Impact of rivastigmine on costs and on time spent in caregiving for families of patients with Alzheimer's disease


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of the cholinesterase inhibitor rivastigmine (6 to 12 mg/day) in patients with Alzheimer's disease (AD). This intervention was compared with placebo.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients meeting the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD and residing in the community with a primary caregiver. The primary caregiver was defined in this study as the individual responsible for the patient's daily care.

Setting
The setting was the community. The economic study was carried out in the USA.

Dates to which data relate
The authors did not report the dates of the study undertaken to estimate the burden associated with care-giving. The delay of progression associated with rivastigmine treatment was derived from a study published in 2000. The price year was 1997.

Source of effectiveness data
To estimate the burden associated with the care-giving of AD patients, the authors undertook a prospective observational study of AD patients and their caregivers. The delay of progression associated with rivastigmine treatment was derived from efficacy trial data (Hauber et al., see Other Publications of Related Interest).

Study sample
No sample size appears to have been determined in the planning phase of the study. The relationship of caregiver burden to disease severity consisted of a 43-patient study conducted by the Mount Sinai Alzheimer's Disease Research Centre. All AD patients were administered the Mini-Mental State Exam (MMSE). The MMSE scale comprises 11 items covering items such as orientation, repetition, attention and calculation, reading and language. The first section of the test only required verbal responses covering orientation, memory and attention. The second test covered the ability to name objects, follow verbal and written commands, to write a sentence spontaneously and to copy a figure. The patients
were subsequently stratified to mild (MMSE score: 21 - 30), moderate (MMSE score: 11 - 20) or severe (MMSE score: 0 - 10) stage of AD. The authors did not report how many patients were stratified to each severity stage. They also did not provide any characteristics of the patient sample (e.g. age or gender).

**Study design**
The study was a prospective evaluation of the relationship of caregiver burden to disease severity. It was conducted by the Mount Sinai Alzheimer's Disease Research Centre.

**Analysis of effectiveness**
All patients included in the study were accounted for in the analysis. For all patients, the time that caregivers spent in care-giving was assessed using the Caregivers Activity Survey (CAS). The CAS is a 5-item scale assessing the amount of time a caregiver spends each day performing caregiver tasks. More specifically, supervising, communicating, dressing, eating and looking after the patient's appearance. The caregivers were asked to report the amount of time they spent in each activity during a "typical" care-giving day. Each item's score reflected the time spent in that activity. The CAS scores for caregivers were tabulated for each patient category (mild, moderate and severe).

**Effectiveness results**
A significant correlation (-0.56) was observed between MMSE scores and hours of care, (p<0.0001). This demonstrated that, as the disease progressed, more time for supervision and assistance from caregivers was required.

The number of daily caregiver hours spent on a patient were 2.0 in the mild stage, 9.40 in the moderate stage, and 13.4 in the severe stage of AD. Thus, the difference in daily caregiver hours between patients in the moderate and mild stages of AD was 7.4 hours. The difference was 4.0 hours between patients in the severe and moderate stages of AD.

**Clinical conclusions**
The results from this study demonstrated that, as the disease progresses, more time for supervision and assistance from caregivers is required.

**Outcomes assessed in the review**
The outcome derived for the study by Hauber et al. (see Other Publications of Related Interest) was the delay in disease progression from stage S to the next stage associated with rivastigmine treatment. The authors also derived the probability of institutionalisation by AD disease stage from this study.

**Study designs and other criteria for inclusion in the review**
The basis of the study was a proportional hazard model developed by Fenn and Gray (see Other Publications of Related Interest). The model used clinical trial data for 1,333 patients recruited internationally in two placebo-controlled studies, which were undertaken in 67 centres. A full series of survival curves was estimated for each baseline MMSE score for each treatment group. By estimating the average number of days saved for each baseline cohort for each disease stage, the model estimated the total delay in cognitive decline that resulted from treatment. The calculation was repeated for each transition (mild to moderate, moderate to severe) and for each time horizon (6 months, corresponding to the trial time period, and 1 and 2 years).

