

Results, Rhetoric, and Randomized Trials: The Case of Donepezil

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(See comments by Dr. Martin Farlow pp 1566–1567)

Whether donepezil provides meaningful benefit to patients with Alzheimer's disease (AD) is controversial, but drug sales annually total billions of dollars. A review of data from published randomized clinical trials (RCTs) found rhetorical patterns that may encourage use of this drug.

To create a reproducible observation, the sentences occurring at five specific text sites in all 18 RCTs of donepezil for AD were tabulated, as were study design, sources of financial support, and outcomes that could be compared between trials.

Rhetoric in the 13 vendor-supported trials (15 publications) was strongly positive. Three early trials used the motif "efficacious (or effective) . . . treating . . . symptoms" four times. "Well-tolerated and efficacious" or an equivalent motif appeared 11 times in five RCTs. Nine RCTs referred 15 times to previously proven effectiveness. Seven trials encourage off-label use, for "early" cognitive impairment, severe dementia in advance of the Food and Drug Administration labeling change, or behavioral symptoms. These rhetorical motifs and themes appeared only in the vendor-supported trials. Trials without vendor support described the drug's effects as "small" or absent; two emphasized the need for better treatments. RCT results were highly consistent in all trials; the small differences do not explain differences in rhetoric.

At these text sites in the primary research literature on donepezil for AD, uniformly positive rhetoric is present in all vendor-supported RCTs. Reference to the limited benefit of donepezil is confined to RCTs without vendor support. Data in the trials are highly consistent. This observation generates the hypothesis that rhetoric in vendor-supported published RCTs may promote vendors' products. *J Am Geriatr Soc* 56:1556–1562, 2008.

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DRUG INDUSTRY, DONEPEZIL, RHETORIC, ALZHEIMER'S DISEASE, RANDOMIZED CLINICAL TRIAL

The proper role of cholinesterase inhibitors (ChEIs) in managing Alzheimer's disease (AD) remains debatable. One influential review states that they "should be considered as a standard of care,"¹ whereas another concludes that "the scientific basis for recommendations of ChEIs for the treatment of AD is questionable."² The American Academy of Neurology Practice Parameter makes the following practice recommendation: "Pharmacologic treatment of AD. Cholinesterase inhibitors should be considered in patients with mild to moderate AD (Standard), although studies suggest a small average degree of benefit."³

To help patients and caregivers when considering ChEIs, the published randomized clinical trials (RCTs) of donepezil for patients with clinical dementia of the Alzheimer's type were reviewed and their findings summarized. In reviewing these papers, unexpected rhetorical patterns were found.

Rhetoric is an acknowledged component of biomedical writing, but routine methods of recognizing its effects are lacking. One study⁴ analyzed strategies of rhetorical influence in a group of articles on headache and produced an illuminating "inventory of discourse features" organized on Aristotelian principles. For example, it identified the common practice of introducing an article with prevalence or cost data—"what Aristotle called the *topos* of degree"—as a logical appeal to readers, within the category of rhetorical means called invention. This critical inquiry focused on authors' efforts to persuade readers of the credibility and importance of themselves and their work. Another study⁵ emphasized the potential for "rhetorical manipulation" by authors and called for linguistic analysis as a third arm of peer review, but its recommendation has not been widely adopted. A third study⁶ documented several instances of interpretive bias that induce "spin" on data from the United

Kingdom Prospective Diabetes Study and proposed several types, such as the “If enough people say it, it must be true,” the “We’ve shown something here,” and the “What the hell can we tell the public?” biases. Going one step farther, a fourth study⁷ advises readers in its “Users’ guide to detecting misleading claims in clinical research reports” to avoid the discussion section altogether. The goal of the current review is to present a primitive linguistic analysis of the primary research literature on donepezil—a systematic sample of prominently displayed rhetoric—along with the RCTs’ funding and findings.

METHODS

All primary analyses of placebo-controlled RCTs of donepezil for AD were identified using a PubMed search in November 2007. Trials of patients with comorbidities (e.g., Down syndrome or Parkinson’s disease) and trials that did not report clinical outcomes (e.g., those that studied functional neuroimaging) were excluded. Sentences from five prominent text sites in each report were tabulated: two from the Abstract (first sentence of results and final sentence) and three from the Discussion section (first sentence and first and last sentences of the final paragraph). These sites were specified after review of the first nine publications. Recurring rhetorical elements were highlighted.

