89

COST-EFFECTIVENESS OF THERAPEUTICS FOR ALZHEIMER DISEASE

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Alzheimer disease (AD), the most common form of dementia, is a progressive neuropsychiatric condition, the expression of which is manifested by neuropsychological deficits (aphasia, apraxia, agnosia, and amnesia), neuropsychiatric signs and symptoms (depression, delusions, hallucinations, aggression, and wandering), and problems with self-care (activities of daily living) (1–3). Caring for a person with dementia places a huge strain on both formal (paid, professional) and informal careers (4).

Alzheimer disease is associated with significant and excess morbidity and mortality. Approximately 30% of elderly people with dementia are severely disabled and require intensive or specialized care and support (2). Studies also indicate that 50% of an incident cohort with dementia will be severely disabled within 3 years, and up to 70% within 7 years (5).

The average survival of people with AD has been estimated at 3 to 6 years from diagnosis, and 7 to 9 years from onset of symptoms (6). The length of survival depends on the age at diagnosis, comorbid conditions, setting of care, family situation, and gender (5,6). Gray and Fenn (7) estimated that AD accounts for 2.5% to 5% of all life-years lost between the ages of 60 and 95 years.

The demographic trend toward an aging population means that the burden of the condition will increase in the next 25 years. Population estimates suggest that the expected number of people with AD will rise from less than half a million in 1999 to more than 600,000 in 2020 in the United Kingdom (8). Similar increases are predicted in Canada, from 161,000 people in 1991 to 314,000 people in 2011 and 509,000 in 2031 (9), and in the United States, where the number of people with AD was 2.9 to 4.8 million in 1994 and is expected to increase to 9 million by 2040.

Data on the prevalence of dementia and AD are shown in Table 89.1. The prevalence and incidence of AD increase with age. The prevalence of the disease broadly doubles for every 5 years of age, increasing from less than 1% of the population ages 65 to 69 years to between 10% and 40% of people ages 85 years and over. The age-specific incidence rates of AD are between 51 and 161 cases per 100,000 person-years for ages 65 to 69; they increase to between 1,000 and 2,855 cases per 100,000 person-years for ages 80 to 84 and to between 1,456 and 5,420 cases per 100,000 person-years for ages 85 and over.

CURRENT TREATMENT OF ALZHEIMER'S DISEASE

Two theoretically distinct treatment options are available for the treatment of AD. *Symptomatic* treatments are aimed at increasing acetylcholine levels without the expectation that they will affect the underlying course of the disease. *Stabilization* treatments are directed at altering the underlying disorder (characterized by the deposition of amyloid and the presence of neurofibrillary tangles and abnormally phosphorylated tau protein); they do not necessarily produce symptomatic improvement but may delay the progression of the disorder.

Symptomatic Treatment

The most successful agents to provide *symptomatic* improvement are the acetylcholinesterase drugs. AD is associated with a number of neurologic and neurochemical abnormalities, particularly depletion of acetylcholine. Acetylcholines-

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TABLE 89.1. AGE-SPECIFIC PREVALENCE OF DEMENTIA AND ALZHEIMER DISEASE (%)

	Eurodem (10)		Framingham (11)		Jorm et al. (12)	
Age	Dementia	AD	Dementia	AD	Dementia	AD
65–69	1.4	0.34	0.9	0.4	1.4	na
70–74	4.1	3.2	2.0	1.1	2.8	na
75–79	5.7		4.3	3.3	5.6	na
80–84	13.0	10.8	8.9	6.9	10.5	na8
85+	21.6–34.7		16.3	12.6	20.8–38.6	na
	Europe (5,6)		**United States (5,6)**		**Canada (6,9)**	
Age	Dementia	AD	Dementia	AD	Dementia	AD
65–69	0.9–1.4	0.3–1	0.8–0.9	0.2–0.8	2.4	1.0
70–74	2.1–4.1	1.1–2.5	1.3–2.0	0.4–1.2		
75–79	4.6–14.6	2.3–8.2	3.6–6.3	2.1–3.7	11.1	4–6.9
80–84	9.6–2.7	4.5–10.6	8.9–12.7	5.1–8.2		
85+	9.6–16.9			8.2–47.2	34.5	10.5–26
85–89	20.4–38.3			16.3–29.7		
90–94	28.3–57.3			40.4–74.3		
95+	42.3–55.8			58.6		

AD, Alzheimer disease.

terase inhibitors (or anticholinesterases) enhance surviving cholinergic neurotransmission by inhibiting the breakdown of released acetylcholine.

Two first-generation anticholinesterases are physostigmine and tetrahydroaminoacradine (tacrine). Early trials suggested that physostigmine has short-term efficacy in improving memory. However, the results of trials vary substantially. In addition, the drug is associated with a high incidence of side effects (13). Tacrine requires a complex dosing regime and has toxic side effects (3). Systematic reviews suggest that the drug has a modest but not clinically or statistically significant effect on cognition in people with mild to moderate AD (14,15). Because administration of the drug has been accompanied by a high rate of adverse events (especially hepatotoxicity), rates of withdrawal from trials have been high.

Second-generation anticholinesterases include donepezil hydrochloride (Aricept, Pfizer) and rivastigmine (Exelon, Novartis).

