Two approaches to the Economic Evaluation of a Drug for Patients with Alzheimers Disease, and a possible "Third Way".

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Summary
The increasing prevalence of Alzheimer's Disease (AD), and the costs of the drugs emerging for its treatment, poses the question of how to evaluate these drugs in economic terms. We examine two approaches to this question, first, an outline proposal [1] examining the requirements of a cost-effectiveness analysis of AD drugs; as defined, this approach faces severe problems in the areas of quality of life measurement, and international cost comparisons. Secondly, we discuss the common approach to economic evaluation of a series of papers[of which only [2] and [3] have been published so far] examining the value of AD drugs. Though the measurement problems and data collection requirements are fewer, it becomes clear that this approach also has its difficulties, mainly in respect of inter-country comparisons. A possible alternative approach to data collection as a basis for economic evaluation is suggested.

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Introduction

There are important problems of principle in relation to the calculation of AD treatment cost-effectiveness. If they are not resolved, new drugs may not be approved, and important health gains may remain unrealised. We consider two approaches to the achievement of cost-effectiveness analysis (CEA), as a basis for understanding the problems which need to be addressed. The first[1] is conventional enough, in relation to the accepted standards of CEA, but the nature of AD presents difficult obstacles. If conventional CEA is problematic, what arguments have been adopted to demonstrate the value for money of AD drugs? We outline a common approach, of which [2] and [3] are published examples; three other drug appraisals remain unpublished so far.

The first approach: applying CEA to Alzheimer's Disease[1]

The weighing of costs against outcomes, usually from the point of view of society as a whole, requires the measurement of both on a consistent basis. The authors examine costing issues, and the measurement of treatment effects.

Costing issues

As is conventional in CEA, the authors advocate the perspective of society; rather than economise from the point of view of a health service, or of a third-party payer, such as a health insurance firm, all resources are itemised, as far as possible, to determine the resource cost of the different alternative treatments from society's point of view. We consider two issues, 1) the generalisation of direct costs between countries, and 2) the valuation of informal care.

1) Generalisation of Direct Costs Between Countries

The cost of treating and caring for AD patients includes drug prescriptions, hospital episodes, and community care. The authors note that the proportions of costs vary between countries; in one, the greatest proportion might be hospitalisation expenses, while in another, the largest proportion might be formal and informal community care. That is to say, the relationship between different resource inputs and health "outputs" (in economic terms, the health care production function) is fundamentally different between countries. This is another reason for careful consideration of international comparisons of cost-effectiveness. Rather than using a multi-national clinical trial to assess whether a drug is cost-effective, it might be more appropriate to either develop such a trial with sufficient numbers of respondents in one country, or split the multi-national trial, by grouping countries according to their type of production function. There are as yet no reports of production function classifications which would allow the latter course to be followed.

2) Valuation of Informal Care

According to the authors, there exists no standardised method for measuring the amount of informal care, for example, for measuring in the same units all the different activities which informal care involves. They propose a "straightforward" questionnaire, as a practical solution, without giving many details of its design; how such a questionnaire is

to be validated, and in particular, how cultural differences are to be taken into account, is not discussed.

It may be that a valid method of measuring the amount of informal care can be devised; the authors go on to discuss two methods for putting a value on each (standardised) hour of care, opportunity cost, and shadow-price, and express a preference for a shadow-pricing approach. It is not clear to us that the difficulties of one approach are appreciably less than the other; without a standardised measure of care, further discussion is not productive.

Measurement of treatment effects

Firstly, the authors' aim is to provide a "minimal framework.... with maximum applicability and international acceptability"[1], because evaluations are usually based on multi-centre international clinical trials. They note that the disease becomes evident in behavioural disturbances, and that hence the disease diagnosis and expression are considered to be determined by cultural factors. It follows that a standard questionnaire, applied in all the countries involved, will not be reliable, and they propose that a research plan to establish cost-effectiveness for AD drugs should include "a minimum number of well-accepted and internationally validated questionnaires and costing principles"[1].

This does not seem to solve the problem of the cultural determination of the diagnosis and expression of the disease. Unless the differences resulting from variations in culture can somehow be identified and measured, all questionnaires will be unreliable. Also, the well-rehearsed problems of extending the results of clinical trials to routine practice are not examined [8-11]; it is fairly well-known that the results of a randomised controlled trial (RCT) constitute the best representation of an intervention's efficacy, not its effectiveness[4]. It follows that the reliance of the approach upon the RCT methodology may be misplaced.

