Savings from sub-groups?: policy guidance and Alzheimer's Disease treatments

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Conflict of interest

J Bond has acted as a consultant to Pfizer and BioScience Communications for European Dementia Forum to raise awareness of dementia in Europe during 2004-5.
All other authors declare that they have no conflict of interest.

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Abstract

Background
A range of new therapeutic agents are now available for the management of Alzheimer's disease. With limited resources available however, policy-makers and other health care professionals have to prioritise and judge competing treatments on criteria such as the magnitude of clinical effectiveness and cost-effectiveness. Policy guidance that restricts treatments to defined patient sub-groups can improve the cost-effectiveness of treatments, and can help limit rises in health care expenditures. Budget impact models that estimate the amount of additional costs and potential savings are being increasingly used by policy-makers. However, the amount of savings estimated in such models depends on the effectiveness of treatment in changing morbidity, and the association between morbidity and costs.

Aim
To examine the magnitude of cost savings arising from provision of treatment to different patient sub-groups, using policy guidance decisions made by the National Institute for Health and Clinical Excellence (NICE) for cholinesterase inhibitor therapies in Alzheimer's Disease (AD) in the United Kingdom National Health Service (NHS).

Method
Cohort simulation modelling.

Results
Policy guidance decisions that restricted treatment to smaller patient sub-groups were associated with lower overall care costs, but did not reduce drug costs.

Conclusions
Given increasing recognition by health policy-makers of the importance of affordability of new treatments, greater attention should be paid to measurement of cost impacts by sub-groups within health economic modelling.

Introduction

Currently there is no cure for dementia, but since 1997 treatments have been available for people in the mild to moderate stages of Alzheimer's disease (1). These treatments, which belong to the cholinesterase inhibitor class of drugs, have been shown to provide some improvement or maintenance of cognitive functioning for a limited period in some eligible patients. Results from clinical trials have found that the treatments, when effective, can postpone the onset of more severe cognitive decline for 6 to 12 months (2-4), although it is not clear whether they affect the progression of the disease in the longer term (5). There is some evidence that they may also help maintain ability to perform activities of daily living (6,7), alleviate some behavioural symptoms (8) and improve mood (9). However, there is inconclusive evidence regarding improvement in overall quality of life (3). Regarding costs and cost-effectiveness, a number of studies have been conducted assessing different cholinesterase inhibitor agents (10-17). In a review of these studies by Jonsson (18), it was noted that the donepezil studies broadly indicated that treatment costs would be likely balanced by cost savings, whilst for galantamine, additional costs would likely be accompanied by some modest improvement in quality of life. More recently, an estimate produced for the UK suggested that cholinesterase inhibitor treatment would be unlikely to be regarded as a cost-effectiveness use of resources (19). Consensus therefore is lacking on the relative cost-effectiveness of treatment, mostly due to difficulties in modelling changes in disease progression and subsequent quality of life, and estimates of cost-effectiveness continue to be regarded with some caution.

The National Institute for Health and Clinical Excellence (NICE) was established in the United Kingdom (UK) to decide whether selected health technologies, such as the cholinesterase inhibitor class of drugs described above, should be made available for use by the National Health Service (NHS). NICE guidance is intended to replace local decisions on use of new health technologies and thereby promote equal access to treatments for patients with similar levels of health needs. Similar bodies that exist elsewhere include the Pharmaceutical Benefits Advisory Committee in Australia and the Common Drug Review in Canada. Policy guidance from such bodies usually takes the form of a single yes (no) decision for all patients who could be offered the health technology, based on whether the mean Incremental Cost Effectiveness Ratio (ICER) is below (above) a threshold value per Quality Adjusted Life Year (QALY). This decision rule however pays no attention to the size or composition of potential beneficiaries, or to the costs or "budget impact" associated with provision of the technology (20).