Clinical trials of rivastigmine show a magnitude of effect similar to that of donepezil in a larger patient database with a longer duration of treatment and less restrictive entry criteria (3,16). Overall, patients taking the drug show an improvement in cognition, global clinical state, and carer ratings of activities of daily living.

Drugs that have a *stabilization* effect on the progress of AD are nonsteroidal antiinflammatory agents (NSAIDs), estrogen, and antioxidant agents. There is good evidence of an inflammatory component in AD, and it is well documented that NSAIDs are protective against the development of AD. The evidence of a symptomatic improvement in patients taking these drugs is inconsistent. The beneficial effects of aspirin on cardiovascular and cerebrovascular disease are well documented, but no evidence has been found that it is effective in AD. Estrogen appears to have a significant protective effect against the development of AD and may work through a number of different mechanisms. Small-scale studies have shown minor benefits in terms of improved cognitive function. A growing body of evidence indicates that free radical formation is a mediator of the excessive lipid peroxidation and cell damage seen in AD. Antioxidant vitamins (e.g., vitamins C and E) have been shown to have biological activity in acting as scavengers for free radicals. Sano et al. (17) showed that α-tocopherol in a daily dose of 2000 IU significantly delays the onset of defined milestones in the development of AD. Therefore, of the three stabilization agents currently available, only vitamin E is supported by evidence that it can delay deterioration in the disease. α-Tocopherol has the advantage that it is not toxic (even at high doses), and it is easily available and suitable for all patients. Sano et al. (17) reported no significant side effects of α—tocopherol. Estrogen has significant potential to cause gynecologic cancer and currently is suitable only for women, and antiinflammatory agents can provoke gastric inflammation and bleeding.

ECONOMIC PERSPECTIVE

Given the constraints on health and social care budgets, those responsible for the provision and financing of such

services need to ensure that resources are used efficiently. Economic evidence about the relative costs and outcomes of health and social care helps decision makers determine the best use of scarce health care resources (18,19). Two approaches have been used to evaluate the economic consequences of AD. These are (a) cost-of-illness or burden-of-disease studies to assess the costs and consequences of a disease to society and (b) full economic evaluations to compare the costs and consequences of alternative health or social care interventions.

Cost-of-Illness Analyses

From an economic perspective, the aim of cost-of-illness or burden-of-disease studies is to describe and value the costs and consequences of a disease to society. A cost-of-illness study should describe and value the direct costs of health and social care for people with the disease. It should also describe the mortality and morbidity consequences. These should be valued in either monetary terms (as indirect and intangible costs) or by utility-based measures such as quality-adjusted life-years (QALYs).

Cost-of-illness studies can be used to estimate the total burden of disease for a given year. In this approach, known as the *prevalence approach,* the costs and health outcomes of all people with the disease in a given year are included. An alternative approach is to estimate the lifetime costs and consequences for a cohort of people with the disease, from onset to death. This is known as the *incidence approach.*

Cost-of-illness studies do not provide information about the economic benefits of introducing or developing new health or social care programs, and they are of limited use in setting priorities or allocating resources (18,19).

Full Economic Evaluation

Economic evaluations compare alternative health or social care interventions and estimates of the relative or incremental costs and benefits of care. In AD, two or more drug therapies to treat the symptoms of the disease or delay progression may be compared for efficacy. The four types of economic evaluation are cost-minimization analysis, cost-effectiveness analysis, cost–utility analysis, and cost–benefit analysis. The analytic framework chosen depends on the perspective of the analysis and the economic questions posed (19).

Cost-Minimization Analysis

In a cost-minimization analysis, the direct costs of two or more health care interventions are compared. This form of analysis does not include a formal economic comparison of the outcomes of health and social care. However, the evidence that patient outcomes do not differ between interventions must be clear and reliable. If such evidence is not available, then the economic evaluation must include a cost-effectiveness, cost–utility, or cost–benefit analysis of patient outcomes.

Cost-Effectiveness Analysis

A cost-effectiveness analysis compares the direct costs of health and social care resources of two or more interventions with patient outcomes, measured in terms of clinical effectiveness. For AD, measures such as years of life with mild or moderate disability or changes in cognitive function are used.

If one intervention, such as a new drug to control symptoms or delay progression, leads to lower direct costs and improved patient outcomes, it is the dominant and preferred option. In other words, it clearly saves resources to provide care and is more beneficial to the patient. More often, a new therapy is associated with improved patient outcomes at additional cost. Incremental cost effectiveness ratios (ICER) provide a measure of the cost of gaining a unit of health improvement, such as cost per life-year gained. The ICER is calculated as follows: (Cost of A − Cost of B)/(Outcome of A − Outcome of B).

Cost-effectiveness analysis is limited by the use of effectiveness measures, which may not capture the total impact of health and social care on quality of life or overall well-being. This is particularly important in AD, in which the impact of the disease and patient care is multidimensional. In this case, an outcome measure is needed that combines several aspects, such as survival and cognitive, physical, and emotional function, into a single index.

Cost–Utility Analysis

Cost–utility analysis is similar to cost-effectiveness analysis, but utility is used as the outcome measure. Cost–utility analysis is used to estimate QALYs. As in cost-effectiveness analysis, incremental cost–utility ratios are calculated to estimate the cost of producing one additional QALY.

Cost–Benefit Analysis

A cost–benefit analysis is based on monetary valuations of the morbidity and mortality consequences of disease or interventions. These allow an estimation of the absolute and relative net social benefit of intervention. This is calculated as the monetary value of the consequences of an intervention minus the direct costs. Any health or social care intervention with a net social benefit greater than zero (i.e., the benefits are greater than the costs) is worth undertaking.

