Assessment of health economics in Alzheimer’s disease (AHEAD): treatment with galantamine in the UK

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SUMMARY

Objective To assess the long-term health and economic impact of treating mild to moderate Alzheimer’s disease (AD) with galantamine (16 mg or 24 mg per day) compared to no cholinesterase therapy in the UK.

Methods The long-term costs and outcomes were assessed using a model developed from longitudinal data on a cohort of AD patients. The model predicts the time until patients require full-time care, defined as the consistent requirement for a significant amount of care and supervision each day. Efficacy data were obtained from three clinical trials comparing galantamine with placebo, forecasts were made for ten years. Costs were determined in 2001 British pounds (£) and discounted at 6% per annum, while outcomes such as time to full-time care were discounted at 1.5%.

Results Without pharmacological treatment, patients are expected to incur costs of £28,134 over ten years, 70% of costs accrue from providing full-time care. Galantamine (16 mg per day) is predicted to reduce the duration of the full-time care state by 12%; approximately five patients need to be treated to avoid one year of full-time care. The ten-year incremental costs per month of full-time care avoided average £192 per patient and £8,693 per QALY. Savings (£1380) are predicted for patients who continue treatment beyond six months and whose cognitive function is maintained or improved. Comparable results were estimated for the 24 mg dose.

Conclusion In addition to the clinical benefits associated with galantamine treatment, the savings predicted from delaying when full-time care is needed may offset the treatment costs. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — Alzheimer’s disease; galantamine; cost-effectiveness; UK

INTRODUCTION

Alzheimer’s disease (AD) affects approximately 10% of the United Kingdom (UK) population over the age of 65 years; prevalence rates rise steeply with age and as many as 47% of people aged 85 years or older may be affected (Souetre et al., 1999). Patients experience a progressive decline in cognitive function, as well as a variety of disturbing symptoms such as hallucinations or delusions, and a loss of the ability to independently perform activities of daily living (Small et al., 1997; Wilson et al., 2000).

The economic burdens associated with AD reflect the progressive nature of this disease and the cost of caring for patients increases substantially as they become less able to care for themselves (Kavanagh et al., 1995). During the early stages patients often rely mostly on informal (unpaid) caregivers, usually family members. When patients have more advanced disease the costs of care increase until the burden of caring exceeds manageable levels for informal caregivers and reliance on paid caregivers and institutionalized care becomes more common (Holmes et al., 1996; Bosanquet et al., 1998; Souetre et al., 1999). The majority of the direct costs of caring for AD patients arise from institutional care (Kavanagh and

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Knapp, 1999; McNamee et al., 1999; Netten et al., 2001b; Wolstenholme et al., 2002).

Galantamine (Reminyl™) is a cholinesterase inhibitor that also modulates nicotinic receptors. It has demonstrated efficacy in improving cognitive, functional and behavioral outcomes for patients with mild-to-moderate AD (Raskind et al., 2000; Tariot et al., 2000; Wilcock et al., 2000). To properly assess the economic impact that galantamine treatment may have, a pharmacoeconomic model was used to predict the long-term outcomes based on the shorter-term data collected in clinical trials.

METHODS

Model

The AHEAD (Assessment of Health Economics in Alzheimer’s Disease) model was created to evaluate the health and economic impact of treatment in patients diagnosed with AD. The model was used in this study to assess the economic impact of galantamine therapy (16 mg and 24 mg) compared to non-pharmacological treatment in patients with mild to moderate AD in the UK. A detailed description of the model is provided in a separate publication (Caro et al., 2001). Briefly, the model uses predictive equations (Caro et al., 2001) derived from longitudinal epidemiological data (Stern et al., 1997) to estimate the time until patients deteriorate to a level requiring full-time care and death. Full-time care is defined as the consistent requirement for a significant amount (for the greater part of the day) of care giving and supervision each day, regardless of the location of care and who provides the care. Patients who do not yet require full-time care are assumed to live at home. The predictors for the need for full-time care were cognitive function, presence of psychotic symptoms, extrapyramidal symptoms (EPS), age at onset, gender, and duration of illness. Mortality is estimated based on an index that consists of the presence of EPS, duration of illness, gender as well as loss of cognitive function.

