INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int. J. Geriat. Psychiatry **13**, 445–453 (1998)

PHARMACOTHERAPY FOR PEOPLE WITH ALZHEIMER'S DISEASE: A MARKOV-CYCLE EVALUATION OF FIVE YEARS' THERAPY USING DONEPEZIL

ALAN STEWART,[1]* RICHARD PHILLIPS[2] AND GRAHAM DEMPSEY[3]
[1]*Research Fellow, PSSRU, University of Kent at Canterbury, UK*
[2]*Head of Outcomes Research, Pfizer Ltd, Sandwich, UK*
[3]*Outcomes Research Manager, Pfizer Ltd, Sandwich, UK*

ABSTRACT

This article combines data from a clinical trial of donepezil with costing figures to evaluate expected direct costs of care over 5 years after diagnosis of Alzheimer's disease (AD) for patients aged 75 years and over at diagnosis. A Markov model simulates the progression of elderly persons through changing levels of severity. The model compares three treatment regimes for each of two patient groups: mild AD at start of treatment; moderate AD at start of treatment. Patients are followed until 5 years after the start of the treatment. Despite the acquisition costs, use of donepezil is approximately cost-neutral for both 5 mg and 10 mg treatment groups and for patients initially at either mild or moderate states of illness. Expected costs are slightly higher than for the placebo group, but higher expenditure on drugs is partly offset by lower costs of care consequent on treated patients not declining as rapidly as those untreated. The model showed that donepezil patients spent less time in the state of severe dementia, where costs of care are higher. Sensitivity analysis on key assumptions demonstrated that expected costs were highly dependent on discount rate and, more significantly, on the mortality rate. © 1998 John Wiley & Sons, Ltd.

KEY WORDS—Alzheimer's disease; dementia; pharmaceuticals; donepezil; costs; cost-effectiveness; Markov model

Alzheimer's disease (AD) is an organic mental disorder the essential features of which (Sainsbury and Lambeth, 1988) are impairment of:

- Memory
- Orientation
- Comprehension
- Calculation
- Learning
- Judgement

There may also be other features showing disturbance of affect or mood.

AD is one of the group of organic mental disorders described as the dementias; they are chronic and progressive in nature and if untreated are usually irreversible and terminal. There are several other types of dementia, but this article focuses on AD. This illness can occur at any age, but is usually associated in the public mind with older persons. It is certainly an age-related condition, with prevalence increasing with age. In one study referred to by Jorm (1990), age-related prevalence figures were:

65–69	2.2%
70–74	3.3%
75–79	8.0%
80 +	17.7% (Kay and Bergman, 1980)

The causes of AD are still unclear, although a variety of hypotheses have been put forward, including virus diseases, aluminium in the central nervous system and defects in the immune system. However, while the causes may be unclear, there is more certainty over the significant risk factors associated with incidence. What is not uncertain is that there are very significant economic costs associated with caring for people with Alzheimer's disease. One recent study (Gray and Fenn, 1993) estimated that the 'burden of illness' for England alone was £1,039 million in 1990–91.

*Correspondence to: Alan Stewart, MEDTAP International, 27 Gilbert Street, London W1Y 1RL, UK. Tel: 44 171 2909400. Fax: 44 171 6299705. e-mail: Stewart@Medtap.co.uk.

CCC 0885–6230/98/070445–09$17.50

Received 16 December 1997
Accepted 25 February 1998

The management of AD has also been highly problematic to date, with no effective therapy or clinical intervention available. Care has been restricted to providing support for patients and caregivers, with no treatments previously available in the UK that will retard or reverse disease progression. Drugs such as tacrine have been used elsewhere, but are not used in the UK mainly because they have been associated with unacceptable levels of hepatotoxicity (Taylor, 1993). A safe, effective therapy might have economic benefits as receipt of services and use of resources has been shown to be linked to cognitive impairment (Kavanagh *et al*., 1995; Ely *et al*., 1996). In the USA, where tacrine has been licensed, studies have evaluated such potential economic benefits. Lubeck *et al*. (1994) modelled cognitive changes in a hypothetical patient cohort, using the level of cognitive ability as a predictor of the point of entry to residential care. By delaying this transition to a higher cost location, use of tacrine produced cost savings of $4,052 per patient.