Secondly, the authors consider quality of life [qol] as the only outcome variable, explicitly addressing the question, "how much is quality of life influenced by a health care programme?". They review the various qol instruments which could be used to assess this outcome for AD patients, and for their carers, and conclude that the "spine" of internationally valid instruments, with locally relevant "branches", envisaged at the outset, cannot be operationalised. This is because validated translations of many instruments are not available, and because generic measures (such as the SF-36, or the Nottingham Health Profile) are often designed for completion by the patient, so that scores cannot be interpreted meaningfully if they are generated by a proxy. This excludes a large amount of recent qol development work. The authors do not resolve the important problems involved in assessing quality of life (qol) for AD patients, and neither of two more recent comprehensive reviews[12,13] identifies a "gold standard" measure.

Given their multi-national orientation, it is interesting that the authors consider only qol impacts as health outcomes. Qol is subject to greater variation than, say, cognitive functioning; a focus on the latter might make international comparisons more feasible, though reliability and validity remain difficult issues.

It is clear that, even for single country studies, there are serious difficulties in the way of measuring the qol impacts of AD drugs; the need for a reliable and valid measure is urgent, and a measure of cognitive functioning, such as the Mini-Mental State Evaluation Scale (MMSE), might be a reliable and reasonably valid measure of outcome in Ireland. This is the measure adopted by the studies (based on multi-national trials) to which we turn in the second section.

To conclude here, the difficulties facing the usual CEA approach, of balancing outcomes measured in quality of life terms against costs measured from society's viewpoint, are quite extensive. Measuring qol does not appear to be feasible, either because instruments are developed for only one country, and have not been validated in their translated form(s), or because the instruments were not designed for completion by a carer. Also, cost definition and measurement is problematic, and cultural factors imply that AD care production functions vary between countries, in ways which have not been formally investigated.

The common approach of the studies

All of the studies presented to the Centre in support of drugs to treat Alzheimer's Disease may be described as follows:

1) Data collection: A multi-national randomised controlled trial is carried out, over a six month period, during which data is collected using the MMSE, at baseline, and at the end of the trial.

2) Cost Relationships: A secondary data source is available, which relates the cost of caring for AD patients to the level of their MMSE scores; this is based on the proportions of patients institutionalised, and the cost of care in institutions and in the community. The data usually comes from one country, and relates therefore to the production of care only in that country.

3) Modelling: The RCT data is used as a basis for extrapolation to between two and five years beyond the six-month trial, using either survival functions or a Markov analysis to determine the time spent by each patient at a particular MMSE level.

4) The drug is justified on the basis that there will be a reduction in the costs of care to the health service, or to society, because the drug reduces the amount of time spent in an institution, and increases the amount of time spent in the community.

The general issues we wish to discuss concern a) the Mini-Mental State Examination Scale, b) modelling, and c) resource identification and measurement.

a) The Mini-Mental State Examination Scale

The MMSE is the chosen psychometric instrument for measuring health impact; we explained above why a measure of cognitive functioning might be more useful than a qol measure in the CEA of AD treatments. However, the validity of the MMSE instrument has been questioned; its positive and negative features have been listed[14] as:

+ high test-retest reliability
+ may be used for staging
- high rate of false positives in low education etc.
- low discrimination of normal ageing to very mild dementia
- low discrimination of moderate to severe dementia
- no patterning of deficits in varying cognitive domains
- predominance of verbal items, visuospatial abilities are poorly evaluated
- some ambiguities exist, which could be overcome

The same source reports findings [15] that the MMSE was valid in moderate to severe dementia, but less so in cases of mild dementia, mostly because of its sensitivity to variations in age, education, and cultural background. In a relatively homogeneous society, such as Ireland, these variations might be less important than in a multi-national trial.

b) Modelling

A modelling approach [16-19] is appropriate, because trial data cover only a six-month period, while costs and benefits over the longer term are likely to be important. Also, AD is poorly understood and difficult to diagnose, so that clear entry to a trial through a defined sequence of events is not possible. It makes sense to specify clear assumptions about patient progress, for comparison with physician or clinical experience, rather than to leave progress beyond the trial completely undefined. The extension of outcomes beyond a trial period is explicitly recognised as a justification for modelling by the Australian pharmacoeconomic guidelines[5] and the Canadian guidelines encourage the use of models, provided that the assumptions are "stated explicitly and thoroughly tested with sensitivity analysis."[6].