To compare results as a possible explanation for the differences in rhetoric, outcomes of all measures that were used in at least three different RCTs were tabulated. Study characteristics and sources of funding were also tabulated for each RCT.

No external funding was received for this study, nor did an institutional review board review it. The investigators were not blinded to author or sponsorship.

RESULTS

Eighteen articles^{8–25} reporting data from 16 RCTs met the inclusion criteria. Three of these articles^{16,18,22} were based on a single RCT. In all but one of the 18 articles, sponsorship was declared. For the remaining article, a letter was written to the author, who provided written verification of the source of sponsorship.¹³

Excerpts from the selected sentences from these articles are shown in Table 1. The complete sentences are not presented, because, in some cases, it was not possible to obtain copyright permission for reproduction. Table 2 presents size, duration, donepezil doses, and funding support for each of the articles. Table 3 presents results of measures that were reported in at least three different trials, along with the scale of these measures.

Several recurrent motifs can be seen in Table 1. “Efficacious (or effective) . . . treating . . . symptoms” occurred four times in three early papers.^{9–11} The phrases “well tolerated and efficacious,” “well tolerated and effective,” and “effective and well tolerated” appeared 11 times in five vendor-supported RCTs.^{10,11,13,15,23} Drug effects were called “significant” 10 times, only once with mention that the significance was statistical.^{8–11,20–22}

References to confirmation of previously demonstrated efficacy were made 15 times.^{9,11,12,14–17,20,25} One publication made the strong claim that “results such as ours raise ethical and practical concerns regarding randomization of

patients with AD to placebo in clinical trials of more than a few months duration.”¹⁴ Another stressed the importance of continuing therapy “long term” on the basis of a 1-year study.¹⁵ Seven articles’ sentences endorsed the drug for unlabeled indications: one for early disease;²⁰ one for neuropsychiatric symptoms and in frail, older patients;²¹ and five for more-severe dementia in advance of the Food and Drug Administration extension of indications to severe disease in October 2006.^{16–18,22,23} The most recent emphasized donepezil’s benefit “throughout the course of AD” in its final sentence, although the study reported in the article examined only severe disease.²⁵

All of the RCTs with these rhetorical devices were sponsored by the vendors of donepezil.

Two trials used the word “small” to describe the effects of donepezil, and both noted the need for better dementia treatments.^{12,19} The vendors of donepezil did not sponsor either of these. A third nonsponsored paper emphasized the drug’s limitations with the negative statements “not more effective than placebo” and “not . . . an effective alternative.”²⁴ There were no nonsponsored trials that contained the positive rhetoric identified in the sponsored trials.

The studies and their results are consistent, regardless of sponsorship. All significant differences favored donepezil except for one sponsored study, in which quality of life was significantly better on placebo or 5 mg than on 10 mg of donepezil.⁹ The 70-point Alzheimer’s Disease Assessment Scale—cognitive subscale (ADAS-cog) was used in seven RCTs, and donepezil was statistically superior to placebo in all comparisons. Treatment effect, defined as the difference between donepezil and placebo at the end of the randomized comparison interval, ranged from 1.5 to 3.2 points; in the trial not sponsored by a vendor,¹⁹ the difference was 2.17. On the 30-point Mini-Mental State Examination (MMSE), used in 13 RCTs, the treatment effect ranged from 0.68 to 1.79 points. Two of these 13 were non-vendor-supported and found statistically significant treatment effects of 0.8 and 1.55 points.^{19,24} For patients with moderate dementia, the average annual change in ADAS-cog score is 7 to 11 points and in MMSE score is 2 to 4 points.²⁵ All treatment effects, whether vendor sponsored or not vendor sponsored, fell within this range. Two other dementia rating scales were used in sponsored and nonsponsored trials. In the Clinical Global Impression of Change, two sponsored trials found an increase of 9% and 23% in the number of subjects scoring 4 through 7 on a 7-point Likert scale,^{8,13} whereas two nonsponsored trials found no treatment effect.^{12,24} In the Neuropsychiatric Inventory, three of five sponsored trials showed no treatment effect,^{15,17} as did two nonsponsored trials.^{19,24}

