International Journal of Technology Assessment in Health Care, **18:3** (2002), 497–507.

CLINICAL AND COST-EFFECTIVENESS OF DONEPEZIL, RIVASTIGMINE, AND GALANTAMINE FOR ALZHEIMER'S DISEASE

A Systematic Review

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Abstract

Objectives: Systematic review of the clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for people suffering from Alzheimer's disease.
Methods: Sixteen electronic databases (including MEDLINE, the Cochrane Library, and Embase) and bibliographies of related papers were searched for published/unpublished English language studies, and experts and pharmaceutical companies were consulted for additional information. Randomized controlled trials (RCTs) and economic studies were selected. Clinical effectiveness was assessed on measurement scales assessing progression of Alzheimer's disease on the person's global health, cognition, functional ability, behavior and mood, and quality of life. Cost-effectiveness was presented as incremental cost per year spent in a nonsevere state (by Mini Mental Health State Examination) or quality-adjusted life-year.
Results: Twelve of 15 RCTs included were judged to be of good quality. Although donepezil had beneficial effects in Alzheimer's patients on global health and cognition, rivastigmine on global health, and galantamine on global health, cognition, and functional scales, these improvements were small and may not be clinically significant. Measures of quality of life and behavior and mood were rarely assessed. Adverse effects were usually mild and transient. Cost-effectiveness base case estimates ranged from £2,415 savings to £49,476 additional cost (1997 prices) per unit of effect for donepezil and a small savings for rivastigmine. Estimates were not considered robust or generalizable.
Conclusions: Donepezil, rivastigmine, and galantamine appear to have some clinical effect for people with Alzheimer's disease, although the extent to which these translate into real differences in everyday life remains unclear. Due to the nature of current economic studies, cost-effectiveness remains uncertain

The authors thank the advisory group for advice and peer review throughout the project, and Dr. Pam Royle and Ms. Liz Hodson for their assistance in obtaining information. This review was funded by the NHS R&D Health Technology Assessment Programme. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NHS Executive.

and the impact on different care sectors has been inadequately investigated. Further research is needed to establish the actual benefits of acetylcholinesterase inhibitors (AChEIs) for people with Alzheimer's disease and their caregivers, the relationship of these changes to clinical management, and careful prospective evaluation of resource and budgetary consequences.

Keywords: Alzheimer's disease, Cholinesterase inhibitors, Review

Alzheimer's disease is the most common cause of dementia, accounting for about half of dementia cases (2). With progressively aging populations in Europe and North America, the number of people with Alzheimer's disease is likely to increase (8;21). Acetylcholinesterase inhibitors (AChEIs), including donepezil, rivastigmine, and galantamine, have attracted growing interest from people with Alzheimer's disease, their caregivers, and specialists, who are used to coping with a devastating disease with no effective remedies. Prescribing of AChEIs varies among healthcare commissioners (3), partly due to uncertainties about the extent and meaning of any benefit to people with Alzheimer's disease and their caregivers (12;15;18;26) but also due to concerns about funding treatment. The provision and funding of care for people with Alzheimer's disease is complex, impacting on different formal and informal care sectors. Concerns remain over funding the provision of new treatments, the effect on competing uses for public funds, whether specific to dementia (such as support for caregivers and long-term residential care) or the provision of other services, and the consequences of any shift between sectors (such as burdens on caregivers).

In view of the continuing controversy over the effectiveness of AChEIs and the "postcode prescribing" that has resulted, the National Institute for Clinical Excellence (NICE) in the United Kingdom was asked to provide national guidance (27). This paper reports the results of an updated version of the original systematic review, commissioned to assist NICE in its deliberations on the clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine (10). Although several reviews of these drugs have been published, they tend to consider the drugs separately with no economic evaluation (6;7;32), appear unsystematic when assessed using standard criteria (39;43), or are known not to include recently published evidence (51).

METHODS

We searched for published and unpublished studies in the English language using 16 electronic databases, including MEDLINE, the Cochrane Library, Embase, and TOXLINE from their inception to May 2001 (details of the search strategy are presented elsewhere [10]). Additional references were identified through searching bibliographies of related publications and through contact with relevant topic experts and industry. Several unpublished industry studies were appraised, but none were included in this review because they were commercial in confidence. Partial information from these unpublished industry studies is reported in other studies (6;7). Studies reported as abstracts or conference presentations were excluded from the review because they inadequately report their methods and results and have not been peer-reviewed, precluding adequate appraisal.

