease (AD) already receiving donepezil, is the *N*-methyl-D-aspartate–receptor antagonist memantine more effective than placebo?

METHODS

Design: Randomized, placebo-controlled trial.

Allocation: {Concealed}†.*

Blinding: Blinded (clinicians, patients, {data collectors, outcome assessors, and data analysts}†)*.

Follow-up period: 24 weeks.

Setting: 37 U.S. sites.

Patients: 404 patients ≥ 50 years of age (mean age 76 y, 65% women) with a diagnosis of probable AD, a Mini-Mental State Examination score of 5 to 14, ongoing donepezil therapy for ≥ 6 months at a stable dose (5 to 10 mg/d) for ≥ 3 months, a knowledgeable and reliable caregiver, ambulatory ability, and a stable medical condition. Exclusion criteria were vitamin B_{12} or folate deficiency, other serious diseases or psychiatric or central nervous system disorders, or modified Hachinski Ischemia Score > 4.

Intervention: Patients were allocated to memantine, 5 mg/d, titrated in 5-mg weekly increments to 20 mg/d at 4 weeks (n = 203), or placebo (n = 201). Patients were required to continue stable donepezil therapy.

Outcomes: Cognitive (Severe Impairment Battery [SIB]), functional (19-item AD Cooperative Study-Activities of Daily Living Inventory [ADCS-ADL_{19}]), and global (Clinician's Interview-Based Impression of Change-Plus caregiver [CIBIC-Plus]) improvement.

Patient follow-up: 322 patients (80%).

MAIN RESULTS

The primary efficacy analysis was done using last observation carried forward. Patients who received memantine had greater improvement than patients who received placebo in all cognitive, functional, and global outcome measures at 24 weeks (Table). Memantine and placebo groups did not differ for adverse events (78% vs 72%), and most were rated mild to moderate in severity.

CONCLUSION

In patients with Alzheimer disease already receiving donepezil, memantine was better than placebo in improving cognitive, functional, and global outcomes.

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*See Glossary.

†Information provided by author.

Change from baseline for memantine vs placebo for Alzheimer disease on stable donepezil therapy at 24 weeks‡

Outcomes	Scale	Least-squares mean score		*P* value
		Memantine	Placebo	
Cognitive	SIB	0.9	−2.5	< 0.001
Functional	ADCS-ADL_{19}	−2.0	−3.4	0.03
Global	CIBIC-Plus	4.41	4.66	0.03

‡SIB = Severe Impairment Battery (score range 0 to 100; higher score = better function); ADCS-ADL_{19} = 19-item AD Cooperative Study–Activities of Daily Living Inventory (score range 0 to 54; higher score = better function); CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus caregiver input (score range 1 to 7; lower score = greater improvement).

COMMENTARY

Unlike cholinesterase inhibitors, memantine inhibits cytotoxic overstimulation of glutamatergic neurons thought to be involved in learning and memory. Patients with moderate-to-severe AD receiving memantine, 20 mg/d for 28 weeks, lost an average of 6.1 fewer points on the 100-point SIB than did those taking placebo and required an average of 45.8 fewer hours of caregiving per month (1). In patients already taking donepezil, Tariot and colleagues found a smaller, 3.4-point difference on the SIB. That donepezil contributed to the smaller decline in the memantine group is suggested by the finding that patients with moderate-to-severe AD given donepezil for 24 weeks declined significantly less in activities of daily living and required an average of 44.5 minutes per day less caregiver time than those receiving placebo (2). Memantine also shows efficacy in slowing decline in vascular dementia (VaD) (3).

Efficacy and safety data support the use of memantine alone or in combination with donepezil in moderate-to-severe AD, as well as alone in mild-to-moderate VaD. Further studies are needed to assess the benefits of memantine over the long term, its efficacy in mild-to-moderate AD, and its efficacy when given with other cholinesterase inhibitors. When valued relative to the cost of caregiver time, memantine seems cost-effective, but its average wholesale cost (U.S. $139.50 for 60 tablets) may pose a barrier to consumers.

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References

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