KEY COMPONENTS OF AN ECONOMIC EVALUATION

Perspective of Analysis

Economic studies should consider all costs and outcomes that are a consequence of the illness (cost of illness) or the

health or social care interventions evaluated (economic evaluation). For AD, these may include the costs of hospital care, community-based health care services, social welfare services, and care provided by voluntary agencies or family and friends. People with AD and their families may also receive social welfare or support payments. However, what constitutes a cost from one point of view may not be a cost from another.

For example, the costs of social care services or patient and family out-of-pocket expenses are a cost to society but not to those responsible for provision or funding of hospital based care. In contrast, social welfare payments are a cost to the agency that pays them, but a benefit to the patients and families who receive them. From the point of view of society, social welfare payments are both a cost and a benefit; when added together, they cancel each other out, so they should not be included.

For these reasons, an economic analysis should be clear about the viewpoint or perspective and therefore the range of costs and consequences included. Ideally, a broad perspective that reflects the costs and outcomes to society should be adopted. At a minimum, the perspective of the analysis should include the costs and outcomes to key health and social care providers or funders and to patients and their families.

Time Frame of Analysis

Economic studies should use a time frame that allows full measurement of the relevant costs and benefits. Comparative economic evaluations should monitor resource use, costs, and outcomes for the full period during which the interventions could be expected to have an effect on resource use, survival, and health-related quality of life.

Target Population and Comparators

The population considered in the analysis should be representative of the population to be treated. The interventions compared should be relevant to the health and social care choices faced by decision makers. Unless "do nothing" is a valid management strategy, comparison of a new intervention with placebo is not appropriate for an economic evaluation.

Opportunity Cost

The economic concept of cost is the value of a good or service in terms of its best alternative use, or opportunity cost. Often, the market price or value of the resources used, such as the time of a health care professional, facilities, or medicines, is a reasonable approximation of the opportunity cost or value to society of the services provided.

Measurement and Valuation of Costs

An economic study should describe and quantify the resources used to produce health and social care and support for the patients and their carers. Costs should be estimated from data on the quantity and type of resources used (e.g., number of hospital-based physician visits, number of hospital admissions, number of days per admission) multiplied by the opportunity cost or market price of those resources. If the evaluation compares two or more interventions, care must be taken to ensure that all relevant types of resource use and costs are identified. These include costs of the intervention, follow-up care and support for patients and carers, and management of side effects or adverse events.

These aspects are termed the *direct costs* to produce of health and social care. From a societal perspective, direct costs also include out-of-pocket expenses and the use of resources that do not have a market price, such as the time of family or volunteers. These should be measured and valued because they are potentially important inputs to the production of care. The time costs of volunteers and family members can be valued with average wage rates or the cost of equivalent services with a market price (e.g., private nurses).

Measurement and Valuation of Outcomes

It is crucial that an economic study include the health-related consequences of morbidity and mortality. For AD, these could be the number of years of life lost and the illness-associated reductions in health status and quality of remaining years of life for both patients and informal carers.

These consequences should also be valued to reflect the cost or loss of utility to individuals and society of reductions in the length of life or health. Two approaches have been advocated. The first is to value the consequences in monetary terms as indirect or productivity costs *and* intangible costs. The second is to combine data about length of life and morbidity to provide a single, nonmonetary measure of impact.

Monetary Valuation

Indirect costs represent the value of changes in the amount or type of work done or use of leisure time as a consequence of morbidity or mortality. They are also called *productivity* or *time costs* (18,19). With AD, the ability to engage in the normal daily activities of life and leisure is reduced by impaired cognitive function and, in some cases, early death. The physical and mental health of carers may also be affected. Typically, these costs are valued in the same way as the time costs of unpaid carers, by using market values of the time in full health lost, such as average wage rates. However, indirect or productivity costs do not include the costs of patient or carer time used to provide health and social care.

Intangible costs represent the monetary value to individuals and society of health and life *per se.* In practical terms, a determination of intangible costs requires an assessment of the amount of money that individuals would accept as compensation for reductions in health or life expectancy, or the amount they would be prepared to pay for improvements in health or life expectancy.

Nonmonetary Valuation

An alternative approach is to estimate individual and social preferences for life, health, or disability states. This approach combines measures of life-years lost because of early mortality with a value for the morbidity or ill health associated with the remaining years of life. Examples are quality-adjusted life-years (QALYs) and disability-adjusted life-years (DALYs). These are calculated as the number of years of remaining life weighted by the quality or utility of that life. The utility weight is the relative value of society for states less than full health.

Discounting

The costs and consequences of a disease and health and social interventions can occur at different times. For analyses that include a time frame of more than 1 year, it is conventional to discount the costs and outcomes to present values, so that the relative importance of events occurring in the future, rather than the present, is reduced. Discounting is based on the assumption that individuals and society prefer to receive benefits sooner rather than later and to delay costs. There is some debate about whether outcomes and costs should be discounted at the same rate. The rule of thumb is to use a discount rate of 5% for both and repeat the analysis with alternative rates for the costs and outcomes.

HOW SHOULD ECONOMIC DATA BE COLLECTED AND ANALYZED?