DISCUSSION

This simple tabulation of sentences identified several rhetorical techniques, including motifs with positive messages; use of ambiguity to imply clinical as well as statistical effects; and recurring invocation of earlier evidence to establish a “weight of rhetoric.” These rhetorical techniques are present only in the vendor-supported trials, and they impart a clear message that these drugs produce important benefits and do so for a wide range of patients. In contrast, rhetoric in two of the RCTs not supported by the

Table 1. Excerpts of Sentences Cited Prominently in Articles About Randomized Clinical Trials of Donepezil for Alzheimer's Disease**Rogers (1996)⁸**

- 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. . . . demonstrate donepezil, at a dosage of 5 mg 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.

Rogers (1998)⁹

- A1. Cognitive function, as measured by the ADAS-cog, was significantly improved . . . at weeks 12, 18 and 24.
- A2. . . . donepezil is a well-tolerated drug that improves cognition . . . and global function in patients with mild to moderate AD.
- D1. This 24-week trial confirms that donepezil is efficacious in treating symptoms
- D2. The results of this trial demonstrate that donepezil improves both cognition and global function
- D3. . . .

Rogers (1998)¹⁰

- A1. . . . donepezil produced statistically significant improvements in ADAS-cog, CIBIC plus, and Mini-Mental State Examinations. . . .
- A2. Donepezil . . . is a well-tolerated and efficacious agent for treating the symptoms of mildly to moderately severe Alzheimer's disease.
- D1. . . . donepezil enhances cognition, measured by standardized psychometric testing, and improves clinician-rated global function.
- D2. . . . donepezil is a well-tolerated and efficacious agent
- D3. Further studies are needed to define the role of donepezil in treating patients more severely affected with AD

Burns (1999)¹¹

- A1. Statistically significant improvements in cognitive and global function were observed,
- A2. The results of this study confirm that donepezil is effective and well tolerated in treating the symptoms
- D1. The results . . . confirm previously published findings that . . . donepezil significantly improve(s) cognitive and global functioning in patients with mild to moderately severe AD.
- D2. Results . . . confirm previous findings that donepezil is well tolerated and efficacious in treating the symptoms
- D3. . . . donepezil therapy is an effective and well tolerated symptomatic treatment

Greenberg (2000)¹²

- A1. . . . subscale scores improved . . . during donepezil
- A2. This independent confirmation . . . suggests that donepezil therapy 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 (2000)¹³

- 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 5 mg/day is well tolerated. . . and is effective*

Mohs (2001)¹⁴

- A1. Donepezil extended the median time to clinically evident functional decline
- A2. . . . treatment with donepezil for 1 year was associated with a 38% reduction in the risk of functional
- D1. . . . the median time to clinically evident functional decline was delayed by five months
- D2. . . . ChE inhibitors have been shown in previous studies to improve cognition, behavior, and function
- D3. . . . results such as ours raise ethical and practical concerns regarding randomization of patients with AD to placebo in clinical trials of more than a few months duration.

Winblad (2001)¹⁵

- 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

Feldman (2001)¹⁶

- A1. Patients receiving donepezil showed benefits
- A2. These data suggest that donepezil's benefits extend into more advanced stages of AD . . . with very good tolerability.
- D1. . . .
- D2. Together with a good tolerability profile, . . . these data suggest that the benefits of donepezil extend into the moderate to severe stages of AD.
- D3. A confirmatory study is currently being undertaken

(Continued)

Table 1. (Contd.)

Tariot (2001)¹⁷

- A1. . . . scores improved relative to baseline for both groups, with no significant differences observed between the groups at any assessment.
- A2. In summary, . . . findings are consistent with previous findings . . . and support the use of donepezil in patients with AD who reside in nursing homes.
- D1. The results . . . provide insight into the efficacy and safety of donepezil in patients who generally are older and more medically complex and have more severe AD . . .
- D2. . . . benefits of donepezil treatment on cognition and overall dementia severity were evident in these nursing home patients
- D3. . . . advanced age, comorbid medical conditions, and concomitant medication usage need not be barriers to donepezil treatment.

Feldman (2003)¹⁸

- A1. . . . scores for donepezil-treated patients showed a slower decline during the study than placebo-treated patients
- A2. The ADL benefits in AD patients treated with donepezil
- D1.
- D2.
- D3. . . . these clinical benefits with donepezil in patients with moderate to severe AD may result in additional measurable benefits to their caregivers.