We included randomized controlled trials (RCTs) and economic studies of donepezil, rivastigmine, or galantamine in people diagnosed with Alzheimer's disease. Outcome measures included global health, cognition, functional ability, behavior and mood, and quality of life for people with Alzheimer's disease and their caregivers. Cost-effectiveness was measured as incremental cost per year spent in Mini Mental Health State Examination (MMSE) state or quality-adjusted life-year (QALY), since these were the outcomes reported in the

economic evaluations. Although MMSE may be viewed as a measure of global health, it provides a general measure of cognition. It is not an ideal outcome measure for judging efficacy or quality of life (QoL) because it is insensitive to subtle changes in cognition or for capturing other medical, emotional, or social conditions.

Quality of studies was assessed using standard methods for internal validity (13;23) and through an adapted method for the external validity of economic evaluations (31) and model bias (41). Inclusion criteria were applied independently by two reviewers. Data were extracted and quality assessed by one reviewer and checked by a second reviewer, with any differences resolved through consensus.

To compare clinical and cost-effectiveness across different studies, consistent information was selected wherever possible. Clinical effectiveness was assessed through a narrative comparison of different outcomes, including mean change or proportion of patients changing from baseline, mean score, or mean difference between comparators with 95% confidence intervals for the different outcome measures. Meta-analysis was precluded due to differences in, or insufficient details on, outcomes used, patient characteristics, and drug dose and administration. Cost-effectiveness reported results using a common base case, defined as differentiating between effects on patients with mild to moderate Alzheimer's disease (measured by MMSE), an incremental change using placebo, or usual care versus low-dose therapy. U.K. currency was measured in 1997 prices, and best and worst case results of sensitivity analysis were reported. By combining evidence on quality of study, clinical effectiveness, base case incremental cost-effectiveness ratios, and reported sensitivity analyses of individual studies, a judgment about valid and generalizable clinical and cost-effectiveness could be reached for each drug.

RESULTS

Quantity and Quality of Studies

We included 15 placebo-controlled RCTs to assess clinical effectiveness; of those, six assessed donepezil (9;17;22;34;35;37), five assessed rivastigmine (1;11;16;38;42), and four, galantamine (33;48;49;50). Nine economic studies were included; of those, five assessed donepezil (24;28;30;44;47), four, rivastigmine (14;19;20;45), and none were found for galantamine. No RCTs with prospective data on resource utilization and cost were found; however, another study, the AD2000 study of donepezil (4), was identified but not included, since it has yet to publish results in full. Characteristics of, and results for, the RCTs and economic studies are summarized in Tables 1 and 2. Comparisons between results of economic studies should be made with caution, not least because they adopted different perspectives and therefore included different component costs and benefits.

Twelve RCTs were judged of good quality (Jadad score $\geq 4/5$), one of fairly good quality (Jadad score $= 3/5$), with only two of poor quality (Jadad score $\leq 2/5$). Eight RCTs lacked an adequate description of randomization (1;9;16;22;34;37;42;49), three RCTs had inadequate descriptions of blinding (16;22;49), and one RCT did not describe withdrawals (49). Nine RCTs failed to report results using intention to treat analysis (ITT) (1;16;17;33;34;35;37;48) or used a definition of ITT that was unclear (22). Of the 15 RCTs, 12 RCTs stated that they were supported by industry—four for donepezil (9;34;35;37), five for rivastigmine (1;11;16;38;42), and three for galantamine (33;48;50). In economic modeling, higher quality is associated with approaches that minimize four sources of bias: framing of the model, model construction, reliability of estimates used, and the way sensitivity analysis is performed (40). On this basis, and with limited access to the models, two studies appeared to be the most robust (28;30). Seven studies reached acceptable standards of internal validity (14;19;20;24;28;30;47), but the issue of generalizability was far less clear.