To be useful to those concerned with choices in the allocation of health and social care resources, the design of economic evaluations should ensure that the results are timely, relevant, credible, and accurate (20). The economic study can use modeling techniques to synthesize secondary and primary data from several sources, or it can analyze data collected prospectively with a controlled study design. Which of these techniques is used depends on the type of question addressed.

The first type of question assesses the available evidence about the relative costs and outcomes of current and new forms of health and social care. The existing literature and data should be reviewed to determine the following: natural history of the disease; incidence and prevalence of the disease; possible indications and target populations for the new intervention; current treatment patterns; relevant comparators; and the costs and benefits of current treatment or health care. The initial assessment should be based on a synthesis of available data and expert opinion, which requires the development of internally and externally valid and logical models that are consistent and robust. If the quality or completeness of existing data is doubtful, sensitivity analysis should be used to generate minimum and maximum values for key clinical and economic parameters. Best and worst case scenarios should be incorporated to ensure that interactions between key parameters are explored.

If the modeling study indicates that clinical or economic evidence is highly uncertain, the prospective collection of data is required. The objective is to establish whether differences in clinical and economic endpoints are directly attributable to the interventions compared. To this end, well-controlled evaluations with a high level of internal validity are required, such as an integrated economic and clinical controlled trial. Whether randomized, controlled trial methodology or alternative study designs are used depends on the feasibility and relative efficiency of conducting a large pragmatic trial, which is typical of routine practice on a representative sample of patients. If the correlation between resource use and the interventions studied is high, even tightly defined explanatory clinical trials may be appropriate to address the question of efficiency. Alternatively, if the correlation is low and other factors, such as patient characteristics, comorbidities, and organization of health care services, are equally important determinants of service use, then the most pragmatic trial may fail to provide usable economic information.

The costs of the interventions studied should be estimated from activity data, which quantify resources used, and price or unit cost data. All health and social care activity data are potentially important and should be collected, particularly if variability in the intensity of resource use between diseases, patients, or centers is likely to be large.

Costs of Alzheimer's Disease

A number of studies have evaluated the burden of AD in different countries. These have focused primarily on the direct costs of illness and so are partial analyses. The costs have been updated to 1997 figures, with the use of health and social care inflation indices, to provide a common price year for comparison. The costs were then converted to U.S. dollars by means of purchasing power parities (PPPs). The PPP is the rate of currency conversion that ensures that the price level in each country, when expressed in dollars, is the same as that in every other country. The advantage of PPPs over conventional exchange rates is that they reflect the price levels and purchasing power of the currencies converted (21).

Table 89.2 presents data on the direct costs of health and social care for cohorts of people with AD. The variations

TABLE 89.2. CARE SETTING, INFORMAL CARE, AND COST PER PERSON (U.S. DOLLARS, 1997)

	Mild/Moderate			Severe			All		
Source	**Cost**	**%ICC**	**%CS**	**Cost**	**%ICC**	**%CS**	**Cost**	**%ICC**	**%CS**
United Kingdom									
Gray and Fenn, 1993 (7)									
Community	—	—	89–94%	—	—	54%	4,747	—	—
Long-stay care	—	—	6–11%	—	—	46%	45,405	—	—
Kavanagh et al., 1993[a,b] (22)									
Private household	—	—		32,567	27%	63%	—		
Long-stay care	—	—		60,180	—	37%	—		
Kavanagh and Knapp, 1999[b] (23)									
Private household	26,442	—	77%	28,911	—	67%			—
Long-stay care	65,586	—	23%	66,157	—	33%			—
Souêtre et al., 1999[a] (24)									
Private household	98,322	69%	100%	156,794	68%	100%		—	
Holmes et al., 1998 (25)									
All settings	—			—			62,807	33%	—
Canada									
Østbye and Crosse, 1994 (26)									
Private household[a]	14,107–22,784		48–56%	27,140		59%	—	—	
Long-stay care	—			38,407		—	—	—	
Hux et al., 1998[a] (27)									
Private household	18,120	80%	67%	25,000	79%	14%	—		
Long-stay care	42,657	4%	33%	50,461	8%	86%	—		
All settings	26,780	42%		47,172	13%	—	—		
United States									
Rice et al., 1993[a] (28)									
Community	53,283	81%	—	70,939	69%	—	63,418	73%	—
Long-stay care	50,819	8%	—	64,929	12%	—	64,102	12%	—
Leon et al., 1998[a] (29)									
Community	14,216–23,005	56–60%	47–78%	27,817	50%	27%	19,015	56%	52%
Long-stay care	34,864–37,675	2%	22–53%	40,363	2%	73%	38,424	2%	48%
All settings	18,826–30,780	22–34%	—	36,953	11%	—	28,308	21%	
Ernst et al., 1997 (30)	—					—	37,870–43,604		

CS, cost setting; ICC, informal care cost.
[a]Cost of care with Alzheimer disease/cognitive disability minus the cost of no cognitive disability.
[b]Estimated.