Courtney (2004)¹⁹

- A1. Cognition averaged 0–8 MMSE (Mini-Mental State Examination) 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. Most importantly, though, more effective medical or non-medical treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

Seltzer (2004)²⁰

- A1. Improvements favoring donepezil on the Alzheimer Disease Assessment Scale-cognitive subscale were found at weeks 12 and 24 and at the end point (last observation carried forward
- A2. . . . significant treatment benefits of donepezil in early-stage Alzheimer disease, supporting the initiation of therapy early in the disease course. . . .
- D1. . . . donepezil treatment resulted in significant improvements in cognitive functions . . . in patients with early-stage AD
- D2. The robust effect of donepezil on cognitive performance provides further evidence of the benefit of early initiation
- D3. Longer-term studies are required

Holmes (2004)²¹

- A1.
- A2. Donepezil has significant efficacy in the treatment of neuropsychiatric symptoms
- D1. . . . support the use of donepezil in the treatment of neuropsychiatric symptoms
- D2. Patients . . . receiving open-label donepezil showed significant improvements in a wide range of neuropsychiatric symptoms
- D3. . . . psychotropic medication may also have a deleterious effect on the potential cognitive improvement afforded by donepezil

Feldman (2005)²²

- A1. . . . scores for donepezil patients were significantly improved
- A2. . . . the treatment effects of donepezil were not driven by a particular stratum within the moderate to severe dementia range.
- D1. . . . the findings reported here for the more severe AD subgroup and the consistency of donepezil's beneficial treatment effects across the range of moderate to severe dementia suggest that donepezil is efficacious beyond the moderate stage
- D3*. . . . discontinuation of treatment based solely on a pre-specified MMSE score may neither be neurobiologically based nor clinically supported.

Winblad (2006)²³

- A1.
- A2. Donepezil improves cognition and preserves function in individuals with severe AD
- D1. . . . donepezil can improve cognition and preserves function . . . in patients' with severe AD.
- D3*. . . . donepezil is an effective and well tolerated treatment even when initiated in patients with severe AD.*

Howard (2007)²⁴

- A1. . . . no significant difference between the effects of donepezil and those of placebo
- A2. . . . donepezil was not more effective than placebo. . . .
- D1.
- D2.
- D3. The results of our trial suggest that the cholinesterase inhibitors do not represent an effective alternative treatment for clinically significant agitation

Black (2007)²⁵

- A1.
- A2.
- D1. . . . further evidence that donepezil benefits cognition and global function
- D2. . . . findings, taken together with those of prior studies, provide evidence to support what more recent basic research has already suggested
- D3. In view of the consistent positive results of trials in mild, moderate, and severe patient populations, donepezil may be considered to be beneficial throughout the course of AD.

From each publication, the first sentence from the Results section of the Abstract (A1) and the final sentence the Abstract (A2) and the first sentence of the Discussion (D1) and first (D2) and last (D3) sentence of the final paragraph of the Discussion are tabulated.

*The final paragraph consisted of a single sentence.

Table 2. Characteristics of Donepezil Randomized Clinical Trials

Reference	Length (weeks)	Number Randomized	Donepezil Dose (mg)	Sponsor
Rogers (1996) ⁸	12	161	1, 3, 5	Eisai
Rogers (1998) ⁹	24	473	5, 10	Eisai
Rogers (1998) ¹⁰	12	468	5, 10	Eisai
Burns (1999) ¹¹	24	818	5, 10	Eisai
Greenberg (2000) ¹²	12 (crossover)	60	5	National Institute of Aging
Homma (2000) ¹³	24	268	5	Eisai
Mohs (2001) ¹⁴	54	431	10	Eisai/Pfizer
Winblad (2001) ¹⁵	52	286	10	Pfizer
Feldman (2001) ¹⁶	24	208	10	Pfizer/Eisai
Tariot (2001) ¹⁷	24	290	10	Eisai/Pfizer
Feldman (2003) ¹⁸			Same RCT as reference 16	
Courtney (2004) ¹⁹	114	566	5, 10	National Health Service, United Kingdom
Seltzer (2004) ²⁰	24	153	10	Eisai/Pfizer
Holmes (2004) ²¹	12	96	10	Pfizer/Eisai
Feldman (2005) ²²			Same RCT as reference 16	
Winblad (2006) ²³	24	248	10	Eisai/Pfizer
Howard (2007) ²⁴	12	272	10	Medical Research Council/Alzheimer's Association
Black (2007) ²⁵	24	343	10	Eisai/Pfizer