Table 1. Summary of the Quality of Studies and the Clinical Effectiveness of Donepezil, Rivastigmine, and Galantamine on Outcome Measures for Alzheimer's Disease

Study	Intervention	Jadad quality score	Global outcome measures	Cognitive outcome measures	Functional and quality of life measures
Donepezil					
Rogers et al. (37)	1 mg/d (n = 42) 3 mg/d (n = 40) 5 mg/d (n = 39) Placebo (n = 40)	4/5	CGIC (+) CDR (NS)	ADAS-cog (+) MMSE (NS)	ADL (NS) QoL (NS)
Rogers et al. (35)	5 mg/d (n = 154) 10 mg/d (n = 157) Placebo (n = 162)	5/5	CIBIC (+) CDR (+)	ADAS-cog (+) MMSE (+)	QoL (NS)
Rogers et al. (34)	5 mg/d (n = 157) 10 mg/d (n = 158) Placebo (n = 153)	4/5	CIBIC (+) CDR (NS)	ADAS-cog (+) MMSE (+)	QoL (−)
Burns et al. (9)	5 mg/d (n = 271) 10 mg/d (n = 273) Placebo (n = 274)	4/5	CDR (+)	ADAS-cog (+)	IDDD(+) QoL (NS)
Greenberg et al. (17)	5 mg/d (n = 30) Placebo (n = 30)	5/5	Caregiver-rated global impression (NS)	ADAS-cog (+) Verbal Memory/Fluency (NS)	Not assessed
Homma et al. (22)	5 mg/d (n = 134) Placebo (n = 129)	3/5	J-CGIC (+)	ADAS-J cog (+)	Not assessed
Rivastigmine					
Sramek et al. (42)	12 mg/d tid (n = 20) 12 mg/d bid (n = 20) Placebo (n = 10)	4/5	Not assessed	Not assessed	Not assessed
Agid et al. (1)	4 mg/d (n = 136) 6 mg/d (n = 133) Placebo (n = 133)	4/5	CGIC (+)	MMSE (NS)	PDS (+)

(*continued*)

Table 1. (*Continued*)

Study	Intervention	Jadad quality score	Global outcome measures	Cognitive outcome measures	Functional and quality of life measures
Corey-Bloom et al. (11)	3.5 mg/d (n = 233) 9.7 mg/d (n = 231) Placebo (n = 235)	5/5	CIBIC-plus (+) GDS (+)	ADAS-cog (+) MMSE (NS)	Not assessed
Forette et al. (16)	9.6 mg/d bid (n = 45) 10.1 mg/d bid (n = 45) Placebo (n = 24)	2/5	CIBIC-plus (+)	ADAS-cog (NS)	Not assessed
Rosler et al. (38)	3.7 mg/d (n = 243) 10.4 mg/d (n = 243) Placebo (n = 239)	5/5	CIBIC-plus (+) GDS (+)	ADAS-cog (NS) MMSE (+)	PDS (NS)
Galantamine					
Wilcock et al. (49)	22.5 mg/d (n = 83) 30 mg/d (n = 54) 45 mg/d (n = 54) Placebo (n = 62)	1/5	Not assessed	ADAS-cog (+)	Not assessed
Tariot et al. (48)	8 mg/d (n = 140) 16 mg/d (n = 279) 24 mg/d (n = 273) Placebo (n = 286)	5/5	CIBIC-plus (+)	ADAS-cog (+)	ADL (+)
Raskind et al. (2000) (33)	24 mg/d (n = 212) 32 mg/d (n = 211) Placebo (n = 213)	5/5	CIBIC-plus (+)	ADAS-cog (+)	ADL (NS)
Wilcock et al. (2000) (50)	24 mg/d (n = 220) 32 mg/d (n = 218) Placebo (n = 215)	5/5	CIBIC-plus (+)	ADAS-cog (+)	Not assessed

Abbreviations: ADL = Uniform Activities of Daily Living; ADAS-(J) cog = Alzheimer's Disease Assessment Scale (Japanese) cognitive subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; (J-) CGIC = (Japanese) Clinical Global Impression of Change; CIBIC plus = Clinicians Interview-based Impression of Change; DAD = Disability Assessment for Dementia scale; GDS = Global Deterioration Scale; IDDD = Interview for Deterioration in Daily Living in Dementia; MMSE = Mini-mental State Examination; mg/d = milligrams per day; n = number of patients; NS = not significant; PDS = Progressive Deterioration Scale; QoL = quality of life; (+) = significant beneficial effect; (–) = significant negative effect; bid = twice daily; tid = three times daily.