TABLE 89.3. ESTIMATED INCREMENTAL COSTS OF ALZHEIMER DISEASE (U.S. DOLLARS, 1997)

	Annual Incremental Cost of Care Per Person[a]			
Source	**No Cognitive Disability**	**Mild/Moderate**	**Severe**	**All**
United Kingdom				
Kavanagh and Knapp, 1999[b] (23)				
Total cost	25,299	35,341	42,886	—
Incremental cost	—	10,042	17,587	—
Souêtre et al., 1999 (24)				
Total cost	4,317	76,315–118,233	156,794	—
Incremental cost	—	71,998–113,916	152,477	—
Canada				
Østbye and Crosse, 1994 (26)				
Incremental cost	—	—	—	18,998
United States				
Ernst and Hay, 1994[a] (32)				
Incremental cost	—	—	—	42,058

[a]Cost of care with Alzheimer disease/cognitive disability minus the cost of no cognitive disability.
[b]Estimated from sample of people with physical or cognitive disabilities.

in costs within each of the countries and also between them are large. The average cost per person ranges between $14,107 and $50,461 in Canada, $4,747 and $156,794 in the United Kingdom, and $14,216 and $70,939 in the United States. These variations reflect differences in the methods used to collect and analyze the epidemiologic and cost data (31), the range of costs included, timing of the study, and disease severity and setting of care of the sample of people with AD included in the study.

Sources of Data

Data for the cost estimates shown in Tables 89.2 and 89.3 were derived from a number of sources. One study used secondary analysis of administrative databases in the United Kingdom (7,33). These gave aggregate measures of the use of hospital inpatient care, residential and nursing home admissions, and general practitioner consultations for people with mental disorders in 1984 and 1985. They were supplemented by surveys and expert opinion to generate measures of the use of day care, home-based care, and payments to informal carers. Cost data from other sources were used to estimate total expenditure for people with AD (7,33). The primary disadvantages of this approach are that the data for resource use may not be detailed enough to allow a complete measurement of the range of resources used. In addition, coding errors and highly summarized diagnostic categories and comorbidities make it difficult to allocate resource use to specific diseases. These problems may account for the substantially lower community-based costs found in this study.

Four of the costs studies were based on detailed data from large-scale national surveys (22,23,26,27). The U.K. studies both used two surveys of people with disabilities living in private households (n = 5,699) and communal establishments (n = 3,037) that had been conducted in the middle to late 1980s (22,23). The Canadian studies both used the Canadian Study of Health and Ageing, which surveyed a total of 10,263 randomly selected Canadians over the age of 65 (26,27). Resource use information was collected by interviewing people with disability and their carers.

The remaining studies in Tables 89.2 and 89.3 used surveys of selected samples of people. The samples of respondents varied in size from 64 to 679 people. Similar methods were used to identify resource use. Two of the studies collected data prospectively from respondents during 6-month (30) and 2-year periods (28). Most studies included validated measures to determine the presence and severity of cognitive disability.

Estimating resource use from individual patient or carer data is associated with several advantages and disadvantages. First, the use of screening instruments allows a clear identification of people with cognitive disability or AD. However, the use of a variety of instruments may lead to differences in the categorization of people with cognitive problems, so that the comparability of results is reduced. For example, the surveys in the United Kingdom used a broad classification of cognitive disability that resulted in a higher prevalence estimate than that obtained in other epidemiologic research (22).

Secondly, the use of individual patient or carer data allows the health and social care services actually used by the people in the study to be identified. It also allows the use of informal care time and personal expenditures to be measured. However, the use of interviews and questionnaires to determine resource use may be subject to problems with accurate recall or recording the type and quantity of services actually used. This problem is illustrated by the greater range of costs found for people living at home, where a greater range of services may be used, than for people in long-stay care. The highest cost estimates for people living at home were 6 to 7 times greater than the lowest, whereas they were 1.7 to 1.9 times higher for people in long-stay care.

Thirdly, if the study is based on large samples, the impact of random variation in the use of health and social care services is reduced. If a small sample by chance overrepresents people with an extremely high or low use of services, substantial underestimation or overestimation of the costs can result. For example, the range of costs found in the large U.K. and Canadian studies was relatively small, with the highest estimate between 1.3 and 1.9 times greater than the lowest estimate. However, the range was far greater for the smaller studies. In particular, for people living at home, the highest costs were 5.6 to 6.9 times greater than the lowest costs.

Measurement and Valuation of Informal Care

A key difference between the studies was the use of unpaid care and the method utilized to cost this care. One study did not include the costs of unpaid informal care time (23). When included, informal care costs ranged from 48% to 81% of home-based care for people with mild to moderately severe disease and from 27% to 79% of home-based care for people with severe disease. For people in long-stay care, the proportion of informal care costs ranged from zero to 12%. Excluding the costs of unpaid care does not reduce the variability in the total costs of care. This suggests that in some cases, unpaid care may be a substitute for rather than an addition to formal health and social care services.

Kavanagh et al. (22) used U.K. social security allowances for carers of people with disabilities as a proxy for the costs of informal care. This gave the lowest proportion of informal care costs for people living at home (27%). Three studies used the replacement cost method to estimate the opportunity cost of unpaid carer time (26,28,29). The time spent by informal carers was estimated and then multiplied by the average wage of professional (paid) caregivers. The informal care costs ranged between $7,900 (50% of costs) (26) and $48,948 (81% of costs) (28).

The other studies used the national average wage (24) or minimum wage (27) to value unpaid carer time. The informal care costs ranged from $14,496 (80% of costs) (27) to $106,620 (69% of costs) (24). These data illustrate the impact of different methods of valuing informal care time on estimates of cost.