The UK model consists of a short-term module based on galantamine trial data and a long-term module which predicts when patients reach a state when they need full-time care and when death will occur (Figure 1). The main states in the model are therefore; before patients require full-time care; when patients require full-time care (in either an institutional or community setting), and death. It was assumed in this model that galantamine would have no impact on survival.

Data sources

Three randomized, placebo-controlled clinical trials provided the basis for determining the effect of galantamine treatment on both cognitive deterioration (Raskind et al., 2000; Wilcock et al., 2000; Tariot et al., 2000) and psychotic symptoms (Tariot et al., 2000). All patients enrolled in these trials were diagnosed with probable AD according to the National Institute of Neurologic and Communicative Disorders

![Diagram of model structure](image-url). Reproduced with permission from S. Karger A. G., Basel (Caro et al., 2002a). Note: Data sources for the short-term module (Raskind et al., 2000; Tariot et al., 2000; Wilcox et al., 2000) and long-term module (Stern et al., 1997; Caro et al., 2001)
and Stroke and AD and Related Disorders Association (NINCDS-ADRDA) classification. The patients had a history of cognitive decline that was gradual in onset and progressive over a period of six months. Cognitive function was assessed at baseline using the Mini-Mental State Examination (MMSE; Folstein et al., 1975), and efficacy was assessed based on changes in the ADAS-cog, the cognitive subscale of the Alzheimer’s Disease Assessment Scale (Rosen et al., 1984). The patients were at the mild to moderate stage of cognitive decline, as the selection criteria included either MMSE scores between 11 to 24 with an ADAS-cog score of $\geq 12$ (Raskind et al., 2000, Wilcox et al., 2000) or MMSE 10 to 22 and an ADAS-cog score $\geq 18$ (Tariot et al., 2000).

Galantamine discontinuation rates over the first six months were estimated as equivalent to those in the three placebo groups because no differences were found in the most recent trial that used the currently recommended titration regimen for galantamine (Tariot et al., 2000). Patients discontinuing treatment were assumed to have changes in cognition and psychotic symptoms equivalent to those of patients who had never received galantamine treatment.

Health state utilities were derived from published data (Neumann et al., 1999) and assigned to the states before (0.60) and after (0.34) patient’s required full-time care; then used as weights to calculate quality-adjusted life years (QALYs). Time to full-time care, survival, and QALYs were discounted at 1.5% per year.

**Costs**

Direct costs, including medical and social service costs, associated with each state of the model were applied over time to yield a total cost of care. Costs were determined in 2001 British pounds (£) and discounted at 6% per annum.

Resources used by cognitively impaired patients residing in the community or in an institution were estimated from two national surveys conducted by the Office of Population Census Survey during 1985 and 1986 (Martin et al., 1988). These have been previously used to examine the effects of cognitive impairment on costs (Kavanagh and Knapp, 1999; Kavanagh and Knapp, 2002). For patients residing in the community resource use included health and social services (e.g. respite care, home help, day care and Meals on Wheels) (Figure 2). For patients resident in institutional settings, costs included both the placement cost and the services provided externally to the institution such as visits by professionals to the patient in the institution as well as visits by the patient to clinics/outpatient departments. Consequently, the perspective of these analyses includes the costs to the National Health Service and Personal Social Services (National Institute for Clinical Excellence, 2001). Although user charges apply to some social services (Rice et al., 1993), these have not be calculated separately.

From these two national surveys (Martin et al., 1988), it was determined that 48% of cognitively impaired patients requiring full-time care are living in an institutional care setting. Following the approach of Isaacs and Neville (1976), patients living in households who required full-time care were defined as fulfilling one or more of the following criteria: need help getting into or out of bed or chair, or getting to or using the toilet, or losing control of the bladder or bowels at least once per day or severely mentally disturbed. Patients were considered severely mentally disturbed if they exhibited behavioral problems such as inappropriate, antisocial, violent, or risky behavior.