Table 2. Characteristics of Economic Studies

Donepezil					
Author	Stein (44)	Stewart et al. (47)	Jonsson et al. (24)	O'Brien et al. (30)	Neumann et al. (28)
Study type	Cost utility model	Cost-effectiveness model	Cost-effectiveness model	Cost-effectiveness model	Cost utility model
Perspective	Healthcare system	Societal	Health and social care systems	Societal	Societal
Base year	Not reported	1996/97 (?)	1995/98 (?)	1997	1997
Country of origin	U.K.	U.K.	Sweden	Canada	U.S.
Results (placebo vs. 5 mg):					(Pooled 5/10mg)
mild	—	£7,048/yr nss	—	—	£6,054/QALY
moderate	—	£1,210/yr nss	—	—	£49,476/QALY
all patients	—	–	£2,011/yr nss	£2,415/yr nss	—
Sensitivity analysis					
mild	—	£5,328–8,239/yr nss	—	—	?–£104,160/QALY
moderate	—	£942–1,310/yr nss	—	—	£2,344–286,440/QALY
all patients	£21,383–139,020/QALY	—	£25,918–?/yr nss	£3,600–11,488/yr nss	—

Rivastigmine				
Author	Stein (45)	Fenn and Gray (14)	Hauber et al. (20)	Hauber et al. (19)
Study type	Cost utility model	Cost-savings model	Cost-effectiveness model	Cost-consequence model
Perspective	Healthcare system	Health and social care systems	?	Societal
Base year	?	1997	1997	1997
Country of origin	U.K.	U.K.	U.S.	Canada
Range of results*	£10,263–88,915/QALY	Cost saving	Cost saving	Net cost–cost saving

Abbreviations: ? = unclear information reported; (–) = cost saving; (—) = not reported; yr nss = year per nonsevere state (measured by MMSE); moderate = Alzheimer's patients with moderate disease; mild = Alzheimer's patients with mild disease; * = no base case, variable/pooled drug doses and units of cost savings unclear.

In seven of the nine economic studies, there was industry collaboration or funding, including four studies of donepezil (24;28;30;46) and three of rivastigmine (14;19;20), although full publishing control was retained by the external authors for two of the studies (28;30).

Clinical Effectiveness of Donepezil

Of the six RCTs (Table 1), five showed statistically significant benefits for global outcomes (9;22;34;35;37) and six for cognitive outcomes (9;17;22;34;35;37). Four RCTs assessed the effect of donepezil on function and quality of life, three showed no significant effect on quality of life (9;35;37), while one RCT found significant worsening of quality of life (34). One of the two RCTs assessing functional outcomes showed significant beneficial effects (9). None of the RCTs examined measures of behavior and mood. Adverse effects of donepezil tended to be mild and transient (e.g., nausea, vomiting, and diarrhea).

Clinical Effectiveness of Rivastigmine

Rivastigmine was shown to have a statistically significant benefit for global outcomes in all four RCTs assessing these measures (Table 1) (1;11;16;38). The beneficial effect on cognitive outcomes was shown in two of four RCTs (11;38). Only two RCTs examined the effect of rivastigmine on functional measures (1;38), with one showing beneficial effects (1). None of the RCTs considered quality of life or behavioral and mood outcome measures. Adverse effects were considered mild and transient (e.g., nausea, vomiting, and diarrhea).

Clinical Effectiveness of Galantamine

Of the four RCTs using galantamine (Table 1), three showed statistically significant benefit for global outcomes (33;48;50) and four for cognitive outcomes (33;48;49;50). Functional outcomes were examined by two RCTs (33;48), with only one showing a significant beneficial effect (48). One RCT assessed measures of behavior and mood (48), finding a statistically significant benefit for Alzheimer's sufferers. No studies looked at the effects of galantamine on quality of life. Adverse effects were mild and transient (e.g., nausea, vomiting, and diarrhea).

Cost-effectiveness of Donepezil

These produced a very wide range of estimates (Table 2). Two reported cost savings of £2,011(24) to £2,415 (30) per year in nonsevere states for all cases. This contrasted with another study that estimated costs of £1,210 and £7,048 per year in nonsevere states for mild and moderate cases, respectively (47). A further study estimated costs of £6,054 and £49,476 per QALY for mild and moderate cases, respectively (28). The fifth study could not be reported in base case format (44). The robustness of these data similarly fluctuated on the basis of the author's own best and worst case estimates including, in some cases, producing conflicting results for subgroups.

Cost-effectiveness of Rivastigmine

The evidence from rivastigmine was harder to interpret (Table 2). The oldest U.K. study (45) has been superseded. Cost-effectiveness ratios in two studies (14;20) could not be extracted because overall effectiveness was not reported and interpretation of their costs was difficult due to the exclusion of drug therapy costs. The Canadian study (19) found average net costs in the first year and cost saving by the end of 2 years, but it was unclear how this translated into an incremental cost-effectiveness ratio.