Organization and Availability of Care

Rice et al. (28) estimated the expected cost per person with AD. This was based on data for a sample of people living in both community and residential care in northern California. The estimated annual costs per person were higher than the estimates from the other studies reported in Tables 89.2 and 89.3. However, the authors stressed that the organization and level of provision of services in California were such that the results should not be generalized to other geographic settings in the United States.

The organization and availability of health and social care vary with time as well as between settings. In many countries, the trend has been toward the provision of mental health and social care services in the community rather than in institutions, with an emphasis on support from family and informal carers (34). This means that earlier studies may overestimate the current costs of institutional care and the potential benefits of reducing the need for such care. At the same time, the costs of community or home-based care and informal carers will be underestimated. This is particularly important if the opportunity costs of informal care are not included or are underestimated in the direct costs of providing health and social care.

Severity of Disease and Setting of Care

The costs of health and social care for people with AD are also affected by two interrelated factors: the severity of disability caused by the disease and the setting of care.

Severity of Disease

The cost data in Table 89.2 indicate a trend toward higher costs of care as the severity of the disease increases. This applies in both community/private home settings and long-stay care settings. Three studies used statistical analysis to compare costs by disease severity. All of them found some degree of statistically significant correlation between some of the costs and disease severity (23,27,29). Holmes et al (25) used regression analysis to estimate average cost by age and years since diagnosis. In their analysis, total costs were positively related to years since diagnosis. Each additional year since diagnosis was predicted to increase costs by roughly $1,100 per person. However, cost was negatively related to age. Each additional year of age predicted a decrease in costs of about $850. The authors suggested that this finding may have reflected more intensive hospital-based care for younger people with AD.

It has also been suggested that as the cognitive and functional ability of people declines, they can no longer live

alone supported by formal health and social care services. They may move to live with family or friends, who provide informal care. In this case, informal care may be a substitute for previous formal care services. If informal care is not adequately costed, then the financial cost decreases, but not the opportunity cost of providing care (35). In contrast, in a secondary analysis of a large-scale disability survey in the United Kingdom, disabled elderly people with more severe cognitive disability received more intensive care and were referred more often to health care services (23).

In an analysis of Canadian data (27) in which a bivariate regression model was used to assess the relationship between severity of disease and costs, each 1-point decrease in Mini-Mental State Examination (MMSE) scores was associated with an average increase in costs of $1,343 (Canadian dollars, 1996 prices). Even when informal care time was valued by using industrial aggregate wage levels rather than minimum wage levels, the relationship between severity and costs remained statistically significant. The relationship between costs of care and severity of disease is complex. Increases in the costs of care as disease becomes more severe represent in part a greater use of institution-based care as people become more cognitively and functionally disabled by their disease. They may also reflect aging and the effect of comorbidities (23). In addition, informal carers age and may be affected by declining health and less ability to provide care.

Setting of Care

An important determinant of the costs of health and social care is the distribution of people with AD by setting of care. For most of the studies reported in Table 89.2, the costs of long-stay care are 1.5 to 2.5 times higher than those of home-based care. The exceptions to this are the study by Gray and Fenn (7), in which the costs of long-stay care were 10 times higher than those of community care. The study by Rice et al. (28) indicated roughly equal costs for long-stay and home-based care.

Determinants of the setting of care include the severity of cognitive and functional disability, the presence of other health problems, the ability of informal carers to support the person at home, and the structure of health and social care service provisions. The data in Table 89.2 indicate that the proportion of people cared for in long-stay care settings is between 6% and 53% for people with mild to moderate disease and 33% to 86% for people with severe disease.

Kavanagh and Knapp (23) found cost variations between long-stay care locations in their sample, and they also found the prevalence of severe cognitive disability to be higher in the more expensive settings. In the regression analysis by Holmes et al. (25), the use of institutional care increased with the number of years since diagnosis and the age of the carer. For each additional year of age of the carer, the costs of institutional care were predicted to increase by roughly $264 per year.

Incremental Costs of Alzheimer Disease

Table 89.3 presents estimates of the additional or incremental costs of care associated with AD only, rather than with other illnesses or age. With the exception of those in the study by Souêtre et al. (24), the incremental costs tend to be lower than the full costs reported in Table 89.2. In the study by Kavanagh and Knapp (23), the costs of people with disabilities, but no cognitive disability, were approximately $25,299. The additional costs of people with cognitive disability in this group can be estimated at $10,042 to $17,587. The studies by Souêtre et al. (24) and Østbye and Crosse (26) estimated the costs of care for people in a similar age group with no disabilities. The study by Ernst and Hay (32) estimated the net costs of care from aggregate data sets and surveys.

Evidence of Cost-Effectiveness

It is clear that the costs of health and social care and informal care for people with AD is high, and evidence suggest that the costs increase with the severity of cognitive disability and need for long-stay care or institutional care. It has been argued that it might be rational to support the introduction of drug treatments to slow down the progression of the disease and delay the onset of institutionalization. This would lead to a saving of costs to offset the acquisition costs of the drugs. However, this proposal has been criticized on the grounds that it would shift the burden of the disease from the public sector budget to private citizens, without a real beneficial effect for society as a whole. A full evaluation from the societal viewpoint of the new drugs used to manage AD is clearly needed (36). A number of economic studies have been published to assess the relative value for money of tacrine, donepezil, and rivastigmine. Table 89.4 gives details of the methods used and comparators of the studies.