It was assumed that, although the composition of institutional care has changed considerably in the period since the surveys were conducted, the proportion resident in institutional care as a whole has remained constant at 48%. The distribution of patients with dementia who require full time care between different types of institutional settings was estimated using more recent national data (Community Care Statistics, 2000; Netten et al., 2001a). It was estimated that
patients are resident in different care settings as follows: 42% in private nursing homes; 37% in private residential care for the elderly; 11% in local authority; 8% in voluntary residential care; and 2% in hospital (Community Care Statistics, 2000; Netten et al., 2001a).

Unit cost data from published sources (Netten et al., 1998; Scottish Health Service Costs, 2000) for each service were combined with the service use data to derive cost estimates. Costs were determined in 2001 British pounds (£). Where necessary unit costs were inflated using the medical component of the consumer price index (Consumer Price Indices, 2001). The monthly cost of providing full-time care to patients in the community (£433) is almost twice the monthly cost incurred by patients at lower levels of dependency (£238) (Figure 2). Full-time care in an institutional setting is substantially more expensive (£1878).

The average daily cost assigned for galantamine 16 mg was £2.44 and £3.00 for 24 mg. In line with current treatment practices, galantamine treatment was assumed to be discontinued once patients need full-time care.

Analyses

Analyses addressed a population of patients with mild-to-moderate AD and two sub-groups of patients: those with moderate disease only (defined as baseline Mini-Mental State Examination (MMSE) < 18) (Folstein et al., 1975) and those who responded to treatment, (defined as having maintained or improved cognition using the cognitive part of the Alzheimer’s Disease Assessment Scale (ADAS-cog) over six months). The characteristics of the populations for these analyses were defined from the patients in three galantamine trials (Table 1). The long-term health and economic outcomes estimated over 10 years for these patients when treated with galantamine (16 mg or 24 mg per day) were compared to the outcomes predicted for the same group of patients if they did not receive cholinesterase therapy.

To explore the stability of the results, sensitivity analyses were carried out on key input parameters and included varying the discount rates for both costs and benefits by 0% and 10%, and also for the combination of a 6% discount rate for the costs and 0% for benefits. In addition the proportion of patients in institutional care were varied over the range of 0 to 100%, the cost per month by ±50% and the utilities also by ±50%.

Table 1. Baseline characteristics of the populations analyzed, mean (standard deviation) (SD) except where indicated (Raskind et al., 2000; Tariot et al., 2000; Wilcock et al., 2000)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient population</th>
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<tbody>
<tr>
<td></td>
<td>All patients</td>
</tr>
<tr>
<td></td>
<td>(n = 2193)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>807 (36.8%)</td>
</tr>
<tr>
<td>Age, (years)</td>
<td>75.7 (8.2)</td>
</tr>
<tr>
<td>MMSE1</td>
<td>27.0 (10.6)</td>
</tr>
<tr>
<td>Psychotic symptoms2 n (%)</td>
<td>18.7 (3.8)</td>
</tr>
<tr>
<td>Extrapyramidal symptoms3 n (%)</td>
<td>734 (33.5%)</td>
</tr>
<tr>
<td></td>
<td>136 (6.2%)</td>
</tr>
</tbody>
</table>

1ADAS-cog, range 0 to 70: cognitive subscale of the Alzheimer’s Disease Assessment Scale (Rosen et al., 1984).
2MMSE range 0 to 30: Mini-Mental State Examination scale (Folstein et al., 1975).
3Psychotic symptoms, presence or absence: measured using the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) hallucinations or delusions subscales (Tariot et al., 2000); or prescription of antipsychotic medication during the trial (Raskind et al., 2000; Wilcock et al., 2000).
4Extrapyramidal symptoms: presence or absence of rigidity, wrist cogwheel phenomena, and involuntary movements assessed during a neurological examination.

RESULTS

Without pharmacological treatment, the mean time to when full-time care is needed for patients with characteristics similar to those in the three clinical trials is predicted to be 3.2 years, and mean survival is estimated to be 5.1 years. When started on galantamine 16 mg, these patients are estimated to require full-time care for 12% less time, and 15% less if the 24 mg dose is used. One year of full-time care is expected to be avoided for every five patients started on galantamine 16 mg treatment, and four patients for the 24 mg dose. A mean gain of 0.06 QALYs is predicted. This is a conservative estimate due to the modest assumption that there is no survival advantage with galantamine.

