Economic considerations in the management of Alzheimer's disease

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Abstract: Alzheimer's disease is a devastating chronic disease that significantly increases healthcare costs and affects the quality of life (QoL) of the afflicted patients and their caregivers. Population aging and other demographic changes may further increase the already staggering costs of this devastating disease. While few pharmacoeconomic studies have used a prospective health economics design to assess resource utilization, most studies showed beneficial treatment effects and suggested potential savings in healthcare costs and reductions in caregiver burden. Various degrees of cost savings have been reported depending on the type of economic model, treatment evaluated, and region used in the studies. Direct comparisons of the results are difficult because different methods have been used in these evaluations. The preference of patients and families for home care for as long as possible suggests that promoting noninstitutional care for these patients should become a priority. Continued home care for patients under pharmacological treatment may reduce caregiver burden, healthcare costs, and ultimately improve patients' and caregivers' QoL.

Keywords: Alzheimer's disease, pharmacoeconomics, cost, economic management

Introduction

Alzheimer's disease (AD), the most common cause of dementia, is a progressive, neurodegenerative brain disease of unknown etiology that primarily affects the elderly. The onset of AD is usually insidious. The disease is characterized by loss of memory and other intellectual abilities with concomitant loss of functional abilities. As the disease progresses, its victims deteriorate until eventually they are no longer able to perform the most basic activities of daily living (ADL). Two-thirds to three-fourths of AD patients are cared for in the community by family members and friends, many of whom live with the caregiver (Dunkin and Anderson-Hanley 1998). Throughout the disease, patients often develop behavioral and psychiatric problems that are difficult to treat and create much stress for the caregivers (Teri et al 1997). The progressive decline in patients' cognition, function, behavioral and psychiatric symptoms, and the tremendous stress faced by the caregivers are often predictive of institutional placement. Alzheimer's disease progression from diagnosis to death is usually about seven to ten years, with pneumonia or sepsis as the usual cause of death (Brookmeyer et al 2002; Cummings and Cole 2002). Approximately 100 000 patients die with AD each year, making it the fourth leading cause of death in the US (Evans 1990). We review the impact of AD on the cost of care as well as the potential economic impact of current therapeutic options.

Incidence and prevalence

Alzheimer's disease constitutes approximately 70% of all dementia cases (Small et al 1997; Fratiglioni et al 1999). Incidence of AD increases with age, doubling every five to ten years. For persons between ages 65–69, 70–74, 75–79, 80–84, and 85 and

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older, the incidence of AD has been estimated at 0.6%, 1.0%, 2.0%, 3.3%, and 8.4% (Hebert et al 1995). Prevalence also increases exponentially with age, rising from 3% among those 65–74, to almost 50% among those 85 or older (Evans 1990; Small et al 1998). Alzheimer's disease affects 25 million people worldwide (Winblad 2002). In the US, prevalence was estimated at 4.5 million in 2000, and as many as 13.2 million (an increase of almost 3-fold) are projected to have AD in 2050 (Hebert et al 2003). Aside from age, other risk factors include family history of dementia, head trauma, genetic factors (eg, apolipoprotein E [APOE] ε4 allele), being female, low education level, vascular disease, and environmental factors (Carr et al 1997; Farrer et al 1997; Small et al 1997; Gao et al 1998).

Because the onset of AD is insidious, many patients with AD are not diagnosed when symptoms are mild. The Canadian Study of Health and Aging showed that among patients living in the community, 11% have mild AD, while 89% have moderate to severe AD (CSHAWG 1994). Evidence suggests that moderate and severe dementia are also under-recognized in clinical settings (Callahan et al 1995). Therefore, the already staggering figure of US$80–100 billion in the US in caring for patients with AD is likely an underestimate of the true disease cost (CDC and NCCDPHP 2000). Population aging and other demographic changes, including possible shortages of informal caregivers because of the higher labor force participation of women who traditionally take up the caregiving roles, may further increase the costs of this devastating disease.