Most of these analyses are modeling exercises that extrapolate the results of randomized, controlled trials to a longer time period and broader population. Only four meet the criteria for full economic evaluations, and these are shown in Table 89.5, which reports the estimates of the expected net benefits and costs likely to occur from the introduction of these drugs. The four studies analyzed the same drug treatment (donepezil) in four different countries/settings: United Kingdom (37), Canada (38), United States (39), and Sweden (40). Stewart et al. (37) evaluated the cost-effectiveness of donepezil in the United Kingdom for individual patients ages 75 years and over with a diagnosis of either mild or moderate AD. O'Brien et al. (38) considered a hypothetical cohort of people with nonsevere AD (MMSE $\geq$ 10) in Canada. Finally, Neumann et al. (39) focused on patients in the United States with mild or moderate AD.

Despite differences in the provision of health care between the United Kingdom, the United States, and Canada, these studies found donepezil to be approximately cost-neu-

TABLE 89.4. ECONOMIC MODELS OF DRUGS FOR ALZHEIMER DISEASE

Study	Country	Drug	Method	Perspective	Costs Included	Discount Rate	Comparators	Time Horizon
Stewart et al., 1998 (37)	United Kingdom	Donepezil	Cost-effectiveness analysis	Societal	Direct costs and costs of informal care	6%	5-mg and 10-mg doses/d vs. placebo	5 y (6-mo cycles)
O'Brien et al., 1999 (38)	Canada	Donepezil	Cost-effectiveness analysis	Societal and government payer	NHC, CCS, CG, drug costs	5%	5-mg dose/d vs. no treatment	5 y (6-mo cycles)
Jönsson et al., 1999 (40)	Sweden	Donepezil	Cost-effectiveness analysis	Not clearly stated	Residential costs, home help, and drug cost	3%	5-mg and 10-mg doses/d vs. no treatment	5 y (6-mo cycles)
Neumann et al., 1999 (39)	United States	Donepezil	Cost-effectiveness analysis	Societal	Direct medical and nonmedical costs; costs of informal care	3%	pooled 5-mg and 10-mg doses/d	1 y (6-mo cycles)
Stein 1997 (41)	United Kingdom	Donopezil	Drug evaluation, NHS report		Acute/geriatric hospital in- and out-patient care, mental hospital care, GP consultations, drug costs	6%	5-mg and 10-mg doses/d and placebo	2, 5, 8, and 10 y
Fenn and Gray, 1999 (33)	United Kingdom	Rivastigmine	Cost-saving analysis	Health and social care system	Long-term care institutions costs, drug costs, costs occurring when living at home	Not stated	1 to 4-mg and 6 to 12-mg doses/d vs. placebo	26 wk, 1 yr, and 2 y
Stein, 1998 (42)	United Kingdom	Rivastigmine	Drug evaluation, NHS report		Acute/geriatric hospital in- and out-patient care, mental hospital care, GP consultations, drug costs	6%	1 to 4-mg and 6 to 12-mg doses/d and placebo	1, 2, and 5 y
Small et al., 1998 (43)	United States	Donepezil	Longitudinal survey	Not clearly stated	Direct medical costs and drug costs	n. a.	drug vs. no drug treatment	6 mo
Henke and Burchmore 1997 (44)	United States	Tacrine	Cost-minimization analysis	Public and private payers	All paid medical and societal services	5%	tacrine 80 mg/d vs. no drug treatment	Lifetime cost for patients newly diagnosed with AD
Lubeck et al., 1994 (45)	United States	Tacrine	Cost-minimization analysis	Not clearly stated	Community and nursing home care, drug costs, treatment-related costs, informal care costs (?)	5%	tacrine 160 mg vs. tacrine (various doses)	Lifetime costs
Wimo et al., 1997 (46)	Sweden	Tacrine	Cost-saving analysis	Public payer	Residential costs, drug costs, laboratory and GP visits costs, costs of diagnostic procedures, cost of informal care	3%	tacrine 160 mg vs. no tacrine treatment (i.e., standard treatment)	Lifetime costs
Wimo et al., 1998 (47)	Sweden	Propentofylline	Cost-saving analysis	Public payer	Direct medical costs	5%	propentofylline vs. usual care without propentofylline	Lifetime costs
Hauber et al., 2000 (48)	United States	Rivastigmine	Cost-saving analysis	Not stated	Not stated	3%	Rivastigmine vs. no treatment	6 mo, 1 yr, and 2 y

AD, Alzheimer disease; CCS, community care services; CG, caregiver's time; GP, general practitioner; n.a., not applicable; NHC, nursing home care; NHS, national health service.

TABLE 89.5. FULL ECONOMIC EVALUATIONS OF DRUGS FOR ALZHEIMER DISEASE

Study	Outcome Measure	Year of Costing	Original Currency	Incremental Cost (Health PPP$, 1996)	Health Gain
Stewart et al., 1998 (37)	Expected life-years in condition less than severe (ELY<S)	1997	British pounds	1,333	0.120 ELY<S
O'Brien et al., 1999 (38)	Expected life-years in condition less than severe (ELY<S)	1997	Canadian dollars	–1,292	0.200 ELY<S
Jönsson et al., 1999 (40)	Expected life-years in condition less than severe (ELY<S)	1998	Swedish kronor	–1,962	0.522 ELY<S
Neumann et al., 1999 (39)	Quality-adjusted life-years (QALY)	1997	U.S. dollars	483	0.015 QALYs

PPP, purchasing power parity.

tral under several alternative scenarios. Three studies found that the distribution of severity states of patients is the most important variable affecting the cost-effectiveness of drugs. However, it is important to note that these results are preliminary and uncertain and that a number of issues must be considered when the results are interpreted.