METHODS AND DATA

Methods

This article evaluates the use of donepezil in the treatment of persons with AD in the UK. Donepezil is a new piperidine-based derivative that is chemically distinct from other drugs used to treat AD (see various references in Rogers *et al*., 1996) and has been developed specifically for this use. It has been tested in clinical trials and shown to have a significant impact on the decline in patients' cognitive function (Rogers *et al*., 1996). A Markov model* was constructed to simulate patients' progression through levels of severity after being diagnosed as suffering from senile dementia of the Alzheimer's type (SDAT). The model was constructed using DATA^{TM} software (Treeage, 1997). Patients in the model are assumed to exist in one of a set of five states. Within a series of 6-month cycles, patients may move from one state into a different state, based on a predetermined set of transitional probabilities. These cycles were set at 6 months to match the clinical data source.

* A Markov model is a method of evaluating deterministic data without the excessive levels of branching often found in standard decision trees (see Sonnenburg and Beck, 1993, for a review of Markov techniques).

The states used in this model are based on levels of severity of cognitive disability, plus an absorbing state:

1. Minimal
2. Mild
3. Moderate
4. Severe
5. Dead

All patients tend to progress towards more severe states of illness. At all stages, some patients move into the final state (dead).

Figs 1 and 2 are diagrammatic representations of the model. In Fig. 1, all patients enter the process and may be allocated to one of three treatment options. These options are developed in Fig. 2, which shows the progression which is duplicated for each of the alternative treatment options. All patients are evaluated over a maximum period of 5 years, with financial costs discounted at an annual rate of 6% (HM Treasury, 1989).

Data

This analysis brings together clinical and costs data from four sources:

1. Cambridge cohort study of frail elderly people. This is an epidemiological study of a local population of over 75 years of age (Ely *et al*., 1995). Data on this population are used as a basis for estimates of progression of dementia-related cognitive impairment for persons not receiving any therapy for dementia. The sample of persons in the study shows a series of annual progression rates. Data highlighting these rates have been extracted from reanalysis of the original data performed by Economists Advisory Group (EAG) for Pfizer Ltd (personal communication from Jeremy Holmes, EAG).
2. Donepezil efficacy (Rogers *et al*., 1998). This was a placebo-controlled double-blind RCT evaluating donepezil at 5 mg per day and 10 mg per day, over a 6-month period of treatment.
3. Mortality data. Two sources are used for mortality rates for the model: Burns and Förstl (1996a,b) and Martin *et al*. (1987). The base case analysis uses Burns and Förstl's research on long-term survival among patients suffering from Alzheimer's disease. These data were selected as they are derived from a more recent study. In the absence of satisfactory annual