For patients not receiving pharmacological treatment, over two thirds of the average cost accumulated over ten years is accounted for by full-time care cost, and about half the total is from the cost of providing care in institutional settings (Table 2). Galantamine is predicted to delay the time to requiring full-time care, so the cumulative cost of care over ten years is expected to be reduced, and this offsets much of the cost of galantamine treatment. Whilst treatment with galantamine increases the annual costs for the first three years, costs in subsequent years are predicted...
to be partially offset by delaying the need for full time care, and 80% of the treatment cost is expected to be offset over ten years.

The model predicted a delay to full time care after treatment with galantamine 16 mg of 2.50 months (2.63 months undiscounted) with a net cost of £481 (discounted); and with galantamine 24 mg of 3.02 months (3.18 months undiscounted) with a net cost of £672 (discounted). The small net expense for patients started on galantamine 16 mg per day translates to £192 per discounted month of full-time care avoided, or an incremental cost of £8693 per QALY. Small savings (£228) are predicted for the sub-group of patients who have moderate disease (Figure 3).

More substantial savings (£1372) are predicted if the sub-set of patients who respond to galantamine (with maintained or improved cognition) after 6 months and continue treatment is considered (Figure 3). Comparable results were estimated for the 24 mg dose (Figure 3).

The sensitivity analyses covered all the key model parameters. For example, we varied the proportion of patients needing full-time care who were admitted to an institution. Reducing the proportion admitted from 48% to 40% resulted in a net cost per patient for galantamine 16 mg per day of £731 (£292 per month of full-time care avoided), if the proportion was reduced to 35% the net cost was £886 (£354 per month of full-time care avoided). Cost neutrality was observed when 64%, instead of the base case 48%, of patients requiring full-time care are institutionalized (for patients treated with the 16 mg dose). The small net additional cost of galantamine treatment also disappears with relatively small increases in the relative cost of full-time care. For example, cost neutrality was observed when the cost of full-time care was increased by 14% (16 mg dose).

Varying the discount rate had minor effects: with zero discount for costs and benefits the net cost for galantamine 16 mg per day was £314 (£119 per month of full-time care avoided). In comparison, with 6% discount for costs and zero discount for benefits, the net cost was £481 (or £183 per month of full-time care avoided), and when 10% discount rates were applied to both costs and outcomes, a net cost of £562 (£295 per month of full-time care avoided). Varying the utility estimates by ±50% resulted in the estimated cost per QALY for galantamine 16 mg per day ranging between £5810 to £17 431 per QALY.

**DISCUSSION**

Our analyses predict that compared to non-pharmacological management, treatment with galantamine delays the need for full time care of patients with initially mild-to-moderate AD at a small additional cost. Galantamine treatment costs accrue earlier than the savings from delaying the need for full time care. In this study, galantamine treatment is predicted to increase the costs over the first three years; the costs in subsequent years are then expected to be partially offset by the delay in the need for full-time care. For patients whose cognition is maintained or improved...
six months after commencement of treatment—broadly consistent with national guidance on treatment continuation (National Institute of Clinical Excellence, 2001, No. 19)—the predicted delay is associated with savings.

Previous pharmacoeconomic models of cholinesterase inhibitors (Stewart et al., 1998; Fenn and Grey, 1999) in the UK have extrapolated the cognition results from short-term clinical trials. The AHEAD model does not project the course of the cognitive measure but rather uses long-term follow-up data to relate the cognitive and behavioral results obtained in clinical trials to the need for care by patients with AD. The care needs of dementia patients whilst impacted by changes in cognitive function, are also influenced by other disabilities, their ability to independently perform activities of daily living, or the presence of psychotic symptoms (Caro et al., 2002b; Kavanagh and Knapp, 2002; Small et al., 2002; Wolstenholme et al., 2002). Our analyses included the effects of treatment on both patients’ cognition and behaviour—a factor strongly associated with costs of care (Kavanagh and Knapp, 2002; Small et al., 2002).