Diagnosis and assessment of disease severity

In the clinical setting, assessment of dementia is most commonly initiated by an informant, such as a family member or friend. This referral is often based on observed loss of function. For example, memory loss is commonly reported as a loss of ability in a social or occupational area (eg, bill paying, shopping, and household tasks) in which there was competence, or in a behavioral change that disrupts a social interaction (eg, asking the same question repeatedly). Other common referrals for assessments come from medical professionals when a patient misses an appointment or has difficulty with adherence to a treatment regimen. The evaluation of dementia begins with a good clinical history and requires a knowledgeable informant to provide information about premorbid functioning and the breadth of deficits.

The diagnosis of AD by both Diagnostic and Statistical Manual of Mental Disorders (DSM) and the more formal research criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) require memory loss in addition to other cognitive deficits with evidence of disturbance of social and occupational impairment (McKhann et al 1984; APA 1994). The clinical history includes questions to assess the onset of these deficits and other social or psychological factors that might account for these changes. Cognitive status is often assessed with the Mini-Mental State Examination (MMSE), which briefly assesses delayed recall, orientation, language, and attention. In some cases, more extensive neuropsychological assessment may be useful such as in the presence of extremes of education (either very high or very low) or comorbidities that may cloud the cognitive profile.

Though not part of the diagnostic criteria, there is growing awareness of behavioral and psychiatric symptoms that are very common in AD and are of major importance in managing the disease. It is commonly recognized that early stages of the disease include apathy, withdrawal, and depressive symptoms with later stages associated with psychotic features (hallucinations and delusions), agitation, and wandering.

Mild cognitive impairment (MCI) has recently been acknowledged as a condition of cognitive impairment that appears to be a prodrome to dementia. The amnesic form of MCI is characterized by severe memory loss with minimal deficits in other cognitive areas and relatively intact social and occupational functioning. This stage may also have associated behavioral disturbances including irritability, apathy, and withdrawal.

Attempts have been made to stage the disease using several instruments including the MMSE, the Geriatric Dementia Scale (GDS), and the Clinical Dementia Rating (CDR). Each focuses on different dimensions of disease severity with little attention to behavioral disturbances. Table 1 offers a model of staging that includes cognition, function, and behavior. The value in staging the disease is 2-fold: it identifies likely present need and predicts future need. This is particularly important in projecting future healthcare costs associated with the disease.

Treatment

Currently there is no cure for AD. The only medications approved by the US Food and Drug Administration (FDA)

Table I Cognitive, functional and behavioral deficits by disease stage in Alzheimer's disease

Domain	MCI	Mild AD	Moderate AD	Severe AD
Duration	3–5 yrs	1–2 yrs	2–12 yrs	1 yr
Cognitive	Memory impairment (isolated deficit)	Recall/Learning Word finding difficulty Judgment and problem solving Calculation impairment	Moderate memory loss Anomia Visuospatial deficits Disorientation Confusion	Severe memory loss Agnosia Apraxia
Functional	Occasional loss of complex social or occupational skills	Difficulty in: Routine chores Complex meal preparation Financial matters Hobbies	Loss of IADL Getting lost Difficulty dressing Poor eating habits Poor hygiene habits	Loss of basic ADL: Dressing Grooming/bathing Eating Continence Mobility
Behavioral	Apathy, Irritability Withdrawal (mild)	Apathy Delusions Depression Withdrawal (moderate)	Agitation Delusions Depression Insomnia Wandering	Agitation: Verbal Physical Insomnia

Abbreviations: AD, Alzheimer's disease; IADL, instrumental activities of daily living; MCI, mild cognitive impairment.

for treating mild to moderate AD (as suggested by MMSE score between 10–26) are the cholinesterase inhibitors (ChEI): tacrine, donepezil, rivastigmine, and galantamine. Cholinesterase inhibitors are considered first line drugs for treatment of AD. They inhibit acetyl cholinesterase, an enzyme responsible for the destruction of acetylcholine, which is reduced in AD (Becker 1991). Tacrine was the first ChEI approved for the treatment of AD. However, because of the risk of hepatoxicity, it is overtaken by newer medications and is now rarely used. Donepezil, the first of the second generation ChEIs, was approved for treatment of AD in the US in November 1996 and became commercially available in February 1997. Since 2001, utilization of ChEIs increased sharply, especially for donepezil. In 2003, 77% of ChEIs prescribed were for donepezil. Donepezil, rivastigmine, and galantamine differ to some extent by their pharmacological properties. Side effects are typically related to the gastrointestinal tract, usually mild in nature, and subside with continued use. Patients not responding to one medication may respond to another.