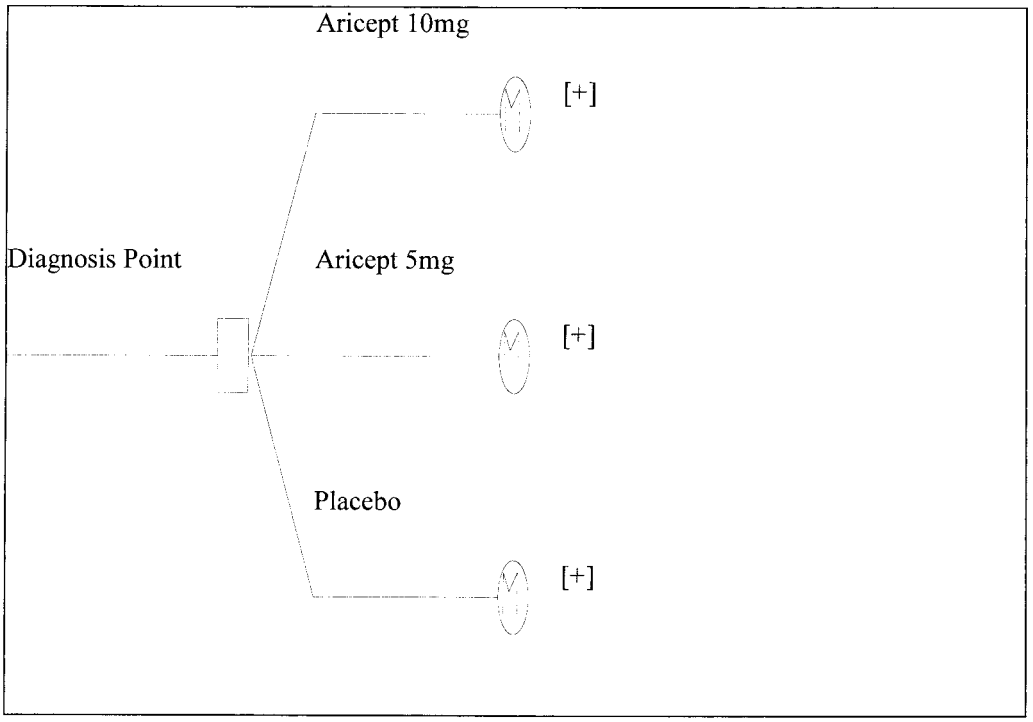

Fig. 1 Treatment option

data, a simplifying assumption is made in that the 3-year survival rate is converted directly to a constant annualized rate.

4. Costs of care packages for elderly people with dementia. Earlier work from the PSSRU (Kavanagh *et al*., 1993; Schneider *et al*., 1993; Kavanagh *et al*., 1995) estimated typical care packages provided for elderly persons at various levels of cognitive disability. The costs of these resources were updated to 1996 price levels (Stewart, 1997a) using the Personal Social Services (PSS) price index (Netten and Dennet, 1997), and applied to the categories of minimal, mild, moderate and severe dementia in earlier papers in this programme (Stewart, 1997b,c).

The above sets of research utilize different measures of severity of cognitive impairment. The Cambridge cohort study uses as its main measures the CAMDEX, Blessed and MMSE scales. In contrast, the PSSRU studies are based on the same measure as that used in the OPCS Disability Survey (OPCS, 1989a,b), the OPCS SEVINT scale. This model required use of the Cambridge information on illness progression in conjunction with the PSSRU estimates on costs, therefore a method was needed to map the SEVINT scores onto MMSE figures. This was performed by using estimates from both sources of cumulative incidence of levels of severity. These levels were mapped across between the scales to establish the nearest equivalents between each point on the two scales. The comparisons were described in detail in Stewart (1997a). That study also explains how severity scores were used to evaluate average costs of care at given levels of severity. Costs for donepezil are for 5 years of therapy. It is assumed that all patients who enter the severe state will cease to receive therapy. Drug acquisition costs are shown in Table 1.

The analysis focuses on two initial disease severity levels: mild dementia and moderate

Table 1. Drug acquisition costs. Five years donepezil, at varying discount rates

Treatment	0%	3%	6%	10%
5 mg	4456.10	4142.75	3866.77	3547.35
10 mg	6204.64	5765.44	5378.61	4930.90

Note: all acquisition costs are quoted in £UK at 1997 prices.