An example of a recent departure from this approach however relates to cholinesterase inhibitor therapies for Alzheimer's Disease (AD). The recommendation is that treatment should be made available only to a sub-group with moderate disease, rather than all or no patients (21,22). Specifically, individuals with Mini-Mental State Examination (MMSE) between 10 and 20 are eligible to receive therapy following a clinical diagnosis in a specialist clinic. Furthermore, they should normally only continue to receive therapy whilst the score remains within these levels and while global, functional and behaviour conditions remain at a level commensurate with therapy continuing to have a worthwhile effect. The previous recommendation was that treatment could be provided to patients with mild or moderate disease, the latter defined as MMSE greater than 12 (23).

The change in guidance was driven by differences in the cost-effectiveness for different patient sub-groups. Although affordability concerns are not formally considered within appraisals of new technologies by national bodies (24-26), policy guidance based on sub-groups may have an important positive spin-off, through generation of expenditure savings. Such savings may be critical for health planners, who are required to identify areas of disinvestment in order to fund new treatments. We may anticipate greater focus in future years on guidance that places restricted access on new treatments, as the current economic climate puts greater pressure on public budgets.

The extent of savings however depends on the association between morbidity and costs, and the effectiveness of therapy on disease progression. In the case of Alzheimer's Disease treatments, although there are more patients with mild or moderate disease relative to moderate disease, treatment of patients with mild disease may lead to substantial delay of disease progression, and avoidance of costs associated with moderate disease may outweigh any additional drug treatment costs. Thus, it is possible that treatment of the larger group, comprising those with mild or moderate disease, may be less expensive than treatment of the smaller group with moderate disease only.

There has been little previous research that has estimated the cost implications associated with sub-group guidance relative to single yes/no guidance. The objective of this paper therefore was to quantify the magnitude of incremental costs (i.e. the difference in health and social care costs with and without treatment) associated with sub-group guidance, using as a case study NICE guidance on cholinesterase inhibitor therapy for AD to the UK health and social care system.

Methods

The cost impact of different policy guidance was estimated using cohort simulation modelling. Figure 1 shows the model structure. Age and gender-specific sub-cohorts start with an initial mean MMSE level and an accompanying distribution. There is a probability of survival, death and MMSE decline each year, leading to a smaller number of individuals eligible for therapy under NICE guidance each year. This cycle is then repeated a further nine times. The cohort comprises the total population with AD in England and Wales, based on the most recent population estimates (27) and AD prevalence rates (28). Treatment costs (price of cholinesterase inhibitor medication) and total AD care costs (cholinesterase inhibitors and other long-term care resources such as nursing home care) were calculated over ten years using three different policy models. First, a "NICE Guidelines-Mild and Moderate" (NG-MM) model, where only those with a level of MMSE greater than 12 commenced therapy and were withdrawn from therapy when MMSE was no longer greater than 12, a "NICE Guidelines-Moderate" (NG-M) model, where individuals with MMSE between 10 and 20 were treated, and were withdrawn from therapy when MMSE fell below 10, and finally, a "NICE Guidelines-All" (NG-ALL), where all individuals with AD were treated, irrespective of MMSE.

All three models relied on the same data sources. The clinical effects of treatment on cognition and survival were modelled using observational cohort data (29) and natural history studies (30,31). Summary information from a systematic review of placebo-controlled trials of donepezil (3) was used to validate the estimates of effectiveness of therapy on cognition. AD care costs were modelled as a function of age, gender, Mini-Mental State Examination (MMSE) score and Activities of Daily Living (ADL) score, in

a generalized linear model framework (32,33). Resource use and cost data were obtained from a previous UK observational multi-centre study that included older people with dementia (34).

The sensitivity of the results to different model assumptions was explored using probabilistic sensitivity analysis. This involved taking repeated random draws from specific distributions of stochastic parameters (MMSE and ADL baseline values, MMSE change per year, proportions eligible to receive therapy, survival, regression coefficients). Ninety-five percent credible intervals were computed by taking the rank ordered 25^{th} and 975^{th} estimates of costs from the 1,000 repeated random draws. All costs are reported in 2002/3 prices. Assumptions for model parameters are outlined in Tables 1 and 2.