pharmaceutical industry characterize benefits as “small,” congruent with the American Academy of Neurology Practice Recommendation’s “small average degree of benefit,” and only these two RCTs refer to the need for better treatments. The data from all trials, regardless of sponsorship, were highly consistent when comparison is possible (Table 3); all showed an average degree of benefit equivalent to a few months’s change in the progression of AD.

The major weakness of the current study is that the rhetorical analysis was not prespecified. The five text sites were selected only after several of the articles had been read. No other rhetorical techniques, such as grammatical structure or argument strategy, or any graphical techniques were prespecified or examined. These sites have not been vali-

dated and may not accurately or optimally represent an article’s interpretive stance. In the absence of blinding, our own interpretive biases may have influenced our choice of text sites. Nevertheless, what has been tabulated here are only the authors’ own words, chosen in a systematic, context-free, reproducible way. Finally, the RCT rhetoric was not compared with the complete data in individual articles, although where comparison is possible, the findings are comparable.

A major strength of this study is its simplicity. Limiting the analysis to RCTs of a single drug for a single disease enhances comparisons of rhetoric by limiting heterogeneity of outcomes. Substantial heterogeneity remains, because “about 23 different scales or instruments (on average 6 per

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	Neuro-psychiatric 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).

trial) were used. . . . Most of them were not validated for the disease for which the drugs were tested and are not currently used in clinical practice” in the RCTs of ChEIs.²⁶ Another strength is the reproducible analytical framework based on specified text sites in uniformly structured scientific articles, which introduces a degree of objectivity into what could easily be a hopelessly subjective inquiry. Although focus on other text sites might yield other insights, the findings here are themselves meaningful.

For several reasons, vendor influence on the rhetoric of vendor-supported RCTs is a valid concern. Rhetorical enthusiasm about donepezil is present if and only if there is vendor support. Employees of the vendors of donepezil are authors of all but one of the vendor-sponsored RCTs. The rhetoric has obvious promotional value. Other promotional devices are found elsewhere in the vendor-sponsored RCTs. For example, in two early vendor-sponsored RCTs, the brand name of the drug is provided in the first line of the abstract or elsewhere on the first page. While evidently permissible in these journals, this placement has promotional value.

The recurrence across several papers of nearly identical positive messages, such as the “efficacious . . . treating . . . symptoms” motif, raises the possibility that company guidance may have influenced authors’ choice of words and phrases or that professional medical writers may have assisted in preparation of the manuscripts. Discussing a lawsuit involving papers alleged to have been produced by drug company writers, then signed by academic physicians as their own, a medical writer in 1999 described her experience: “I was given an outline, references, and a list of drug-company approved phrases. . . . I was pressured to rework my drafts to position the product more favorably.”²⁷ The problem has been described in detail.²⁸ Since 2004, the World Association of Medical Editors has required that writers who “draft or revise the article” and their sponsors be identified.²⁹ There was no evidence about whether any of the RCTs discussed here were in any way ghostwritten.

Documents from a successful lawsuit against gabapentin’s vendors demonstrated clearly how a vendor can develop a “publication strategy” with promotional intent. A medical education company’s proposal to the vendor of gabapentin, for example, promised that “all articles submitted will include a consistent message.” It has been shown how this lawsuit uncovered “activities traditionally considered independent of promotional intent, including continuing medical education and research, (that) were extensively used to promote gabapentin. New strategies are needed to ensure a clear separation between scientific and commercial activity.”³⁰

Intentionally promotional rhetoric within the text of an RCT may be particularly effective because the difference between scientific and commercial activity is so unclear. Thus, readers of scientific articles may not anticipate embedded promotional rhetoric, because “public discourse about this 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.”³¹

Our hypothesis-generating study suggests that industry-sponsored authors may have taken advantage of this

assumption. The uniformly favorable rhetoric in their published RCTs may have helped promote the multibillion-dollar commercial success of a drug whose clinical relevance remains uncertain.

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