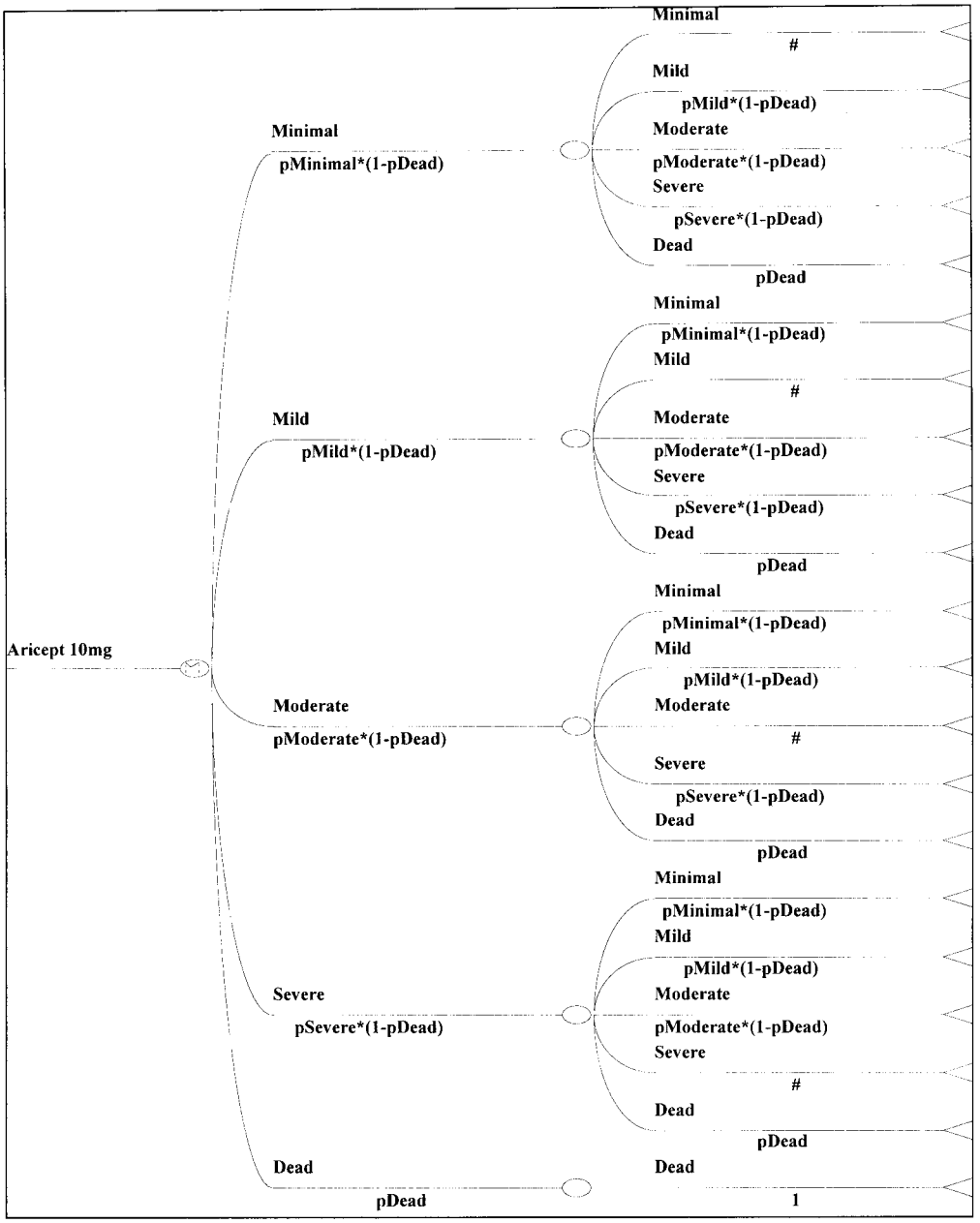

Fig. 2. Treatment path

dementia. The definition of minimal, mild, moderate and severe follows that used in the Rogers *et al.* (1998) study; corresponding to MMSE scores as shown in Table 2.

Transitional probabilities between states were based on outcomes from Rogers *et al.* (1998). The initial 6 months of drug therapy is assumed to show the active drug efficacy rate, while the remaining period is assumed to have only placebo efficacy. A matrix of probabilities was set up for each state, with the values of transitional probabilities for each patient group shown in Table 3. All patients cease treatment when they reach a state of severe, after which their

Table 2.

Severity category	MMSE score
Minimal	21+
Mild	15–20
Moderate	10–14
Severe	<10

progression is assumed to match that of untreated patients, as evaluated from the Cambridge cohort study and the EAG reanalysis. Their costs of care in each subsequent cycle are therefore at the same level as untreated patients who have reached this state. These data showed that such patients always remain in the severe state, except for those who die. A very small number of patients will show an improvement from one cycle to the next, but this is only a temporary phenomenon followed by a continued decline in cognitive state in subsequent cycles.