Donepezil has been shown in several randomized controlled trials (RCT) to benefit patients' cognitive status (measured by the Alzheimer's Disease Assessment Scale – cognitive subscale, [ADAS–cog], and MMSE) compared with placebo (Bucks et al 1996; Small et al 1998; Winblad et al 2001; Gauthier et al 2002; Birks and Harvey 2003; Feldman et al 2003; Courtney et al 2004). The first long-term RCT of donepezil, the AD2000 study, found statistically insignificant benefits in the treatment group in patient function (measured by ADLs) (Courtney et al 2004). The only RCT of a ChEI in the treatment of community-residing patients with moderate to severe AD (MMSE scores between 5–17) reported significant though modest benefits of donepezil over placebo on global function, cognition, ADLs, and behavior (Feldman et al 2001).

Modest improvements of cognitive function, behavior, and delays in transition to more severe stages of the disease have been reported in patients treated with rivastigmine (Corey-Bloom et al 1998; Rosler et al 1999; Farlow et al 2000, 2001). Two large, multi-center, double blind placebo-control studies in Europe and the US of patients with mild to moderately severe AD (MMSE scores 10–26) reported improvement in ADAS-cog in the high dose group (6–12 mg/day) than the placebo and low-dose groups (1–4 mg/day) by 4.9 and 2.6 points after 26 weeks (Corey-Bloom et al 1998; Rosler et al 1999). Since on average ADAS-cog increases by 8 points per year, a 4.9-point improvement suggests that treatment of rivastigmine maintains the patient in less severe stages of AD by approximately 6 months longer. The US study also reported significantly better preservation in MMSE (0.85 points) and GDS (0.19 points)

in patients in the high-dose group (DeJong et al 1989). More recently, open label trials extending the earlier studies by an additional 26 weeks showed that benefits of rivastigmine continued for at least a year as measured by treatment–placebo differences in ADAS-cog scores (Farlow et al 2000, 2001).

Preservation of cognition and function among patients with mild to moderate AD have been reported in several RCTs of patients treated with galantamine (24 mg/day or higher) (Raskind et al 2000; Tariot et al 2000; Wilcock et al 2000). Galantamine treatment also was shown to benefit patients' psychiatric and behavior symptoms and reduce caregiver stress (Tariot et al 2000; Kaufer and Sadik 2002; Cummings et al 2004). In these clinical trials, cognitive function was consistently better for the treatment group compared with the placebo group, with between group differences ranging from 2.9–3.9 points in 6 months (Raskind et al 2000; Tariot et al 2000; Wilcock et al 2000). Patients' function (measured by Alzheimer's Disease Cooperative Study [ADCS]–ADLs) was 2.3 points better in the galantamine group at 5 months (Tariot et al 2000). Studies also reported no change in Neuropsychiatric Inventory (NPI) scores in the higher dose groups (16 mg or 24 mg per day) while NPI scores deteriorated among patients in the placebo group or low dose (8 mg per day) groups (Tariot et al 2000). Recent studies separately showed sustained benefits at 52 weeks (Raskind et al 2000; Wilcock et al 2003). Subgroup analysis also showed that beneficial effects of galantamine were maintained among patients 80 years or older (Tariot et al 2000; Marcusson et al 2003).

The only medication currently approved by the FDA for the treatment of moderate to severe AD is memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor inhibitor, which blocks excess release of glutamate thought to be associated with cholinergic damage. In clinical trials, memantine is well tolerated. Side effects include hallucination, dizziness, confusion, headache, and tiredness. Several RCTs in patients with moderate to severe AD showed global and functional improvement associated with memantine treatment (Winblad and Poritis 1999; Reisberg et al 2003; Tariot et al 2004). A separate analysis showed that controlling for baseline autonomy and disease severity, the memantine group was three times more likely than the placebo group to remain autonomous (versus dependent) at 28 weeks (Rive et al 2004).