**Sources searched to identify primary studies**
Not relevant.

**Criteria used to ensure the validity of primary studies**
Not relevant.
Methods used to judge relevance and validity, and for extracting data
Not relevant.

Number of primary studies included
The authors only reviewed the study by Hauber et al.

Methods of combining primary studies
Not relevant.

Investigation of differences between primary studies
Not relevant.

Results of the review
Compared with patients who received no treatment, patients in the mild stage of AD who were initially treated with rivastigmine spent an extra 56 days in the mild stage and an extra 69 days in the moderate stage before progressing to the severe stage. Patients initially treated in the moderate stage of AD spent an additional 51 days in the moderate stage before progressing to the severe stage. Combining these results with those from the observational study conducted by the authors, this translated to 204 hours. The probabilities of institutionalisation for patients in the mild, moderate and severe AD stages were, respectively, 0.0171 (mild), 0.3451 (moderate) and 0.8675 (severe).

Methods used to derive estimates of effectiveness
To estimate the effect of rivastigmine on time spent in care-giving, the difference in total caregivers hours between two disease stages was multiplied by the number of days by which progression to a more severe stage of the disease was delayed due to treatment with rivastigmine.

Estimates of effectiveness and key assumptions
For patients initially treated in the mild stage of AD, the combination of the results translated to 414 hours of care-giving saved in the mild to moderate group, and 276 hours saved in the moderate to severe group. A total of 690.4 caregiver hours were saved.

For patients initially treated in the moderate stage of AD, the combination of the results translated to 204 hours of care-giving saved.

Measure of benefits used in the economic analysis
No summary benefit measure was used in the economic analysis. In effect, a cost-consequences approach was used.

Direct costs
The costs and resource use were reported separately. The direct costs of the payers of formal care were included in the analysis. Payers of formal care included private or public insurers, and AD patients and/or their family members. The potential savings in the cost of institutionalisation related to delayed disease progression, owing to treatment with rivastigmine, were calculated by multiplying the change in the number of days in each stage of disease by the probability of institutionalisation and by the estimated per diem cost of nursing home care. The cost of nursing home care was obtained from a published study (Smith, see Other Publications of Related Interest). Discounting was not relevant and, appropriately, was not performed since all the costs were incurred during 2 years. The price year was 1997.
Statistical analysis of costs
The resources used and costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The costs and resource use were reported separately. To estimate the effect of rivastigmine on the economic burden of informal care-giving, the difference in total caregiver hours between two disease stages was multiplied by the number of days by which progression to a more severe stage of AD was delayed due to treatment with rivastigmine. The hours saved were then multiplied by $16.30, the average hourly wages for a nurse's aide.

A final analysis, which representing the perspective of the caregiver responsible for both time spent care-giving in the informal care setting and the costs of formal care, was also performed. This attempted to account for the fact that delayed institutionalisation will result in an increased duration in the informal care setting. The informal care-giving costs thus incurred were calculated by multiplying the change in the number of days of each stage of disease by the probability of remaining in informal care and also by the daily cost of care-giving for each stage of disease. All the costs and savings were summed to determine the net incremental cost of informal care giving. Finally, this cost was subtracted from the savings due to delayed institutionalisation to yield a resultant overall net savings.

Discounting was not relevant and, appropriately, was not performed since all the costs were incurred during 2 years. The price year was 1997.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were conducted to reflect the impact of assumptions on the results of the analysis. Also, to measure the sensitivity of the model to each of the input variables, to identify those variables to which the model was most sensitive. A multivariate analysis was conducted using the Crystal Ball Analysis tool (4.0g, Decision Analysis). Each of the assumptions made was varied simultaneously within a predefined range (10,000 iterations), according to a probability distribution intended to reflect the assumed variability. In particular, the economic value of 1 hour of care-giving was varied within the range of estimates found in the literature. The number of extra days a patient remained in a less severe disease stage and the number of hours spent caring for an AD patient (according to disease severity) were varied by +/- 20% of their respective values. After all 10,000 iterations were completed, the range of results was summarised in the form of a frequency distribution. This was then used to identify the upper and lower bounds of the 95% confidence interval (CI) of the simulated results.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
For patients initially treated with rivastigmine in the mild stage of AD, who remained at home during the first 2 years of treatment, the savings incurred in informal caregiver costs were $11,253.52 per patient.

