Donepezil for Patients with Severe Alzheimer's Disease: Small But Significant Benefits

Winblad B, Kilander L, Eriksson S, et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006;367:1057–65.

Study Overview

Objective. To determine if donepezil improves cognition and functional status in individuals with severe Alzheimer's disease.

Design. Double-blind, parallel-group, placebo-controlled study with an intention-to-treat analysis.

Setting and participants. Patients were recruited from 50 nursing care facilities in Sweden. Patients were eligible to participate if they were aged ≥ 50 years and able to ambulate (either alone or with assistance) and if they had a probable or possible diagnosis of Alzheimer's disease based on standard diagnostic criteria, a Mini-Mental State Examination (MMSE) score ≤ 10, and a functional assessment staging rating of stage 5 (needs assistance in dressing) to stage 7c (unable to walk without assistance). Patients were excluded if they had a concomitant diagnosis of another type of dementia other than Alzheimer's or any psychiatric or neurologic diagnosis.

Intervention. Participants were randomized to either oral donepezil (5 mg daily for the initial 30 days and 10 mg daily thereafter) or matching placebo. The trial duration was 6 months.

Main outcome measures. The primary outcome was change from baseline to 6 months in scores on the severe impairment battery (SIB) and the modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL-severe). For both scales, lower scores translate to greater degrees of impairment. Secondary outcomes included change from baseline in scores on the MMSE, the neuropsychiatric inventory (NPI), and the clinical global impression of improvement scale (CGI-I).

Main results. Of 334 eligible patients, 248 were enrolled and assigned to study group. 128 patients were allocated to the treatment arm and 120 to placebo. Baseline and psychometric characteristics were similar between the 2 groups. 95 patients randomized to the treatment arm and 99 patients in the placebo arm completed 6 months of follow-up. 20 patients dropped out of the intervention arm because of adverse events compared with 8 patients in the placebo arm. For donepezil-treated patients, the mean score on the SIB increased by 2.6 compared with a decrease of 1.9 in the placebo group (mean difference, 4.5 [95% confidence interval {CI}, 1.1–7.9]; $P = 0.01$). On the modified ADCS-ADL-severe, mean scores in the treatment group decreased by 1.5 compared with a 2.9 decrease in the placebo arm (mean difference, 1.4 [95% CI, 0.1–2.7]; $P = 0.03$). Greater improvements were also seen in scores on both the CGI-I and MMSE in donepezil-treated patients as compared with placebo-treated patients (3.5 versus 3.8 [$P = 0.01$] and 1.1 versus 0.1 [$P = 0.01$], respectively). There was no significant difference in NPI scores. No statistically significant differences were found in the overall incidence of adverse events, severe adverse events, or death.

Conclusion. In nursing home residents with severe Alzheimer's disease, donepezil appears to slightly improve cognition and functional status with only a minimal increase in side effects.

Commentary

Alzheimer's disease is a progressively debilitating condition with few therapeutic options. Most pharmacologic therapies have involved the use of cholinesterase inhibitors such as donepezil, galantamine, and rivastigmine. Clinical trials have suggested that these agents may slow disease progression in patients with mild-to-moderate Alzheimer's disease [1,2]. With respect to patients with more severe disease, many guidelines have recommended stopping treatment altogether; however, there is little evidence on which to base these suggestions. To evaluate specifically how cholinesterase inhibitors might impact outcomes in patients with severe dementia, Winblad et al completed a well-designed, 6-month, double-blind, placebo-controlled trial. The results of this study lend support to the use of donepezil in patients with severe Alzheimer's dementia.

One challenge in interpreting clinical research data from Alzheimer's patients is translating changes in cognitive and functional scores into clinical outcomes. Indeed, this study,

like most past studies, demonstrated statistically significant (yet small) changes. In the primary outcomes, there was only a mean difference of 4.5 on the SIB, which ranges from 0 to 100, and a mean change of 1.4 on the modified ADCS-ADL-severe, which ranges from 0 to 54. With respect to more "hard" outcomes, cholinesterase inhibitors have not altered time to nursing home placement or progression of disability for patients with mild-to-moderate dementia [3].

Although clinical trials such as this one demonstrate only modest changes in cognition scores, it is important to note that the range of responses to these agents tends to be very variable and that these are only mean scores. Thus, any 1 patient may have a significantly greater improvement than that described in this study. As these agents appear reasonably tolerated (the number of adverse events and serious adverse events were similar to placebo in this study), a trial of cholinesterase inhibition may be worthwhile, with little overall risk to the patient.

Applications for Clinical Practice

For nursing home residents with severe Alzheimer's disease, therapy with donepezil appears to offer a short-term, small improvement in cognition and functional status. Overall, donepezil was well-tolerated, but 1 in 6 patients stop therapy due to adverse effects.

—Review by Harvey J. Murff, MD, MPH

References

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