Data on the relationship between antioxidant vitamin intake and risk of AD have been conflicting (Engelhart et al 2002; Luchsinger et al 2003). To date there has been only one large ADCS clinical trial of patients with moderate AD providing evidence of efficacy of vitamin E in slowing functional decline (Sano et al 1997). The study is a four-arm parallel group design in which patients were randomized into one of three active treatment groups or placebo for 2 years. The active treatment groups consisted of vitamin E (2000 IU/day), selegiline (10 mg/day), or combination therapy. Primary outcomes are progression from moderate to severe dementia, loss of two or three ADLs, nursing home placement, or death. Results showed that vitamin E and selegiline both delayed progression to study endpoints. The average delay was 230 days for vitamin E compared with placebo. There was no additional benefit of combination therapy. Because of its low cost and relative safety, vitamin E was recommended in addition to ChEIs to slow the progression of AD. A number of other treatments such as ginkgo biloba, antiinflammatory drugs, and hormone replacement therapy have been suggested as possible treatment (Parnetti et al 1997; Richards and Hendrie 1999; Doody et al 2001). There is currently insufficient evidence to recommend for or against their use.

Economic impact

The costs of caring for patients with AD have been extensively studied (Ernst and Hay 1994; Stommel et al 1994; Max et al 1995; Hux et al 1998; Leon and Neumann 1998; Gutterman et al 1999; Langa et al 2001; Moore et al 2001; Murman et al 2002, 2003; Small et al 2002; Andersen et al 2003). In terms of total costs to society, AD is the third most costly disease in the US after cancer and coronary heart disease (Meek et al 1998). Average annual costs of caring for patients with AD have been estimated at US$80–100 billion in the US (CDC and NCCDPHP 2000). Total costs include direct, indirect, and intangible costs. Direct costs include multiple dimensions of medical care costs (eg, nursing home care, medications, physician visits, hospitalizations) and nonmedical care costs (eg, home health aides, respite care, adult daycare). Indirect costs are imputed values of resources lost due to the illness, including premature deaths, patient and caregiver lost productivity, and unpaid caregiving time. Intangible costs are those related to pain and suffering endured by patients and families, and those related to deterioration of patient and caregiver quality of life (QoL). Because the inclusion of intangible costs in economic studies is highly controversial and their evaluation notoriously difficult, most studies have focused on estimating direct and indirect costs of AD.

Several important factors that influence the cost of AD have been identified in the literature, including dementia disease severity (Rice et al 1993; Max et al 1995; Ernst et al 1997; Hux et al 1998; Leon and Neumann 1998; Souetre et al 1999; Taylor and Sloan 2000; Moore et al 2001; Small et al 2002; Zhu et al 2003), comorbid medical conditions (Leon and Neumann 1998; Gutterman et al 1999; Fillit 2000), behavioral problems (Beeri et al 2002; Murman et al 2002; Zhu et al 2003), and extrapyramidal signs (Murman et al 2003). The presence of comorbid conditions significantly increases the cost of caring for patients with AD. The effects of comorbidities are particularly important in AD patients as the majority of them have at least one comorbid condition. One study reported that 93% of AD patients had at least one comorbid condition, and 61% had three or more (Fillit 1999). A study of Medicare enrollees reported that each comorbid condition in patients with AD was associated with disproportionately higher cost (US$10 435) than in patients without AD (US$526) (Fillit 2000). Other studies reported that the cost of managing comorbid conditions also was greater among AD patients (Gutterman et al 1999). It has been hypothesized that cognitive decline with AD may be associated with under-reporting of all symptoms and complicate the management of other chronic conditions (Rice et al 1993; Fillit 1999).

Alzheimer's disease costs depend strongly on caregiving settings. Early in the disease, indirect costs often exceed direct costs as the majority of AD patients are cared for by informal caregivers in the community. For patients living in the community, some 60%–70% of the total cost of caring for AD patients has been attributed to informal caregiving. When patients are institutionalized, costs shift from indirect to direct (Huang et al 1988; Ernst and Hay 1994; Wimo et al 1997; Leon and Neumann 1998). About three-fourths of the total costs of AD occur during severe stages of AD, mainly due to institutionalization (Wimo, Winblad, Stoffler, et al 2003). One study suggests that relatively small delays in the onset and progression of dementia could substantially reduce disease costs (Brookmeyer et al 1998). It has been estimated that a 1-month delay in institutionalization of a patient with moderate to severe AD would result in savings of US$1863 per month (Leon and Neumann 1998). The incidence and prevalence of AD is likely to rise as the population continues to age, and the already staggering costs of caring for patients with AD also will increase.

