Does treatment with donepezil improve memory for patients with mild cognitive impairment?

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EVIDENCE-BASED ANSWER

Donepezil (Aricept) has potential benefit in delaying risk of progression to Alzheimer's disease in the first year of treatment, but this benefit is not seen at 3 years. Donepezil does not improve memory for patients with mild cognitive impairment (strength of recommendation: **B**).

CLINICAL COMMENTARY

Donepezil's cost, limited proven benefit, side effects argue against it as standard of care

The downward spiral of a patient with Alzheimer's disease is heartbreaking, so any possibility of slowing this process is welcome. Many physicians, when challenged with the desire to assist the patient with mild cognitive impairment and their family, review the data showing that donepezil slows progression in Alzheimer's disease, as well as briefly from mild cognitive impairment to Alzheimer's disease. They discuss with the family the imprecise nature of diagnosis,[1] risks vs benefits of therapy, and start an 8-week trial of therapy. If the family notes improvement (or stabilization), treatment can be continued. However, the cost of the medication, the limited proven benefit, and the side-effect profile argue against any clear standard of care.

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Evidence summary

Mild cognitive impairment is defined as memory loss that is out of proportion to that expected for one's age but which does not meet the clinical criteria for dementia. The diagnosis of dementia requires cognitive impairment plus functional impairment. In mild cognitive impairment, function is preserved by definition.

Several studies have shown that patients with mild cognitive impairment progress to Alzheimer's disease at a higher rate than normal elderly patients.[2,3] Research has focused on therapies that have shown a positive benefit for patients with Alzheimer's disease.[4,5] Cholinesterase inhibitors, including donepezil, have shown some benefit in cognition and function for patients with mild to moderate Alzheimer's disease. Two randomized controlled trials (RCTs) address the effect of donepezil on mild cognitive impairment.

The National Institute of Aging conducted a double-blind RCT multicenter study, which enrolled a total of 769 subjects with mild cognitive impairment. The

primary outcome was the development of possible or probable Alzheimer's disease, and secondary outcomes included cognition and function. Subjects were randomly assigned to receive 2000 IU of vitamin E, 10 mg of donepezil, or placebo daily for 3 years. Of the total, 214 (28%) of the study subjects progressed to dementia, with 212 classified as possible or probable Alzheimer's disease. Analysis of the treatment effects at 6-month intervals showed a decreased probability of progression to Alzheimer's disease in the donepezil group during the first 12 months of the study, compared with placebo (14.7% vs 6.3%; *P*=.04; number needed to treat [NNT]= 12), but this change did not persist to 3 years.

Several of the psychometric tests showed statistically significant differences (scores for Mini-Mental State Examination [MMSE], Clinical Dementia Rating [CDR] sum of boxes, Global Deterioration Scale, and modified Alzheimer's disease Assessment Scale-cognitive subscale [ADAS-cog]) early in the study, but the effect was only detected in the first 12 months of the study.[6,7] The donepezil group had significantly higher rates diarrhea, muscle cramps, insomnia, nausea, and abnormal dreams (*P*<.01). There was no difference in discontinuation rates between the groups.[7]

The second study was a 24-week multicenter RCT, which included 270 patients with amnestic mild cognitive impairment. Patients were randomized to receive placebo or donepezil (5 mg/d for 42 days, followed by 10 mg/d). The primary endpoints were changes on the New York University Paragraph Delayed Recall test and the Alzheimer's disease Cooperative Study Clinician's Global Impression of Change for Mild Cognitive Impairment (ADCS CGIC-MCI). No significant differences were found in the primary endpoints at 24 weeks—32.6% in the donepezil group vs 24.3 % in the placebo group showed minimal or moderate improvement, and 51.7% in the donepezil group vs 60.4% in the placebo group showed no change. Secondary endpoints included the modified ADAS-cog, the Patient Global Assessment (PGA) and other neuropsychological tests.

The ADAS-cog focuses on psychomotor speed and attention tests. Analysis of the ADAS-cog favored the donepezil group, with 22.3% showing a ≥7-point score vs 12.1% in the placebo group. There were no significant differences on the PGA in the intention-to-treat analysis.[8] The donepezil group had a higher rate of adverse drug reactions (*P*<.03) including diarrhea, nausea, vomiting, leg cramps, and abnormal dreams. The discontinuation rate was 22% in the donepezil group compared with 8% in the placebo group (number needed to harm=7).[8]

Recommendations from others

We found no recommendations about using cholinesterase inhibitors in mild cognitive impairment.

FAST TRACK

The cost of cholinesterase inhibitors and their limited benefit for mild cognitive impairment argue against any clear standard of care

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