Donepezil for treatment of agitation in Alzheimer’s disease
CALM-AD Trial N Engl J Med 2007;357:1382-92 (October 4)

Study Type: POEM

Purpose: Because agitation and related symptoms like anxiety, irritability, aggression occur frequently in the AD patient, and frequently causes transition to residential care and is often distressing to the caregiver, and atypical antipsychotics are often prescribed and have metabolic side effects, donepezil was studied for BPSD in patients that had failed traditional antipsychotic therapy.

Study Duration: 12 weeks

Trial Design: Prospective, randomized, double-blinded, placebo-controlled trial, intention-to-treat, multicenter (8 clinical centers in England). Patients were enrolled into a 4-week psychosocial treatment program given by the caregiver who was trained, patients scoring poor on the CMAI were randomized to donepezil 5 mg daily vs placebo, after 4 weeks, dose was increased to 10 mg.

Patients: n = 262, mean of 84 years, 85% female, 98% white, 95% in residential care, more regular use of psychotropics at trial entry in donepezil group (26% vs 14%, p=0.02) – but all had similar 4-week psychosocial run-in treatment effects

Baseline Scores: mean CMAI score ~61, mean CGIC score 4.3, mean NPI score 23.6, Caregiver NPI score ~7.5, mean SIB score 55, mean MMSE score 8

Inclusion Criteria: Diagnosed probable AD by specified criteria, had clinical agitation through specified criteria, > 39 years of age, lived in residential care or with caregiver in community, not on cholinesterase therapy

Exclusion Criteria: sensitivity to donepezil, severe, unstable medical conditions, delirium, Lewy body dementia, evidence of poor compliance

Primary outcome: Cohen-Mansfield Agitation Inventory (CMAI) score at 12 weeks

Secondary outcome: Neuropsychiatric Inventory (NPI), Severe Impairment Battery (SIB), Mini-Mental State Exam (MMSE), Clinician’s Global Impression of Change (CGIC)

1. Are the results valid?
   * Randomized? Yes
   * Double-blind? Yes
   * Allocation concealment? Yes
   * Placebo-controlled? Yes

2. What were the results?

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Donepezil</th>
<th>Placebo</th>
<th>P-value</th>
<th>Mean Baseline Scores</th>
<th>Instrument Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average CMAI Score change</td>
<td>- 5 points</td>
<td>- 6 points</td>
<td>NS</td>
<td>61</td>
<td>Score range 29 to 203, higher score denote severe agitation (&gt; 40 clinically significant)</td>
</tr>
<tr>
<td>Response rate*</td>
<td>19.5%</td>
<td>20.4%</td>
<td>NS</td>
<td></td>
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</tr>
</tbody>
</table>

Secondary outcomes

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th>Donepezil</th>
<th>Placebo</th>
<th>P-value</th>
<th>Mean Baseline Scores</th>
<th>Instrument Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI score reduction</td>
<td>- 3.6</td>
<td>- 3.8</td>
<td>NS</td>
<td>24</td>
<td>Score range 1 to 144, lower score less frequent symptoms</td>
</tr>
<tr>
<td>NPI Caregiver</td>
<td>- 1.5</td>
<td>- 1.3</td>
<td>NS</td>
<td>7.5</td>
<td>Scores range 0 to 60, with higher scores indicating higher distress</td>
</tr>
<tr>
<td>SIB</td>
<td>+1.9</td>
<td>- 4.8</td>
<td>.02</td>
<td>55</td>
<td>Score range 0 to 100, higher scores mean better performance</td>
</tr>
<tr>
<td>MMSE</td>
<td>+0.5</td>
<td>- 0.9</td>
<td>.02</td>
<td>8</td>
<td>Score range 0 to 30, higher is best</td>
</tr>
</tbody>
</table>

*response rate was > 30% reduction in CMAI from baseline to 12 weeks

3. Will the results help me?
   * Adverse events were as expected and were similar across groups. Diarrhea 1.6% in donepezil group, rash 1.6% vs placebo (0%). Death rates were same in each group.

Conclusion: No significant treatment advantage was shown for donepezil as compared to placebo for the treatment of agitation of dementia. There was a modest benefit to the SIB and MMSE, but these are just score changes and these were not extrapolated to quality of life.