An important objective of economic analysis is to show the value of a medical treatment or intervention. This is a complex issue. For example, if a treatment delays institutionalization, but does not affect survival, the overall disease costs may be lowered if reductions in the cost of institutionalization outweigh the increases in treatment cost. Cost reductions, however, may be partially offset by potential increases in informal caregiving costs. If on the other hand, treatment prolongs survival, lifetime disease cost may in fact increase. Further complicating the issues are the possible impact on patient and family QoL. However, these important issues are often neglected.

Several different methods have been used in analyzing the effects of treatment on the costs of caring for patients with AD, including RCT, matched-control trials, pre-post designs, observational studies, and modeling analyses. Each of these methods is subject to a number of criticisms. Collecting resource utilization data prospectively in large, multicentered RCTs is a preferred method in economic analyses. However, while these analyses have superior internal validity, they are expensive to conduct and are often limited by their relatively short time horizon, and may not be applicable outside the trial settings. Because other studies are not of random design, possible selection effects cannot be ruled out. For example, in matched-control trials, caregivers of patients who tolerated the drugs better may have selectively delayed institutionalization and artificially lowered the costs of care. Because utilization and costs are expected to increase overtime as a result of disease progression, possible cost savings in studies with pre-post designs may be underestimated. In pre-post studies, it also is not meaningful to adjust for other covariates that influence disease cost (eg, comorbid conditions).

Dementia patients are expected to live approximately seven to ten years after diagnosis (Brookmeyer et al 2002; Cummings and Cole 2002). Pharmacological treatments may have substantial effects on long-term costs, which is particularly important because of the progressive nature of the disease. However, long-term effects of pharmacological treatments are not yet known. In the absence of long-term clinical data, modeling studies often use clinical data from short periods of time (eg, 6 months, 26 months) and project longer term costs (2, 5, or 10 years) relying on data from a variety of external sources. The underlying assumption is that clinical benefits observed in the short run will persist at the same rate at later time points. This assumption may not be valid. Making matters worse, clinical data often are derived from other countries. It is possible that there may be differences in drug efficacy between populations in different countries that are yet unknown. Therefore, even if studies are robust to plausible changes in key variables,

Table 2 Pharmacoeconomic studies with approved treatments for Alzheimer's disease

Study type	Author	Drug studied	Study length	Costs included	AD severity	Per patient cost savings	Country
RCT	Courtney et al 2004	Donepezil	5 yrs	Direct medical cost and cost of caregiver time	Mild to moderate	No cost difference	UK
RCT	Feldman et al 2004	Donepezil	24 wks	Patient and caregiver direct medical cost, and cost of caregiver time	Moderate to severe	Direct medical cost: US$21; informal care cost: US$265	Canada
RCT	Sano et al 2003	Galantamine	6 months	Cost of caregiver time	Mild to moderate	32 minutes per day	US
RCT	Wimo, Winblad, Stoffler, et al 2003	Memantine	28 wks	Direct medical cost and cost of caregiver time	Moderate to severe	Direct medical cost: US$1090 per month; caregiving time: 51.5 hrs per month	US
Matched-controlled	Small et al 1998	Donepezil	6 months	Direct medical costs	Not specified	No cost difference	US
Matched-controlled	Hill et al 2002	Donepezil	12 months	Direct medical costs	Not specified	US$3891	US
Pre-post design	Fillit et al 1999	Donepezil	Pre-treatment: 15 months Post-treatment: 7 months	Direct medical costs	Not specified	US$2.11 higher per day	US
Modeling study	Stewart et al 1998	Donepezil	Markov, 5 yrs	Direct medical costs	Mild to moderate	No cost difference	UK
Modeling study	Neumann et al 1999	Donepezil	Markov, 2 yrs	Direct medical cost and cost of caregiver time	Mild	US$73	US
Modeling study	O'Brien et al 1999	Donepezil	Markov, 5 yrs	Direct medical cost and cost of caregiver time	Mild to moderate	CA$882	Canada
Modeling study	Hauber, Gnanasakthy, Mauskopf, et al 2000	Rivastigmine	Hazard, 2 yrs	Direct medical cost and cost of caregiver time	Mild to moderate, moderate	US$2.51 per day at 1 yr; US$4.93 per day at 2 yr	Canada
Modeling study	Hauber, Gnanasakthy, Snyder, et al 2000	Rivastigmine	Cox proportional hazard model, 2 yrs	Direct medical cost of caregiver time	Mild to moderate	Mild AD: US$4289; moderate AD: US$2290	US
Modeling study	Getsios et al 2001	Galantamine	AHEAD, 10 yrs	Direct medical costs	Mild to moderate, moderate	Mild to moderate: CA$528; moderate disease: US$2533	Canada
Modeling study	Caro et al 2002	Galantamine	AHEAD, 10 yrs	Direct medical costs	Mild to moderate, moderate	US$1676	Netherlands
Modeling study	Garfield et al 2002	Galantamine	AHEAD, 10 yrs	Direct medical costs	Mild to moderate, moderate	Mild to moderate: €3131; moderate: €5594	Sweden
Modeling study	Ward et al 2003	Galantamine	AHEAD, 10 yrs	Direct medical costs	Mild to moderate	£1380	UK
Modeling study	Migliaccio-Walle et al 2003	Galantamine	AHEAD, 10 yrs	Direct medical costs	Mild to moderate	US$2408–US$3601	US
Modeling study	Jones et al 2004	Memantine	Markov, 2 yrs	Direct medical costs	Moderately severe to severe	£1,963	UK
Modeling study	Francois et al 2004	Memantine	Markov, 5 yrs	Direct medical costs	Moderately severe to severe	€1,687	Finland