RESULTS

Table 4 shows results for the base case model and for the subsequent sensitivity analysis, giving figures for four types of outcome:

1. Expected costs
2. Years in state less than severe
3. Costs per year less than severe
4. Incremental costs per additional year less than severe

The base case results show that there is little difference in the expected costs of all three groups: 10 mg, 5 mg and placebo. For those patients mild at onset, the spread is just over £1400, ranging from £44 278 for placebo up to £45 694 for the 10 mg group. Given that this is an estimate of costs over 5 years, the outcome is almost neutral. The outcome is different when one views as a measure of effectiveness the number of years (within the 5-year horizon of the model) that the patient spends in a

Table 3. Transitional probabilities (base case)

Start	Finish	Donepezil 10 mg	Donepezil 5 mg	Donepezil placebo
Minimal	Minimal	0.873	0.879	0.778
	Mild	0.127	0.108	0.222
	Moderate	0	0.013	0
	Severe	0	0	0
	Dead	Mortality	Mortality	Mortality
Mild	Minimal	0.233	0.245	0.096
	Mild	0.617	0.49	0.058
	Moderate	0.15	0.225	0.307
	Severe	0	0.04	0.019
	Dead	Mortality	Mortality	Mortality
Moderate	Minimal	0	0.032	0
	Mild	0.154	0.226	0.166
	Moderate	0.615	0.516	0.300
	Severe	0.231	0.226	0.533
	Dead	Mortality	Mortality	Mortality
Severe	Minimal	0	0	0
	Mild	0	0	0
	Moderate	0	0	0
	Severe	1	1	1
	Dead	Mortality	Mortality	Mortality
Dead	Minimal	0	0	0
	Mild	0	0	0
	Moderate	0	0	0
	Severe	0	0	0
	Dead	1	1	1

Note: Mortality indicates that a mortality rate is used here. The other probabilities refer to the population remaining after allowing for the mortality rate. All transitional probabilities refer to discrete 6-month periods.

Table 4. Results

Treatment group	Cost	Years < severe	C/Y < S	Incremental C per extra Y < S vs placebo	vs 5 mg
Base case					
Mild					
10 mg	45694.43	1.82	25121.25	5697.71	4450.68
5 mg	45119.18	1.69	26702.40	7047.684	NA
Placebo	44277.72	1.57	28196.80	NA	NA
Moderate					
10 mg	46716.27	0.87	53777.53	3565.44	*1*
5 mg	46193.20	0.98	47100.35	1209.71	NA
Placebo	45719.45	0.59	77607.00	NA	NA
0% discount rate					
Mild					
10 mg	51025.05	1.82	28051.85	6090.86	4106.13
5 mg	50494.34	1.69	29883.52	8239.41	NA
Placebo	49510.59	1.57	31529.18	NA	NA
Moderate					
10 mg	52169.55	0.87	60055.08	3717.99	*1*
5 mg	51642.94	0.98	52657.11	1309.58	NA
Placebo	51130.07	0.59	86791.32	NA	NA
3% discount rate					
Mild					
10 mg	48203.69	1.82	26500.76	5884.18	4354.52
5 mg	47640.86	1.69	28194.78	7540.11	NA
Placebo	46740.61	1.57	29765.21	NA	NA
Moderate					
10 mg	49283.66	0.87	56732.98	3638.01	*1*
5 mg	48755.18	0.98	49712.64	1247.77	NA
Placebo	48266.52	0.59	81930.56	NA	NA
10% discount rate					
Mild					
10 mg	42757.94	1.82	23506.87	5475.96	4435.06
5 mg	42184.71	1.69	2465.72	6602.78	NA
Placebo	41396.37	1.57	26361.91	NA	NA
Moderate					
10 mg	43710.77	0.87	50317.75	3478.29	*1*
5 mg	43201.35	0.98	44049.74	1182.36	NA
Placebo	42738.31	0.59	72546.64	NA	NA
Martin et al. mortality rate					
Mild					
10 mg	59249.72	2.28	25984.27	4957.55	4569.33
5 mg	58500.17	2.12	27644.30	5328.370	NA
Placebo	57585.07	1.94	29615.32	NA	NA
Moderate					
10 mg	60582.51	1.04	58208.48	3371.97	*1*
5 mg	59927.64	1.19	50346.88	942.29	NA
Placebo	59478.14	0.71	83387.98	NA	NA

1, No incremental benefit.
Cost, £UK at 1997 prices; Years < severe, average number of years (within model) in state of minimal, mild or moderate; C/Y < S, cost per year in state less than severe; Incremental C per extra Y < S, incremental investment in treatment required to achieve extra year in state less than severe

state of minimal, mild or moderate dementia, that is, less than severe dementia. This shows that treatment with 10 mg donepezil has the best outcome and placebo is the least desirable. Combining this with costs shows that in terms of costs per year in a state less than severe, 10 mg donepezil is more cost-effective than 5 mg or placebo (£25 121 compared to £26 702 and £28 197 respectively). As an incremental cost, the results in Table 4 show that only an additional £5698 would be required to secure an additional patient year in a state of minimal, mild or moderate rather than severe dementia.