DISCUSSION AND CONCLUSIONS

Evidence of clinical effectiveness appeared to be of good quality, showing donepezil, rivastigmine, and galantamine to have some beneficial effect for people with Alzheimer's disease when assessed using global and cognitive outcomes. It has been suggested that the benefits of donepezil in delaying progression extend beyond a year, although this was based on an open label extension to an RCT (36). On outcomes of functional ability, behavior and mood and quality of life evidence was inconclusive. Adverse effects were mild and transient.

Evidence of cost effectiveness was more equivocal. Quality of economic studies was mixed, with internal validity acceptable in most studies but external validity less clear. The economic impact of these new drugs is not just prescribing costs *per se* but also their ability to delay entry into institutional care and displace residential care costs to the community. Estimates were based on international studies and models, which varied markedly in context, limiting the reliability and applicability of findings to other countries.

Some economic studies based estimates of savings on predicted delay in admission to institutional care. However, such estimates need to be interpreted with caution. First, if one person is not admitted, the place may just be used by another, with no real savings. Second, those on the margins of institutionalization may require the highest level of support in the community but the lowest in institutions, and there may be little or no cost difference. Third, the question of who pays is important, whether the patient, family members, social care, or health care.

Consistent methods for undertaking systematic reviews were applied throughout the review (29), with support from an expert advisory group including clinicians, patient representatives, and academics. Possible limitations were lack of follow-up with authors to clarify potential overlaps of studies, focus on RCTs to the exclusion of observational designs due to concerns over potential bias, use of the Jadad scale for assessing methodologic quality when it may more accurately reflect how well a study was reported (25), and the use of the National Health Service and Personal Social Services perspective for the economic evaluation, which excludes the costing of informal care.

Possible inadequacies in individual studies may undermine any evidence of effectiveness. Limited attention was paid to measures of function, quality of life, and behavior and mood, as well as to the meaning of other outcomes to people with Alzheimer's disease and their caregivers, rendering the judgments of effectiveness unclear. This may reflect the reliance of drug licensing authorities on global and cognitive outcomes and on the difficulties in developing valid and reliable quality of life measures. Research is under way to evaluate current methodology and to develop a more responsive measure (http://www.hta.nhsweb.nhs.uk/). Studies assessing the clinical effectiveness of AChEls were of short duration ($\leq$52 weeks), considerably less than the usual period over which people may suffer from Alzheimer's disease (up to approximately 10 years). Limited information on patient characteristics was provided by studies, affecting any assessment among different patient subgroups or the generalizability of findings to patients referred in practice (6;7). Many of the studies failed to report results using ITT analysis or used an unclear definition. When coupled with the high attrition of patients, usually among those with more advanced disease, there is the opportunity for bias (6;7). Several studies were either sponsored or undertaken by the manufacturers of the drugs, which may bring into question their independence and lead to fears of bias (5). Although excluded from the review, the unpublished commercial in confidence studies provided by industry would not have changed our overall conclusions. Subsequently, partial information from these manufacturer studies has been published (6;7).

Several areas for further research have become evident, including assessment of quality of life outcomes and the meaning of outcomes to patients and caregivers, the measurement

of longer term outcomes to closer reflect the progression of Alzheimer's disease and the likely use of these drugs, assessment of effectiveness among patient subgroups, comparison with nondrug therapies, and prospective economic analysis. Many of these questions are being addressed for donepezil (4). Similar research is needed for rivastigmine, galantamine, and other AChEIs under development.

POLICY IMPLICATIONS

Although clinically effective, the benefit of donepezil, rivastigmine, and galantamine for people with Alzheimer's disease and their caregivers remains unclear. Due to the nature of current economic studies, cost-effectiveness remains uncertain, while the impact on different care sectors remains inadequately investigated. The decision to recommend the use of donepezil, rivastigmine, and galantamine to people with Alzheimer's disease would need financing from additional funding or from other competing uses of health and social care funds for dementia. There is considerable demand for these drugs, and this is likely to increase with the aging population. It is important that the impact of any policy change on the formal and informal care sectors is assessed prior to implementation. With important new evidence on the horizon, we recommend that our findings be periodically reviewed/revised.

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