Costs

First of all, no prospective measurement of resource use associated with the drug or usual care was made. Costs were estimated from retrospective analysis of available data sets (40) or analysis of published literature (37), sometimes integrated with expert opinion (38,39). The range of cost items and the costing methodologies employed in each study were heterogeneous. Some authors included both direct costs and informal carers' time (37–39), whereas others considered only direct medical costs (40).

Three analyses (37,38,49) directly or indirectly associated the dynamic of treatment costs with the progression of disease severity, measured with the MMSE. The MMSE score was shown to be strongly correlated with costs of dementia care, but it is unclear to what extent the use of this instrument is robust in modeling studies. It has been suggested (49) that other factors may be strongly correlated with costs, such as indices of activities of daily living and instruments that measure behavioral disturbances.

Outcome Measures

One study used QALYs to measure the benefits derived from introducing the drug (39). In the other studies, benefits were measured in terms of "time spent in condition less than severe." The QALYs were estimated with the Health Utility Index Mark II in a sample of patients and carers. However, this instrument has not been validated in patients with AD, and its ability to detect small improvements in potentially important clinical aspects is doubtful. The QALY data were collected alongside a cross-sectional study, which means that no information was obtained on how the effectiveness of the drugs and utilities varied over the course of the disease. In addition, the sample of patients used to elicit utility values may have been unrepresentative of the population of people with AD (39). There were also potential problems with the use of proxy respondents. However, given the cognitive and behavioral degenerative process associated with AD, the use of alternative respondents may be unavoidable. Additionally, measuring outcomes as "time spent in less than severe state" does not inform health and social care decision makers about the value of quality of life for people with AD and their family and carers.

Effectiveness

Effectiveness data about the new drugs were derived from a limited number of trials that were short in duration and explanatory rather than pragmatic in design. Some of these trials have been criticized elsewhere (50) for having enrolled a carefully selected subgroup of patients with mild-to-moderate AD and excluded those with coexisting illness or concurrent treatment. In real practice, the eligible population may be considerably different. Consequently, only a limited proportion of people may be adequately and safely treated.

Furthermore, the lack of data meant that the duration of the treatment effect of the drug was based on experts' opinions (38,39) or was disregarded by assuming that the treatment effect ceased after 6 months (37). The cost-effectiveness of cholinesterase inhibitors depends on the distribution of patients across different severity states (38). In this context, the correct assessment of the duration of the treatment effect of anticholinesterase drugs assumes a central role because it affects the number of people having mild-to-moderate AD at any one time.

Modeling

Some authors have recently challenged the use of Markov models in the evaluation of antidementia drugs (33,48).

The use of alternative modeling tools, such as statistical models, to extrapolate the results of a short trial to a longer time horizon needs to be explored. Given the considerable uncertainty surrounding the available data, deterministic models in which simplistic sensitivity analysis techniques are used may not be adequate to assess the robustness of the results. The application of stochastic models allows the uncertainty associated with relevant parameters of a model to be incorporated and quantified.

CONCLUSION

As a direct consequence of changes in the age structure of the population, elderly generations are expected to become the largest consumer group of health care resources. Because no cure for AD is yet available, the management of the disorder focuses on assisting patients in their daily activities and supporting carers. The progressive nature of AD and the aging of the population mean that many people with this condition will require intensive support and long-term residential or nursing home care. A number of factors may trigger the need for long-term institutional care, including the age of family carers, the behavioral problems of patients, and the loss of self-care ability for those who live alone in a private household. Institutionalization has been identified as one of the main cost drivers in the care of people affected by AD (2,51).

Some clinical evidence indicates that anticholinesterase drugs may slow the progression of AD or relieve some of the symptoms. If the drugs are effective in controlling symptoms or slowing progression of the illness, they may delay the need for intensive support or institutionalization of patients. The high acquisition cost of the drugs, however, has raised considerable concern about the potential value for money associated with their use, which has prompted a significant number of studies addressing the issue of costs and patient benefits.

To date, a conclusive analysis has not clarified the most appropriate management strategy for the disorder. In the near future, new drugs for the treatment of AD are expected to be licensed, and it would be extremely valuable to be able to compare them in a clear and well-defined framework. In addition, if economic evaluation is to inform health and social care providers and policy makers about the potential impact of new interventions in practice, an estimation of the value for money of these new interventions requires consideration of (a) the perceived and objective risks and benefits of care; (b) the attitudes of people with dementia, carers, and health and social care providers to risk; (c) the utility to these groups of health care interventions; and (d) quantification of the uncertainty surrounding estimates of risk, utility, and costs.

Although the first attempts to analyze currently available antidementia drugs provided limited conclusive results, the contribution of simulation models may help to shed light on several aspects that have not yet been explored. In a context largely characterized by uncertainty surrounding the value of the key variables, modeling techniques can be used to assess the value for money of new management strategies for the treatment of AD and compare them with the alternative policy options. Further primary and secondary research is required to provide robust estimates of the formal and informal care costs associated with the new drugs and the value of health improvements to patients and carers.

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