Abbreviations: AD, Alzheimer's disease; RCT, randomized controlled trials.

results may not be applicable to other settings or regions. In the very long-term studies, proper discounting of costs has not been employed. Table 2 highlights the findings of pharmacoeconomic studies.

Randomized controlled trials

The first long-term RCT of donepezil, the AD2000 study, did not find any difference in disease costs and caregiving time between treatment and placebo groups (Courtney et al 2004). In the Moderate to Severe Alzheimer's Disease (MSAD) study of patients with moderate to severe AD, excluding the costs of prescription drugs, donepezil treatment was associated with a decrease of US$224 in total direct medical cost at 24 months (Gauthier et al 2002). Most of the cost reduction, however, was offset by the higher cost of prescription drugs: When prescription drug costs were included, total direct medical costs were only US$23 less for the donepezil group. Donepezil treatment also was associated with almost an hour per day less of caregiving time. Using the minimum hourly wage (US$4.63) as a conservative measure of caregiver's time, the authors found donepezil treatment reduced total informal costs by US$265 per patient per year (Feldman et al 2003, 2004).

Several studies have reported the effects of galantamine on informal caregiver time. Results from a 6-months RCT showed that while time spent supervising patients in the placebo group increased by 2 hours a day at 6 months, there was no change in the time spent in the galantamine group (Blesa 2000). In addition, there was a net gain of an hour a day in the time spent on helping with ADLs in the galantamine group (a 23 minute per day increase in the placebo group vs 38 minute decrease in the galantamine group). Combining data from two similarly designed clinical trials of patients with mild to moderate AD, Sano and colleagues (2003) examined the effects of galantamine on time spent helping with ADLs and time patients could be left unsupervised (measured by the Allocation of Caregiving Time Survey). Results showed that compared with caregivers of patients in the placebo group, caregivers in the galantamine group were more likely to report decreases (41% vs 37%), maintenance (19% vs 15%), or smaller increases (26% vs 35%) in time helping patients. On average, caregivers in the galantamine group provided 3.5 hours of less care per week (32 minutes per day) than the control group. Among patients with moderate AD, treatment effects were greater.

A recent RCT of the effects of 28 weeks of memantine treatment found that controlling for baseline characteristics (patient and caregiver sex, caregiving time, caregiver–patient relationship), patients receiving memantine were less likely to be institutionalized and needed an average of 51.5 hours per month less caregiving time than those receiving placebo (Wimo, Winblad, Stoffler, et al 2003). Mainly because of the cost of memantine, direct medical costs were US$160 per month higher in the memantine group. However, increases in direct medical costs were offset by savings in caregiving costs (US$824 per month) and direct nonmedical costs (US$431 per month). Total costs to society were US$1090 lower in the memantine group per month.