We are not prepared to comment here on the success or otherwise of the studies modelling procedures. In general terms, all models based on trial results still leave us ignorant of what actually happened to patients in the months and years that followed the trial.

c) Resource Identification and Measurement

The studies do not resolve the problems of valuing carer time, discussed above. Patients with AD are cared for either at home or in institutions; if the drug reduces hospital care, it must increase informal care, to achieve its cost reductions. Other things equal, the greater the value placed on home care, the less cost-effective the drug will be. It is apparent that carers' interests are directly opposed to those of taxpayers; detailed discussion is needed of how carers' time should be valued.

In summary, the MMSE's validity in multi-country studies is under question. While its validity may be adequate to an Irish study, this claim should be tested. Secondly, while modelling is a reasonable response to the problems of the CEA of AD treatments, careful attention needs to be paid to the assumptions necessary to extrapolate from a six-month trial. Finally, the valuation of informal care is the most important single issue in the area of rersource identification and measurement.

Discussion

Both of the approaches discussed attempt economic evaluation based on RCT results; the following conditions militate against an RCT-based approach to the CEA of Alzheimer's treatments:

a) the diagnosis and expression of the disease are believed to be culturally determined
b) its nature and progression are poorly understood
c) patients are unable to communicate either symptoms or quality of life effects
d) there is no consensus on the efficacy of any preparation to relieve symptoms or progression
e) the relationship between costs and care outcomes is also culturally determined; in particular, local factors will determine whether patients are institutionalised or not.

It follows that efficacy is difficult to establish in the normal way, and it seems unlikely that prioritising drugs, on the basis of the balancing of effect against per unit cost, to achieve maximum health from a limited budget, will be feasible using international RCTs.

However, the scope for variation in the results could be reduced by confining a comparison of treatments to a single country, with a relatively homogeneous population (such as Ireland), and by confining the enquiry to cognitive functioning as an outcome measure. Any local trial would require the selection of the cognitive functioning measure best suited to this purpose; in what follows, we assume that the MMSE is selected.

The appropriate trial for measuring the impact on costs of different AD treatments in Ireland may be an extended post marketing surveillance trial, including all licensed treatments for AD plus no treatment. Some of the problems discussed would remain, but such a trial might provide a set of data from a (relatively) homogenous population which would not only prove to be beneficial in the pharmacoeconomic evaluations of these drugs in Ireland, but could be adapted for other countries if cultural differences could be mediated, using some further research on the translation process necessary between countries.

The trial proposed is designed to be as close to routine practice as possible, with the following features:

Patient Selection: Diagnosis by GP of probable AD, plus a score, on initial administration of the MMSE of 30 or less, and presence of dedicated carer also willing to participate.

GP Role: Treatment and care, as in normal practice, with freedom to alter prescription if necessary.

Duration: Up to 24 months

Treatment Arms: All drugs licensed (in the relevant country), plus no treatment

Data

Initial: MMSE score; carer questionnaire, to include qol, medications, own GP visits, and health treatments; current AD treatment details; history of previous AD treatment; approximate date of diagnosis of AD; details of participation in any other clinical trials in the last 12 months

Every 2 months: MMSE Score, carer questionnaire, and, as appropriate, date of institutionalisation, date of death, and reason for withdrawal

At closure: calculation of time to institutionalisation, duration of survival, MMSE scores profile, carer well-being profile from questionnaire scores.

Care production and cost would also be measured by estimating total number of respite care places, numbers of patients in institutions by end of epriod, and their expected survival duration from institutional entry, consumption cost of care (that is, annual purchasing power minus subsistence cost), numbers of visits to GP by carers and patients.

Possible problems with the proposed trial

It would be unethical to have a placebo arm, to introduce drugs blind (at any level) or randomly to control the treatment groups. Two years is a long time in the AD patient's expected survival of (approximately) five years, and the patient, GP, and/or carer should not be constrained from choosing the patient's treatment, in particular from changing the treatment if they wish to do so. It follows that a bias could be introduced in favour of a known treatment, and there could be significant differences in the number of patient receiving each treatment. Patients might also change between treatment arms, or move to a new licensed therapy, if a product was introduced during the course of the trial. As a result, it would be necessary to have sufficiently large numbers of patients participating in the trial to try to ensure that any of the problems mentioned above would not have a significant impact on the trial results.