Results

Table 3 shows that for the NG-MM model, mean incremental AD care costs were £116 million over 10 years, or £603 per patient over 10 years (£1=US$1.53=€1.31, at 2008 purchasing power parities). Costs of cholinesterase inhibitor treatment amounted to £237 million (£1231 per patient over 10 years). For the NG-M model, mean incremental AD care costs were £100 million, or £582 per patient over 10 years. Treatment costs totalled £245 million (£1421 per patient over 10 years). For the NG-ALL model, mean incremental AD care costs were £607 million over 10 years. On a per patient basis, this equated to £1977. Treatment costs were £865 million (£2816 per patient over 10 years).

Table 3 also indicates that the findings from the probabilistic sensitivity analysis reveal that the results were robust to changes in model assumptions; in particular credible intervals were always higher than zero, showing that treatment is unlikely to produce savings large enough to offset the immediate direct costs of treatment. Out of the 1,000 repetitions, there was a 0.1% probability of cost savings of £53 per patient per year in the NG-MM model, and a 0.6% probability of cost savings ranging of £1-£165 per patient per year in the NG-M model. There was a zero probability of cost savings in the NG-ALL model, where the lowest incremental cost per patient per year was £1,041.

Discussion

The analyses in this paper suggest that provision of cholinesterase inhibitors for the management of AD imposes additional costs to the health and social care system. Secondly, relative to providing treatment for all patients with AD, restriction of therapy to sub-groups is associated with significant cost savings. Provision of therapy to the patient sub-group with mild or moderate disease instead of to all patients was estimated to provide drug acquisition cost savings of £628 million. However, further restriction to those with moderate disease produced no additional savings in the drugs budget. On the contrary, drug costs were found to be larger amongst the smaller sub-group with moderate disease. This result arose as, over time, more patients enter a state of moderate disease and exit from the group with mild disease, and, in addition, a lower cut-off is used to define moderate disease under the most recent guidance (MMSE=>10 instead of MMSE>12). In terms of overall care costs however, the moderate sub-group was less expensive than the mild to moderate group by approximately £16 million over 10 years.

This paper, to the best of our knowledge, is the first to quantify the costs and cost savings associated with different types of guidance decisions using currently recommended methods for estimation of budget impact (24). Thus, it is difficult to compare the results with other studies. Previously NICE estimated that treatment for mild and moderate patients would cost £42 million per year in drug expenditure (23). No comparable information is available however on the cost implications associated with therapy for the moderate disease only sub-group. Further, there are no estimates on the impact on other resources, such as long-term care in residential or nursing homes, nor quantification of the uncertainty surrounding the estimates.

In generating cost estimates using modelling, it is important to assess model validity. A recent study calculates mean annual health and social care costs per person (2005/6 prices) of £7,400 for mild and £8,700 for moderate dementia respectively (35). Within our model, mean annual costs were £8000, providing evidence of convergent validity. A further consideration is the credibility of the values generated; here a one point reduction in MMSE was associated with a mean cost saving of £414 per person per year (pp/py). This implies a saving of approximately 1 week in long-stay residential care, consistent with the estimate of 2-5 days less institutional care pp/py for a 0.8 MMSE reduction demonstrated in the AD2000 trial (36). It should be noted however that informal care costs were not estimated here, as these are not included in NICE budget impact values.