The outcome is slightly different for patients diagnosed as moderate at onset. In this group, 5 mg donepezil appeared to show better clinical outcomes than 10 mg, a factor that is reflected in the expected costs. The range of expected costs is narrower than for those patients mild at onset. Only £1000 separates the lowest cost group, placebo, from the highest cost group, 10 mg. In terms of years in a state less than severe, the differences between placebo and treated groups are proportionally wider, although in absolute terms the numbers are lower, with all three groups showing an expected outcome of less than 1 year in such a state. The best outcome is for 5 mg patients, generating the best results for cost per year in a state less than severe (£47 101 compared to £53 778 for 10 mg and £77 607 for placebo). This also results in a very positive outcome for the incremental costs: only an incremental £1210 would need to be invested in treatment using 5 mg donepezil to achieve an additional year of patient time in a state of minimal, mild or moderate dementia rather than progressing to severe dementia.

For the base case model, outcomes vary slightly between the patients in a mild state at onset and those with moderate dementia. However, the same general points can be observed. Use of donepezil is almost cost-neutral, resulting in only a slight increase in costs of care over 5 years. The drug acquisition costs are substantial, but they are largely balanced by a longer time spent in the less severe, and therefore less costly, states of severity of dementia. This results in lower non-drug costs of care.

SENSITIVITY ANALYSIS

Some of the key factors within the model were tested by sensitivity analysis, following standard principles (Briggs *et al*., 1994), to confirm the robustness of the model and the contribution of specific assumptions.

Discount rate

The discount rate measures time preference, society's valuation of future costs relative to current costs. Valuation of future costs is important in this type of model, where costs are accumulated over a period of up to 5 years. The base case analysis uses a rate of 6%, the current Treasury discount rate (HM Treasury, 1989) for public sector projects in the UK. Three alternative settings were tested. Table 4 shows expected costs at the three alternative discount rates.

1. 0%. At this rate, future costs are not deflated and hence costs in later years have an equal weighting with current year costs.
2. 3%. This rate reduces the relative value of future costs, but to a lesser extent than the base case rate of 6%.
3. 10%. By increasing the discount rate, future costs are given a lower weighting in calculation of expected costs.

The figures for expected costs increase as the discount rate falls, as would be expected. The relative positions of the subgroups do not alter, however, demonstrating that there is no significant difference in the timing of costs.

Mortality rate

In the Markov model, the mortality rate is the transition rate at which patients move into the absorbing state (dead) in which there are no further costs of care. It is therefore very important to the model, as it will affect future costs by varying the rate at which patients cease to accumulate further costs of care. Table 4 also shows the expected costs at two difference mortality rates:

- Burns *et al*. (1996a), the base case rate of 53% over 3 years;
- Martin *et al*. (1987), 30% over 3 years.

As the mortality rate declines, more patients remain alive at later stages and thus continue to incur costs, as shown by the rise in expected costs. However, the rankings of the three treatment groups remain unchanged from the base case assumptions using the Burns *et al*. mortality figures. This also applies to the effectiveness measure of

years in a state of less than severe and the cost-effectiveness measure of costs per year in a state of less than severe. The incremental costs reduce slightly at the lower mortality rate, with incremental costs (for an additional year less than severe) of 5 mg versus placebo falling to under £1000 (£942.30).

DISCUSSION AND CONCLUSIONS

This study has used data from several different sources to evaluate the economic impact of using an innovative therapy, donepezil, for elderly people with Alzheimer's disease. Consequently, there must be some caution in viewing the results. In particular, the costs data are drawn from a different set of persons to those evaluated in the clinical trial, although it can be assumed that they are very similar groups. And data from a clinical trial does, of course, provide evidence of efficacy, not effectiveness, that is, possible health improvements rather than real changes obtained in general use.

