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


**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).

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

<table>
<thead>
<tr>
<th>Outcomes at 12 wk</th>
<th>Donepezil</th>
<th>Placebo</th>
<th>Difference in change (95% CI)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in mean CMAI score</td>
<td></td>
<td>6.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Responded to treatment, %¶</td>
<td>19.5</td>
<td>20.4</td>
<td>4.4% (−61 to 43)</td>
</tr>
</tbody>
</table>

*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.

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

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

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

**References**