Long-term donepezil treatment in 565 patients with Alzheimer’s disease (AD2000):
randomized double-blind trial
Lancet 2004;363:2105-15 (June 26)

Study Type: POEM
Purpose: Trials so far show a small benefit of donepezil on simple cognitive function test (average of 3 pts over placebo on ADAS-cog). Does this 3 pt change make a difference clinically, socially and financially? Does donepezil produce worthwhile improvement in non-cognitive and behavioral symptoms? What is the optimal dose? How long should we treat? Does response to 12 weeks of therapy predict outcomes?

Study Duration: Potentially a 3 year trial: all patients 60 weeks or 15 mths (this was due to funding) - after 60 weeks, a 6-week no-treatment washout was done on those deciding to stay in the trial for a further 48 weeks. After this 48 weeks, those choosing to stay with the trial were again washed out for 4 weeks, then another 48 weeks. Total of 156 weeks (39 mths, 3.3 yrs).

Trial Design: randomized, double-blinded, placebo-controlled, intention-to-treat, multicenter (28 hospitals in West Midlands), 12 week run-in randomized to donepezil or placebo, then randomized a second time to long term treatment (donepezil 5 to 10 mg vs placebo)

Patients: 566 patient; mean age ~76 (24% > 80); 42% male; mean MMSE = 19 (52% had MMSE of 19 to 26, 48% had MMSE of 10 to 18); 18% had vascular dementia present; 4% Parkinson’s; 10% psychotic symptoms; ~67% had at least one APOE-4 alleles (~62% were unknown) baseline scores (BADLS = ~15; NPI = 15; GHQ-30 = ~4.5)

Inclusion: those referred to a memory clinic; AD consistent with DSM-IV; doctors had to be uncertain to the benefit of donepezil; not currently on an ACase inhibitor; reliable caregiver

Exclusion: none mentioned

Primary Outcomes: entry to institution; and progression of disability as measured by:
BADLS - assesses functional ability was assessed by BADLS , score 0-60
NPI - severity of behavior and psychological symptoms, score 0-144
MMSE - to measure cognition, score 0-30 and progression to severe cognition, scores < 10
GHQ-30 - caregiver score of psychological well-being
death from AD

1. Are the results valid?
* randomized? yes
* double-blinded? yes
* were groups similar? yes
* all patients accounted for? yes

2. What were the results: n = 282 (Donepezil grp); n = 283 (Placebo grp)

<table>
<thead>
<tr>
<th>Outcome at 3 yrs</th>
<th>Donepezil</th>
<th>Placebo</th>
<th>p-value</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry to institution care at 3 yrs</td>
<td>42%</td>
<td>44%</td>
<td>NS</td>
<td>dose made no difference</td>
</tr>
<tr>
<td>loss of ADL’s + institution care</td>
<td>55%</td>
<td>53%</td>
<td>NS</td>
<td>no difference at 1 or 2 yrs</td>
</tr>
</tbody>
</table>

MMSE - donepezil improved MMSE by 0.9 points at 12 weeks with no change in placebo group; and 0.8 points by 2 years (p = .02); there was no delay in patients reaching severe cognitive disability (MMSE < 10).
BADLS score - no changes at 12 weeks, donepezil had 1 pt better change than placebo, 10 mg better than 5 mg donepezil.
NPI - no significant difference in scores at any timepoint, no improvement in those with severe baseline scores
GHQ-30 - no significant caregiver psychological morbidity scores
Active caregiver daily time was reduced by 0.2 hours on donepezil (p = 0.2) and passive care by 0.4 hrs (p = 0.4)
Death - no significant difference
Adverse events - no difference
Those with a higher NPI score or those with prior diagnosis of Parkinson’s disease had less effect on donepezil. If the patient had a baseline vascular component to AD, response was better on donepezil. There was less response to donepezil in those with 2 APOE alleles. Power is in question for these results.

3. Will the results help me?
* no reduction in the rate of institutionalization
* improvements in functional decline does not equate to delay institutionalization
* donepezil was not shown to be cost effective based on caregiver time and hospital care
* rate of decline of MMSE is 2.8 per year in an AD patient, the FDA recognizes a 1.4 point change as significant, the change in this study was 1.2 points
* the minimal significant change in the BADLS is 3 points, the change in this trial was 1 point
* the NPI improvement of 1.5 is of questionable clinical relevance

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