Matched-controlled trials

One of the first economic analyses of donepezil in the treatment of AD followed 108 community-living AD patients in the US taking donepezil for 6 months or longer and 268 patients matched on age, sex, and comorbidity and estimated total direct medical costs (doctor visits, emergency use, hospital stays, and prescription drugs) for the two groups (Small et al 1998). The study found rate of institutionalization was significantly lower for the donepezil group than the control group (5% vs 10%), and cost of institutional care was accordingly lower (US$710 vs $1487). The lower institutional cost largely offsets the higher cost of prescription drugs (US$1072 vs $392). As a result, there were no group differences in total direct medical costs (US$3443 for the donepezil group vs US$3476 for the placebo group).

A recent study using claims data in a large managed care organization (MCO) compared costs for 204 AD patients receiving donepezil with a control group of 204 AD patients who had matching characteristics, but who were not receiving donepezil. After controlling for age, gender, pharmacy benefits, comorbid conditions, and complications of dementia, the annual costs for medical services and prescription drugs were found to be US$3891 lower for the donepezil group (Hill et al 2002). Cost savings were mostly due to lower use of hospitalization and skilled nursing facilities.

Pre-post design

Fillit and colleagues examined cost of medical services and prescription drugs from claims data from a sample of AD patients (n=70) in an MCO before and after donepezil use (Fillit et al 1999). Average lengths of follow-up in the pre- and post- donepezil period were approximately 15 and 7 months. Results showed that while median per diem cost for medical services decreased by US$1.22 after donepezil

use, because of the increase in prescription drug cost by US$2.59 per day (US$946 per year), total per diem cost rose by US$2.11 per day (US$771 per year).

Modeling studies

A number of studies have modeled longer-term effects of donepezil on disease costs. Results depend on the assumptions made by the models, including the duration of the drug effect and whether treatment delayed institutionalization. Steward and colleagues (1998) modeled the costs of donepezil for 5 years and found the drug to be approximately cost neutral. Neumann and colleagues simulated the effects of donepezil using data from a 24 week RCT and a national longitudinal data of dementia patient (Morris et al 1989; Rogers et al 1990; Neumann et al 1999). They found that the costs of donepezil were offset by a delay to more severe disease stages if drug effects exceeded 2 years. O'Brien and colleagues, on the other hand, using data from the same clinical trial, estimated a cost savings of CA$882 associated with donepezil treatment (Rogers et al 1990; O'Brien et al 1999).

Several economic studies estimated potential cost savings attributable to the use of rivastigmine. Two similar studies in the US and Canada found that rivastigmine delayed the transition to more severe stages of AD and institutionalization and resulted in modest savings in direct costs of caring for patients with AD (Hauber, Ganasakthy, Mauskopf, et al 2000; Hauber, Gnanasakthy, Snyder, et al 2000). In the Canadian study, rivastigmine treatment was associated with an overall delay in transition to the next disease stage by 5 days in 6 months, 36 days in one year, and 137 days in two years, with cost savings of CA$0.71, CA$2.51, and CA$4.93 per day per patient (Hauber, Gnanasakthy, Snyder, et al 2000). Delays in disease progression and resulting cost savings are greater for patients who begin treatment while in the milder stages of the disease. Cost savings for patients who began treatment during mild stages of AD were mostly from delays in transitions to moderate AD. For those who began treatment during moderate stages of AD, cost savings were mostly attributable to delayed institutionalization during the first year of treatment. In the US study, rivastigmine treatment was associated with delayed disease progression for patients who started treatment in the mild stage by 56 days in 2 years, then delays from moderate to severe stage by 69 days (Hauber, Gnanasakthy, Snyder, et al 2000). For patients who began treatment at moderate stages of the disease, rivastigmine treatment was associated with delayed disease

progression to severe stage by 51 days in 2 years. Cost savings were estimated to be US$132 and US$137 for mild and moderate AD at 6 months, respectively. After two years of treatment, cost savings were estimated to be US$4389 and US$2290 for mild and moderate AD, respectively. As in the Canadian study, most cost savings were attributed to delays in institutionalization. Neither study included cost of treatment itself, which may reduce the potential cost saving. However, this problem may not be severe as the costs of the drug therapy per se are moderate.