For patients initially treated with rivastigmine in the moderate stage of AD, who remained at home during the first 2 years of treatment, the savings incurred in informal caregiver costs were $3,325.20 per patient.

The potential savings in the cost of institutionalisation if treatment began in the mild stage of AD were $6,374.35 per patient over the 2-year period.

The net savings for a caregiver with both formal and informal care responsibility over an AD patient were $5,272.80 if the patient was treated with rivastigmine in the mild stage of the disease.
**Synthesis of costs and benefits**

The costs and benefits were not combined as a cost-consequences analysis was carried out. Results from the sensitivity analysis revealed that the model was most sensitive to the total number of hours spent providing care for a patient with AD. The potential mean cost-savings due to delayed progression from mild to moderate AD were $6,532 (95% CI: 3,961 - $9,748). The mean cost-savings due to delayed progression from moderate to severe AD were $4,314 (95% CI: 1,219 - 8,300). Finally, if treatment began in the moderate stage, the mean cost-savings were $3,212 (95% CI: 926 - 6,137).

**Authors' conclusions**

Early pharmacologic intervention, which allowed patients to remain at home longer by delaying disease progression, had a beneficial impact on the patients, caregivers and payers.

**CRD COMMENTARY - Selection of comparators**

The authors used placebo or no treatment as the comparator. They did not mention whether any other medication, besides rivastigmine, was being used to slow AD progression.

**Validity of estimate of measure of effectiveness**

In order to estimate the burden associated with care-giving according to disease progression, data were collected from a prospective observational study of AD patients. Even though the authors failed to report the proportion of patients in each stage of AD, a statistically significant correlation was observed between the MMSE scores and hours of care-giving, as measured by the CAS. However, the authors did not report any characteristics of the patient sample. Therefore, there is a high probability of bias and confounding factors that may have affected the result. The delay of disease progression associated with rivastigmine treatment was derived from a study using clinical trial data for over 1,000 patients recruited in two placebo-controlled international trials, which were undertaken in 67 centres. Although the internal validity of these two trials appears to have been high, the results of these trials, which lasted for 26 weeks, were then extrapolated to a 2-year period. Thus, there is the potential for introducing extrapolation bias. Comprehensive sensitivity analyses were conducted to mitigate these possible biases.

**Validity of estimate of measure of benefit**

The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences study.

**Validity of estimate of costs**

All the categories of cost relevant to the perspective adopted were included in the analysis. However, the costs of rivastigmine were not included. The authors assumed they would be in the order of $1,600/year based on twice-daily long-term therapy. Hence, the potential savings will be around $3,200 per patient lower than those reported by the authors. The costs and the quantities were reported separately, which will aid the generalisability to other settings.

Resource use, in the form of informal care-giving hours and days in formal care, were taken from the observational study undertaken by the authors and the study by Hauber et al. A sensitivity analysis of the quantities was conducted, using what appear to have been appropriate ranges. The prices were obtained from published sources. A sensitivity analysis of the prices was conducted to account for any variability in such parameters. Since all the costs were incurred during 2 years, discounting was unnecessary. The price year was reported, which will aid any possible reflation exercises.

**Other issues**

The authors made appropriate comparisons of their findings with those from other studies that also found that treatments such as rivastigmine might result in significant savings in caregiver time (as well as in costs), especially if the
treatment was initiated when the patient was in the mild stage of AD. The issue of generalisability to other settings was addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The limitations that the authors reported were those associated with modelling and extrapolating to longer time periods. Also, the fact that the prospective collection of economic data for each patient was not possible.

**Implications of the study**
The authors stated that, as the baby-boom generation ages, early pharmacologic interventions such as the use of rivastigmine could benefit society as a whole by placing less demand on the public and private sectors.

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**Other publications of related interest**


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