

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

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Medical Professionalism in the New Millennium: A Physician Charter

Project of the ABIM Foundation, ACP-ASIM Foundation,
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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

Results	Alzheimer's Disease Assessment Scale—Cognitive Subscale	Mini-Mental State Examination	Clinical Global Impression of Change	Clinician's Interview-Based Impression of Change	Clinical Dementia Rating—Sum of the Boxes	Quality of Life—Patient Rated	Neuropsychiatric Inventory
Number of points in scale	70	30	7	7	18	350	144
Vendor-sponsored trials							
Trials, n	6	11	2	4	8	4	5
Range of significant results	1.5–3.2	0.68–1.8	9.0–23%*	0.34–0.54	0.4–0.85 [†]		1.7–5.6
Negative trials, n	—	2	—	—	4	3	3
Non-vendor-sponsored trials							
Trials, n	1	2	2	—	—	—	2
Range of significant results	2.2	0.8–1.55	—	—	—	—	—
Negative trials, n	—	—	2	—	—	—	2

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

Rogers SL, Friedhoff LT. Dementia 1996;7:293-303

- A1 – Patients treated with donepezil showed dose-related improvements in the Alzheimer’s Disease Assessment Scale – cognitive subscale score (ADAS-cog) and MMSE scores
- A2 – Importantly, donepezil was not associated with any hepatotoxicity, as observed with acridine-based cholinesterase inhibitors.
- D1 ...demonstrated donepezil, at a dosage of 5mg daily, to be clinically effective...
- D2 ...donepezil...provides significant clinical improvements....
- D3 – The close relationship between RBC AChE inhibition and clinical response...a potential marker of its effectiveness

Greenburg SM, Tennis MK, Brown LB et al.
Arch Neurol 2000;57:94-99

- 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 *

Winblad B, Engedal K, Soininen H et al.
Neurology 2001;57:489-495

- 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....

Courtney C, Farrell D, Gray R et al.
Lancet 2004;363:2105-2115

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.

Rhetoric in 15 sponsored papers

“Effective...treating...symptoms”	4x in three early papers
“Well tolerated and efficacious”, “well tolerated and effective”, “effective and well tolerated”	11x in 5 papers
“significant” drug effects	10x; only once modified by “statistically”
Confirmation of prior demonstrated efficacy	15x
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
Ethical challenge against further randomization	1x

Rhetoric in 3 non-sponsored papers

“small” effects	2x
Call for better dementia treatments	2x
Emphasis on negative results (“not more effective than placebo”, “not...an effective alternative.”)	1x

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

“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.”

Disclosure of industry affiliation does not relieve us of the responsibility to conduct and present research in accordance with the principles of medical professionalism