Donepezil was no better than placebo for agitation in patients with Alzheimer disease

Howard RJ, Juszczak E, Ballard CG, et al. **Donepezil for the treatment of agitation in Alzheimer's disease.** N Engl J Med. 2007;357: 1382-92.

Clinical impact ratings: Geriatrics ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with Alzheimer disease, is donepezil better than placebo for clinically significant agitation that has not responded to psychosocial treatment?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (patients and caregivers, clinicians, outcome assessors, and {data monitoring committee}†).*

Follow-up period: 12 weeks.

Setting: 8 clinical centers in England, United Kingdom.

Patients: 259 patients > 39 years of age (mean age 85 y, 85% women) who had probable or possible Alzheimer disease (on the basis of National Institute of Neurological and Communication Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria); had clinical agitation (patient distress, at least moderate management problems for caregivers ≥ 2 d/wk for 2 wk, and a Cohen–Mansfield Agitation Inventory [CMAI] score ≥ 39); lived in a residential care facility or with a caregiver in the community; had not received neuroleptic agents or cholinesterase inhibitors in the previous 4 weeks and were not to receive such drugs in the following 16 weeks; and were able to give consent or to assent with caregiver agreement. Exclusion criteria were sensitivity to donepezil; severe, unstable, or uncontrolled medical conditions; delirium; dementia with Lewy bodies; and evidence of poor compliance with medications.

Intervention: Donepezil, 5 mg/d for 4 weeks and 10 mg/d for 8 weeks (n = 128), or placebo (n = 131).

Outcomes: Change in CMAI score (scores of 29 to 203; higher scores indicate more severe or frequent agitation) and treatment response (> 30% reduction in agitation). The study had 90% power to detect a 25% difference between groups in patients who responded to treatment (α = 0.05).

Patient follow-up: 88% (intention-to-treat analysis).

MAIN RESULTS

At 12 weeks, donepezil and placebo did not differ for mean reduction in CMAI score or treatment response (Table).

CONCLUSION

Donepezil was no better than placebo for clinical agitation in patients with Alzheimer disease.

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*See Glossary.

†Information provided by author.

Donepezil vs placebo in patients with Alzheimer disease and significant clinical agitation‡

Outcomes at 12 wk	Donepezil	Placebo	Difference in change (95% CI)§	
Change in mean CMAI score‖	6.3	5.0	–0.06 (–4.4 to 4.2)	
			RBR (CI)	NNH
Responded to treatment, %¶	19.5	20.4	4.4% (–61 to 43)	Not significant

‡RBR = relative benefit reduction; other abbreviations defined in Glossary. RBR, NNH, and CI calculated from data in article.
§Adjusted for baseline values.
‖CMAI = Cohen–Mansfield Agitation Inventory. Scores range from 29 to 203; higher scores indicate frequent or severe agitation.
¶Response to treatment: ≥ 30% reduction in total CMAI scores from baseline.

COMMENTARY

Agitation is common in Alzheimer disease and is an important cause of suffering, impairment, institutionalization, safety risk, caregiver distress, and societal cost. Although antipsychotic drugs remain the most commonly prescribed medications for agitation in Alzheimer disease, the evidence suggests that efficacy is limited, and adverse events (e.g., stroke, extrapyramidal symptoms, falls, and death) are more common than with placebo (1–4). Therefore, alternative treatment options should be explored.

Preliminary evidence (5) suggested a possible role for cholinesterase inhibitors, including donepezil. The trial by Howard and colleagues compared donepezil with placebo. Patients were selected on the basis of agitation, and the primary outcome was improvement in agitation. Importantly, and consistent with practice guidelines (6), the inclusion criteria specified persistent agitation despite participation in a 4-week psychosocial treatment program. The study methodology was generally sound, and therefore the results can be interpreted with considerable confidence, at least for patients similar to the study population (generally older, white women who had relatively severe Alzheimer disease and, for the most part, lived in institutions).

The results of this trial suggest that cholinesterase inhibitors are not efficacious for the treatment of agitation in this population (although these medications may yet be found to be efficacious for some of the other behavioral changes caused by Alzheimer disease). Research into the potential benefits of alternative strategies (e.g., nonpharmacologic therapies, antidepressant medications, or combination strategies) for the treatment of agitation in Alzheimer disease is needed.

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