A potential limitation of the study relates to the integration of data from various sources to arrive at an estimate of costs and cost savings. In particular, disease progression with and without treatment was modelled using data from two different patient groups in the United States recruited from secondary care (29,30), and applied to cost data generated from a community based sample in the United Kingdom (34). In the disease progression with treatment study (29), diagnosis was made according to neurological examination and neuropsychological assessment. Respondents had a mean age of 73 years, 66% of the sample was female, and mean baseline MMSE was 19. In the natural history without treatment study (30), diagnosis of probable AD without stroke was based on neurological examination, brain scan, neuropsychological assessment and laboratory analysis. Respondents had a mean age of 75 years, 71% of the sample was female, and mean baseline MMSE was 19.5. In the UK study, data were drawn from those resident in the community at baseline with a score of three or more on the organic section of the Automated Geriatric Examination Computer Assisted Taxonomy (`AGECAT'), which is approximately equivalent to moderate (or more) clinical dementia. Respondents had a

mean age of 81 years, 63% of the sample was female, baseline MMSE was 17 and mean education an MMSE. Thus, aside from the somewhat higher age and slightly lower MMSE in the third study, the samples appear to be drawn from reasonably similar patient groups. Further, all three studies used data from non-selected cohorts, so the risk of problems related to selection bias should be minimised. Finally, the age-specific MMSE reductions used in the model approximate the mean value of 1.8 (95% confidence interval 0.5-3.1) estimated from a systematic review of randomised controlled trials (3), suggesting that the data from the non-selected cohorts is not adversely affected by attrition bias from patients being lost to follow-up.

Given increasing recognition by policy-makers of the importance of identifying cost-effective treatments that are financially sustainable, greater attention should be paid to measurement of affordability in health care modelling. The work reported here describes and applies a technique that can be used to assess the affordability of different forms of policy guidance. Further modelling studies that consider the cost as well as the health impact associated with sub-group policy guidance for other treatments and diseases would be welcome.

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Table 1. Model Assumptions and Parameters

Parameter	Value/assumption	Data Source
Population of England and Wales aged 65 years or over in mid 2002	8,385,800	National Statistics (27).
Prevalence of AD	50% of age & sex specific rates for dementia	MRC CFAS (28).
Cohort size	192,000 (NG-MM) 172,000 (NG-M) 307,000 (NG-ALL)	National Statistics (27), MRC CFAS (28).
Cohort distribution by baseline MMSE	Age & sex specific values; mean score ranges from a minimum of 12.7 to a maximum of 18.6	McNamee et al (34).
Cohort ADL distribution	Age & sex specific values' mean score ranges from a minimum of 6.5 to a maximum of 13.8	McNamee et al (34).
Cohort distribution by baseline costs per person per year	Age & sex specific values from a minimum of £1584 to a maximum of £14,457	McNamee et al (34).
MMSE reduction per year without therapy	Age specific values from a minimum of 2 to a maximum of 3	Mungas et al (30).
MMSE reduction per year with therapy	Age specific values from a minimum of 1.2 to a maximum of 1.8	Lopez et al (29).
Therapy costs per person per year	£891	BMA RPS British National Formulary (37).
Cost savings per person per year per MMSE point reduction	£414	Regression estimates.
Discount rate	3.5%	HM Treasury Green Book (38).
Five year survival probability	Age & sex specific values from a minimum of 0.18 to 0.69	Neale et al (31).