Within the framework provided by this model, the effects of treatment with donepezil 10 mg or 5 mg are approximately cost-neutral. As discussed earlier, this is largely due to the effect of donepezil in retarding patients' decline through the levels of measured disease severity. This delays the gradual shift to higher cost patterns of care and thus creates a more favourable profile of resource use over time. The conclusion contrasts with Lubeck *et al.* (1994), who concluded that use of tacrine reduced expected costs. Two factors may partly explain this difference. One is the very different set of health and social care unit costs that apply in the US context, which will affect the relative costs of particular outcomes. The other, probably more significant difference is that the costs of care used in this study include an element covering informal care. Therefore, this study provides a more accurate view of the real costs of care outside of residential accommodation and does not overestimate the economic impact of moving between locations.

The analysis in this article links costs of care to cognitive ability. There is a debate as to whether these two factors are directly linked, but the costing approach in this article does cover these concerns. The original costing estimates (Kavanagh *et al.*, 1995) calculate average costs across a total population at a given level of cognitive disability, thus allowing for the range of other influences that lead to variations in the actual costs for individuals within their sample. The resource use patterns on which the costs data are based reflect health and social care structures that have since been substantially changed; however, they were used as the best available estimates.

Sensitivity analysis demonstrated that discounting of costs has a significant effect on outcomes. However, varying the time preference rate did not affect judgements between alternative treatment regimes. Most of the costs are front-loaded, with the mortality rate leading to a rapid fall-off in numbers of patients remaining alive and incurring costs. Therefore, only a small proportion of costs are affected by discounting in the later years of the modelling process.

A more significant factor was the mortality rate used. The rate at which patients move into a state of no resource use, ie dead, is obviously very important to costs over time. Varying this rate affects the present value of the expected total costs of care. However, as stated earlier, it did not affect the comparative judgements between the three treatment options. One qualification is that treatment of these patients may possibly affect their mortality rate. However, no suitable data were available on this and therefore the mortality rate was assumed not to be different from the untreated population.

The general conclusion from the model is in favour of using donepezil, at either the 10 mg or 5 mg level. Both treatment regimes result in an approximately neutral impact on expected costs, albeit one in which total costs are raised slightly. However, the manner in which this is accomplished is by retaining patients at lower levels of severity of dementia, which most people would view as a positive outcome in itself. There are qualifications to this view, however. Delaying the move to residential accommodation shifts the burden of care further onto informal caregivers. While this burden is reflected in the costs, it may have quality of life implications for caregivers that are not fully reflected in the model. There is also a possible issue that if treatment reduces mortality rates, then patients may be spending more time in a state of suffering from, albeit less severe, dementia. Therefore, if we move away from a focus on cost minimization as an objective in itself and on to the use of economic analysis to identify the most effective means to a desired objective, the model demonstrates that donepezil is a cost-effective way to increase the time that patients suffering from Alzheimer's disease remain at lower levels of

disability. This is a broader outlook, which values patients outcomes as well as costs, and leads to our final conclusion, that donepezil must be viewed as an economically desirable innovation.

REFERENCES

Briggs, A., Sculpher, M. and Buxton, M. (1994) Uncertainty in the economic evaluation of health care technologies: The role of sensitivity analysis. *Health Econ*. **3**, 95–104.

Burns, A. and Förstl, H. (1996a) The Institute of Psychiatry Alzheimer's disease cohort: Part 1—clinical observations. *Int. J. Geriatr. Psychiat*. **11**, 309–320.

Burns, A. and Förstl, H. (1996b) The Institute of Psychiatry Alzheimer's disease cohort: Part II—clinicopathological observations. *Int. J. Geriatr. Psychiat*. **11**, 321–327.

Ely, M., Brayne, C., Huppert, F. A., O'Connor, D. W. and Pollitt, P. A. (1997) Cognitive impairment: A challenge for community care. A comparison of the domiciliary service receipt of cognitively impaired and equally dependent physically impaired elderly women. *Age and Ageing* **26**, 301–308.