Such a study would not prove that one drug was more efficacious than another, but it should demonstrate whether one drug lowered costs or not, when administered for up to two years under routine conditions in Ireland.

Conclusion

The conventional approach to CEA, if based on a randomised clinical trial approach, is particularly difficult to apply to treatments of Alzheimer's Disease, and especially when the trial is carried out with centres in different countries. The evidence put forward to assess drug companies' treatments of this disease relies on RCT evidence, plus modelling, and there remain important problems associated with this approach also. It may be more effective to carry out a cost-outcome study of AD treatments locally (for instance, within Ireland), and to apply foreign RCT results to it later, than to reason from foreign RCT results and cost-impact studies, to the local situation.

References

1. Busschbach J, Brouwer WBF, van der Donk A, Passchier J, Rutten FFH An Outline for a Cost-Effectiveness Analysis of a Drug for Patients With Alzheimer's Disease *Pharmacoeconomics* 1998; **13**: 21-34.
2. Stewart A, Phillips R, Dempsey G Pharmacotherapy for People with Alzheimer's Disease: A Markov-Style Evaluation of Five Years' Therapy Using Donepezil *International Journal of Geriatric Psychiatry* 1998; **13**: 445 - 453.
3. O'Brien B, Goeree R, Hux M, Iskedjian M, Blackhouse G, Gauthier S, Gagnon M Economic Evaluation of Donepezil for the Treatment of Alzheimer's Disease in Canada *Journal of the American Geriatric Society* (forthcoming, in 1999).
4. Gold MR, Siegel JE, Russell LB et al editors *Cost-effectiveness in health and medicine* New York: Oxford University Press 1996.
5. Commonwealth Department of Human Services and Health (CDHSH) *Background Document (on the use of economic analysis as a basis for inclusion of pharmaceutical products on the Pharmaceutical Benefits Scheme)* Canberra: Australian Government Publishing Service 1993.
6. Canadian Co-ordinating Office for Health Technology Assessment [CCOHTA] *Guidelines for Economic Evaluation of Pharmaceuticals: Canada* 2nd edition Ottawa: CCOHTA, 1997.
7. Chisholm D Characterising mental health: implications for health economic research *Mental Health Research Review* Number 3, PSSRU/CEMH (University of Kent at Canterbury) 1996.
8. Bailey KR Generalising the results of randomised clinical trials *Controlled Clinical Trials* 1994; **15** 15-23.
9. Fayers PM, Hand DJ Generalising from phase III clinical trials: survival, quality of life, and health economics *The Lancet* 1997: **350** 1025-1027.
10. Herman J The Demise of the Randomized Controlled Trial *Journal of Clinical Epidemiology* 1995; **48**(7) 985-988.
11. Rothwell PM Can overall results of clinical trials be applied to all patients? *The Lancet* 1994; **345** 1616-1619.
12. Walker MD, Salek SS, Bayer AJ. A review of quality of life in Alzheimer's Disease. Part I: issues in assessing disease impact 1999 **14**(5) 499-530.
13. Salek SS, Walker MD, Bayer AJ. I review of quality of life in Alzheimer's Disease. Part2: issues in assessing drug effects 1999 **14**(6) 613-627.
14. Almqvist O Assessment of Cognitive Functioning In: Health Economics of Dementia, by Wimo A, Jonsson B, Karlsson G, Winblad B, New York: Wiley 1998.
15. Tombaugh TN, McIntyre NJ The Mini-Mental State Examination: A Comprehensive Review *Journal of the American Geriatric Society* 1992 **39** 876-880.
16. Buxton MJ, Drummond MF, van Hout BA et al Modelling in Economic Evaluation: An Unavoidable Fact of Life *Health Economics* 1997 **6**(3) 217-228.
17. Maynard A, Cookson RF Computer Modelling: The Need for Careful Evaluation and Public Audit *Pharmacoeconomics* 1998 **14** Suppl 2 67-72 .
18. Beck JR, Pauker SG The markov process in medical prognosis *Medical Decision Making* 1983 **3** 419-458.
19. Nuitjen M, Hadjadjeba L, Evans C, van der Berg J Cost Effectiveness of Fluvoxamine in the Treatment of Recurrent Depression in France *Pharmacoeconomics* 1998; **14**(4) 433-445.