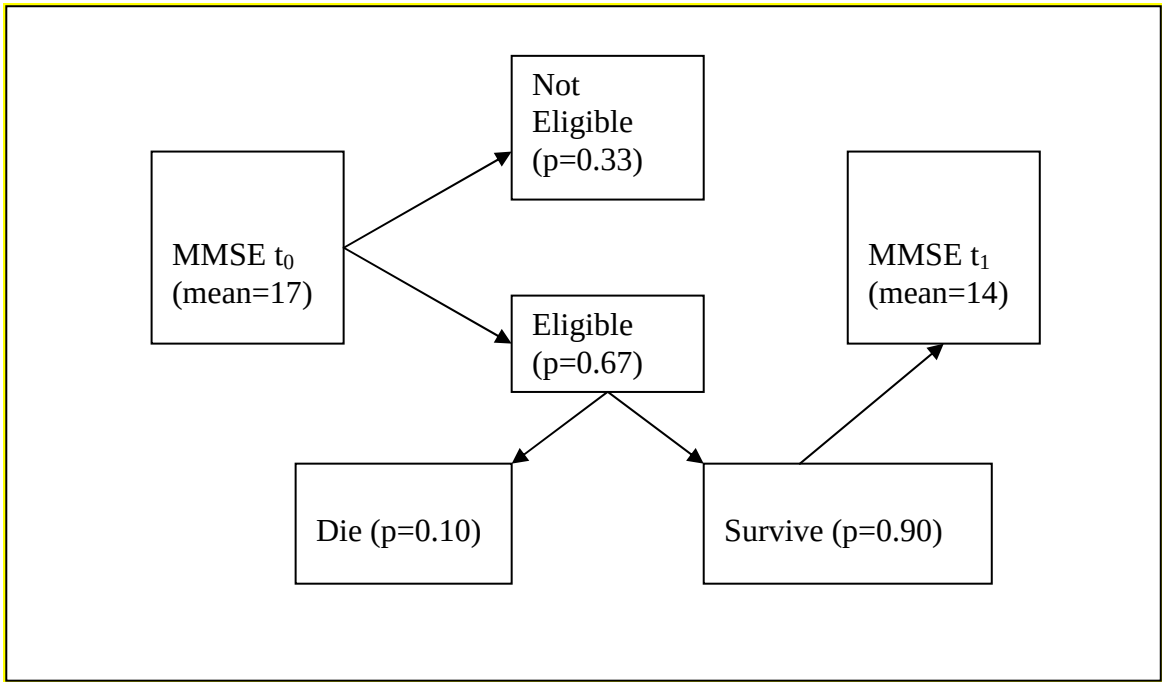
Table 2. Age and sex specific model parameters

Age (years)	Prevalence	AD population	Costs per year (£)	Survival 5 yrs	MMSE baseline	ADL baseline	MMSE reduction per year – no treatment (treatment)
MEN							
65-69	0.7	7807	5287	0.605	16.9	12.3	3 (1.8)
70-74	1.5	14726	6664	0.605	17.8	11.6	3 (1.8)
75-79	2.8	20451	7993	0.395	18.1	11.4	2.5 (1.5)
80-84	5.1	23959	10738	0.395	16.7	10.0	2.5 (1.5)
>=85	9.8	27930	14457	0.18	14.5	7.2	2 (1.2)
WOMEN							
65-69	0.7	8992	1584	0.69	17.7	13.8	3 (1.8)
70-74	1.1	12375	2603	0.69	18.6	13.8	3 (1.8)
75-79	3.5	35443	6986	0.51	16	10.1	2.5 (1.5)
80-84	7.0	55363	10522	0.51	12.7	8.6	2.5 (1.5)
>=85	13.8	100031	12921	0.35	12.8	6.6	2 (1.2)

Table 3. Mean incremental AD care and drug costs per cohort and per patient over 10 years

Policy Guidance	Incremental AD care costs cohort £m (95% credible interval)	Incremental AD care costs patient £ (95% credible interval)	Drug acquisition costs cohort £m (95% credible interval)	Drug acquisition costs patient £ (95% credible interval)
NG-MM	116 (42-187)	603 (218-971)	237 (221-254)	1231 (1146-1318)
NG-M	100 (20-189)	582 (102-983)	245 (227-264)	1421 (1315-1531)
NG-ALL	607 (461-759)	1977 (1502-2473)	865 (823-906)	2816 (2680-2952)

Figure 1. Outline of Model Structure



Note: The figures in parentheses show the values for males aged 65-69 years, without therapy, under the NG-MM model (eligible if MMSE is greater than 12). Different values apply to other sub-cohorts, please see Table 2.