Ely, M., Melzer, D., Brayne, C. and Opit, L. (1995) The cognitively frail elderly: Estimating population characteristics and needs of people with cognitive disability, including dementia. Report to the NHSME.

Ely, M., Melzer, D., Opit, L. and Brayne, C. (1996) Estimating the number and characteristics of people with cognitive disability in local populations. *Res. Policy Planning***14**(2), 13–18.

Gray, A. and Fenn, P. (1993) Alzheimer's disease: The burden of illness in England. *Health Trends* **25**(1), 31–37.

HM Treasury (1989) Discount rates in the public sector. Press Office, Parliament Street, London.

Jorm, A. F. (1990) *The Epidemiology of Alzheimer's Disease and Related Disorders*. Chapman and Hall, London.

Kavanagh, S., Schneider, J., Knapp, M., Beecham, J. and Netten, A. (1993) Elderly people with cognitive impairment: Costing possible changes in the balance of care. *Health Soc. Care Commun*. **1**, 69–80.

Kavanagh, S., Scheider, J., Knapp, M., Beecham, J. and Netten, A. (1995) Elderly people with dementia: Costs effectiveness and balance of care. In *The Economic Evaluation of Mental health Care* (M. Knapp, Ed.). Arena, Aldershot.

Kay, D. W. K. and Bergman, K. (1980) Epidemiology of mental disorders among the aged in the community. In *Handbook of Mental health and Aging* (J. E. Birren and R. B. Sloane, Eds). Prentice-Hall, Englewood Cliffs.

Lubeck, D. P., Mazonson, P. D. and Bowe, T. (1994) Potential effect of tacrine on expenditures for Alzheimer's Disease. *Med. Interface*, October, 130–138.

Martin, D. C., Miller, J. K., Kapoor, W., Arena, V. C. and Boller, F. (1987) A controlled study of survival with dementia. *Arch. Neurol*. **44**, 1122–1126.

Netten, A. and Dennett, J. (1997) *Unit Costs of Health & Social Care*. Personal Social Services Research Unit, University of Kent at Canterbury.

Office of Population Censuses and Surveys (OPCS) (1989a) *Survey of Disability among Adults in Communal Establishments, 1986*. ESRC Data Archive, Colchester.

Office of Population Censuses and Surveys (OPCS) (1989b) *Survey of Disability among Adults in private Households, 1985*. ESRC Data Archive, Colchester.

Rogers, S. L., Farlow, M. R., Mohr, R., Friedhoff, L. T. and the Donepezil Study Group (1998) A 24-week double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* **50**(1), 136–145.

Rogers, S. L., Friedhoff, L. T. and the Donepezil Study Group (1996) The efficacy and safety of donepezil in patients with Alzheimer's disease: Results of a US multicentre, randomized, double-blind, placebo-controlled trial. *Dementia* **7**, 293–303.

Sainsbury, M. J. and Lambeth, L. G. (1988) *Sainsbury's Key to Psychiatry*, 4th edn. Wiley, Chichester.

Sonnenberg, F. A. and Beck, J. R. (1993) Markov models in medical decision making: A practical guide. *Med. Decision Making* **13**, 322–338.

Schneider, J., Kavanagh, S., Knapp, M., Beecham, J. and Netten, A. (1993) Elderly people with advanced cognitive impairment in England: Resource use and costs. *Ageing and Soc*. **13**, 27–50

Stewart, A. (1997a) Costs of care for people with dementia aged 75 and over. Discussion Paper 1303/2, PSSRU.

Stewart, A. (1997b) Donepezil in the treatment of people with Alzheimer's disease: A pilot Markov approach. Discussion Paper 1324, PSSRU.

Stewart, A. (1997c) Pharmacotherapy in the treatment of people with Alzheimer's disease: A Markov-cycle evaluation of donepezil. Discussion Paper 1342/2, PSSRU.

Taylor, P. (1993) Anticholinesterase agents. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th ed. McGraw-Hill, New York, pp 131–149.

Treeage Software Inc (1997) DATA™ 3.0.14 for Windows. Treeage Software, Williamstown, MA.