Although admission to institutional care is associated with severity of disability, other factors such as relationships with caregivers, access and availability of both community and institutional care services are also important and can vary between regions and over time (Ribbe et al., 1997; Miller et al., 1998; Payne et al., 1999; Wolstenholme et al., 2002). These analyses have the advantage that they predict the need for full-time care independent of the location of care, therefore allowing adaptation to different services and policy situations (Getsios et al., 2001; Caro et al., 2002a; Garfield et al., 2002). The results of our cost-effectiveness analyses are therefore directly applicable only to the UK, and cannot be generalized easily to other health care systems, where for example there may be less access to nursing home care or a different range of services.

There is some uncertainty about whether the proportion of patients with AD requiring full time care that are institutionalized (48%) has decreased, as this estimate was obtained by analyzing survey data collected in the 1980s. The extent to which community care expanded is uncertain, but a comparable estimate (45%) was also derived by combining data from recent studies of the number of institutional care beds (Community Care Statistics, 2000), assuming 90 per cent occupancy (Laing and Buisson, 2001), the number of people aged 65 and over (Office for National Statistics, 2002) with the prevalence of severe cognitive impairment amongst those living in the community (2%) or institutional care (33%) (Tait and Fuller, 2002).

In this paper, we also examined the impact on QALYs. The derivation of utility scores, especially in the cognitively impaired elderly, is methodologically difficult, however, and remains controversial. The utilities used were based on assessments using carers (both paid and unpaid) as proxies for patients (Neumann et al., 1999). The results presented assume that galantamine will not improve life expectancy, therefore only the time spent in full-time care, which has a lower utility, contributes to the QALY difference.

One important limitation of these analyses is that the model predictions are based on the changes in cognitive function and psychotic symptoms observed at the end of short-term trials. In addition, the trials have specific selection or exclusion criteria, and as is always the case there will be some uncertainty about the generalizability of the trial efficacy result to other patient populations. We have based the long-term predictions of the time to requiring fulltime care on the predictors identified by Stern and colleagues (Stern et al., 1997). They conducted a cohort study of 236 patients diagnosed with mild-to-moderate AD. Those patients were recruited at specialist centres but were not trial participants, and did not have a life-threatening illness at their initial visit. The significant predictors identified were presence of EPS, psychotic symptoms, age, duration of illness and cognitive function. Although we might expect that other factors such as certain comorbidities not present in the population in the clinical trials could shorten survival time to full time care, these were not predictors in the study that formed the basis for this model.

It is possible that more patients will discontinue treatment in routine clinical practice than in the trial. Whilst this would mean fewer patients benefited from the treatment, it would also reduce the treatment cost and would mean our typical cumulative costs are a conservative overestimate. The analyses also assume that patients who remained on treatment for six months would continue treatment and accumulate drug costs until they required full-time care similar to the NICE guidelines being employed in the UK (National Institute of Clinical Excellence, 2001, No. 19; Mace and Taylor, 2002). As with any model making long-term projections from trial data the precise results that would actually be observed need to be determined using long-term observational studies.
The NICE guidelines call for specialist initiation of treatment and monitoring but allow shared management with primary care (National Institute of Clinical Excellence, 2001, No. 19). Care for an elderly person involves a range of services from different agencies and budgets. Our analyses took a comprehensive perspective including all formal (paid) care, from social services and the National Health Service. Social services accounted for almost a third of the monthly cost of providing full time care in the community, so this approach provided a broader view of the costs associated with caring for patients outside an institution.

Galantamine has been shown to improve cognitive function (Raskind et al., 2000; Tariot et al., 2000; Wilcock et al., 2000) and psychiatric symptoms (Tariot et al., 2000) and is predicted to reduce the number of months when full-time care is required. In the UK galantamine treatment is predicted to lead to a small net cost in the base case scenario, but the costs of drug therapy are offset in some situations. These conservative results demonstrate that galantamine will prove to be good value for money in the treatment of mild-to-moderate AD. Future longitudinal research will be necessary to determine the long-term costs and outcomes for patients treated with galantamine in the UK.

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