Conflict of Interest and Professional Responsibility

An American Study of Rhetoric in the Medical Literature

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Results, Rhetoric, and Randomized Trials: The Case of Donepezil
John R Gilstad and Thomas E Finucane
Journal of the American Geriatrics Society, August 2008

Medical Professionalism in the New Millennium: A Physician Charter
Project of the ABIM Foundation, ACP-ASIM Foundation, and European Federation of Internal Medicine
Annals of Internal Medicine, 5 Feb 2002
2001 American Academy of Neurology practice guideline for management of Alzheimer’s Dementia:

“Cholinesterase Inhibitors should be considered in patients with mild to moderate AD (Standard), although studies suggest a small average degree of benefit.”
Table 3. Summary of Comparable Data from All Donepezil Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Results</th>
<th>Alzheimer's Disease Scale—Cognitive Subscale</th>
<th>Mini-Mental State Examination</th>
<th>Clinical Global Impression of Change</th>
<th>Clinician's Interview-Based Impression of Change</th>
<th>Clinical Dementia Rating—Sum of the Boxes</th>
<th>Quality of Life—Patient Rated</th>
<th>Neuropsychiatric Inventory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of points in scale</td>
<td>70</td>
<td>30</td>
<td>7</td>
<td>7</td>
<td>18</td>
<td>350</td>
<td>144</td>
</tr>
<tr>
<td>Vendor-sponsored trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials, n</td>
<td>6</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Range of significant results</td>
<td>1.5–3.2</td>
<td>0.68–1.8</td>
<td>9.0–23%*</td>
<td>0.34–0.54</td>
<td>0.4–0.85†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative trials, n</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-vendor-sponsored trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials, n</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Range of significant results</td>
<td>2.2</td>
<td>0.8–1.55</td>
<td></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Negative trials, n</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Treatment effects for measurement scales used in at least three trials are presented. If multiple doses of donepezil were used, the best result is presented.

* Percentage difference in number of patients scoring in 4–7 range (better).
† Five-mg dose not different, 10-mg dose significantly worse (8 points).
Proposed rhetorically prominent sites of a primary research article

Abstract
   A1 - First sentence stating results
   A2 - Final sentence

Discussion section
   D1 - First sentence
   D2 - First sentence of last paragraph
   D3 - Last sentence of last paragraph
Patients treated with donepezil showed dose-related improvements in the Alzheimer’s Disease Assessment Scale – cognitive subscale score (ADAS-cog) and MMSE scores.

Importantly, donepezil was not associated with any hepatotoxicity, as observed with acridine-based cholinesterase inhibitors.

...demonstrated donepezil, at a dosage of 5mg daily, to be clinically effective...

...donepezil...provides significant clinical improvements....

The close relationship between RBC AChE inhibition and clinical response...a potential marker of its effectiveness.
A1 …subscale scores improved…during donepezil
A2 – This independent confirmation…suggests that donepezil modestly improves cognition in patients with Alzheimer disease who are encountered in clinical practice
D1 – The results of our study show a modest beneficial effect of donepezil therapy….
D2 …our results demonstrate a small beneficial effect of donepezil therapy on cognitive performance without evidence for improved global function.
D3 – Our results support the use of donepezil in clinical practice but also highlight the need for new and more effective treatment for AD.
Homma A, Takeda M, Imai Y et al.  
Dement Geriatr Cogn Disord 2000;11:299-313

A1 …better effects than that of placebo were confirmed
A2 – These results indicate that donepezil appears to be effective and well tolerated…
D1 ....
D2 …donepezil hydrochloride at 5mg /day is well tolerated…and is effective….
D3 *
A1 – The benefit of donepezil over placebo was demonstrated….

A2 …these data support donepezil as a well tolerated and effective long-term treatment….

D1 – This study…confirms the beneficial effects of donepezil

D2 ….

D3 – This study therefore confirms…that donepezil is an effective treatment in the long term, and stresses the importance of continued donepezil treatment….
A1 – Cognition averaged 0.8 MMSE points better (95% CI 0.5-1.2; \( P < .0001 \)) and functionality 1.0 BADLS points better (0.5-1.6; \( P < .0001 \)) with donepezil over the first 2 years.

A2 – More effective treatments than cholinesterase inhibitors are needed for Alzheimer’s disease

D1 – The findings….accord with those of previous reports that donepezil produces small improvements…. 

D2 …

D3 – More importantly, though, more effective medical or non-medical treatments than cholinesterase inhibitors are needed for Alzheimer’s disease.
<table>
<thead>
<tr>
<th>Rhetoric in 15 sponsored papers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“Effective…treating…symptoms”</td>
<td>4x in three early papers</td>
</tr>
<tr>
<td>“Well tolerated and efficacious”, “well tolerated and effective”, “effective and well tolerated”</td>
<td>11x in 5 papers</td>
</tr>
<tr>
<td>“significant” drug effects</td>
<td>10x; only once modified by “statistically”</td>
</tr>
<tr>
<td>Confirmation of prior demonstrated efficacy</td>
<td>15x</td>
</tr>
</tbody>
</table>
| Advocacy of unlabeled indications | Early disease 1x  
Neuropsychiatric sx 1x  
More severe dementia 5x (in advance of FDA labeling extension) |
| Strong advice on drug use        | “Long term” 1x  
“throughout the course of AD” 1x |
<p>| Ethical challenge against further randomization | 1x |</p>
<table>
<thead>
<tr>
<th>Rhetoric in 3 non-sponsored papers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“small” effects</td>
<td>2x</td>
</tr>
<tr>
<td>Call for better dementia treatments</td>
<td>2x</td>
</tr>
<tr>
<td>Emphasis on negative results (“not more effective than placebo”, “not…an effective alternative.”)</td>
<td>1x</td>
</tr>
</tbody>
</table>
Physicians’ professional commitments

Professional competence
Honesty with patients
Patient confidentiality
Maintaining appropriate relations with patients
Improving quality of care
Improving access to care
Seeking just distribution of resources
Fostering scientific knowledge
Maintaining trust by managing conflict of interest
Self-governance of the profession

Adapted from
ABIM Foundation et al, Annals 2002
“Public discourse about...published evidence of efficacy and safety rests on the assumption that clinical trials data have been gathered and are presented in an objective and dispassionate manner.”

Davidoff et al NEJM 2001
Disclosure of industry affiliation does not relieve us of the responsibility to conduct and present research in accordance with the principles of medical professionalism.