To date, most pharmacoeconomic analyses of galantamine have been based on Assessment of Health Economics in Alzheimer's Disease (AHEAD), a model developed to estimate long-term health and economic effects of galantamine treatment for patients with mild to moderate AD from short-term clinical data (Caro et al 2001). The AHEAD model has two parts: the first part is a 6-month short-term model based directly on trial data; the second part is a long-term (10-year) model that predicts time to death or need for full time care (FTC), defined to be consistent requirement for care and supervision for the great part of the day, regardless of care setting. Patients who do not need FTC are assumed to live at home. The prediction equations used in AHEAD are derived from published equations of estimating the risk of needing FTC or death (Stern et al 1997).

Because the AHEAD model predicts equivalent FTC not specific to location of care, it can be adapted to diverse healthcare systems by customizing country specific costs and other inputs (eg, care types and resource use). Possibly because the same underlying model structure was used, similar results have been reported in studies from different countries (Getsios et al 2001; Caro et al 2002; Garfield et al 2002; Ward et al 2003). Most studies reported net savings with galantamine treatment over 10 years. Per patient net cost savings ranged from €313, CA$788, £3376, US$2408, and NLG3050 for patients with initially mild to moderate AD. Several studies that estimated potential savings among patients initially with moderate AD reported substantially higher cost saving over time, ranging from US$2533 to US$4995 (Getsios et al 2001; Garfield et al 2002). Not surprisingly, countries with lower institutional care costs were associated with the lower potential cost savings.

Two similar studies to date estimated potential economic gains of memantine treatment over longer treatment period (Francois et al 2004; Jones et al 2004). Both studies constructed a Markov model to simulate patient progression through a series of health states related to severity,

dependency, and residential status (community vs institutionalization). Patient dependency was measured by ADCS–ADL modified for severe dementia (Galasko et al 2000). For both studies, data on dependency, institutionalization, and transition probabilities from one health state to another were derived from earlier studies (Reisberg et al 2003). Epidemiological and resource utilization data were country specific. The UK study included only utilization of formal services over 2 years (Jones et al 2004). The Finnish study additionally included utilization of informal care over 5 years (Francois et al 2004). Both studies found a 40% increase in time in independence (1.3 and 4.1 additional months in the UK and Finnish study, respectively) and a 15% increase in time before institutionalization (0.8 and 1 additional month in the UK and Finnish study, respectively) in the memantine group compared with the placebo group. Cost savings were estimated to be £1963 over 2 years and €1687 over 5 years. These studies suggest that memantine provides cost savings compared with no pharmacological treatment. The studies also may have underestimated the overall benefit of memantine because the assumed duration of clinical efficacy was shorter than the duration of memantine therapy.

In summary, while few studies have used a prospective health economics design to assess of resource utilization, most studies suggest beneficial effects of treatment with potential cost savings. Various degrees of cost savings have been reported depending on the type of economic model, treatment evaluated, and region used in the studies. Because different methods have been used in these evaluations, direct comparisons of the results are difficult.

Unpaid home care

An integral part of the management of AD is the caregivers of the afflicted patients. Most AD patients live in the community, many with the caregiver, and the bulk of the costs of caring for these patients often are borne by these unpaid (informal) family caregivers. On average, informal caregivers provide 70 hours of care per week to AD patients (Rice et al 1993; Stommel et al 1994; Max et al 1995). Larger components of the total cost of caring for patients living in the community are unpaid caregiving time and caregivers' lost earnings (Moore et al 2001). In addition, more than 60% of formal services provided for AD patients are financed by the family, regardless of care setting (Rice et al 1993). Caregiving families' out of pocket expenditures for non-reimbursable medical equipment and services, prescription

drugs, paid care of non-family persons have been estimated at US$4564 annually (Stommel et al 1994).

Caregiver burden associated with AD is not only financial. Caregivers of AD patients are twice as likely to provide the most intense level of care than other caregivers (AA and NAC 1999). Numerous studies have shown higher rates of depression and greater physical and psychiatric problems among AD caregivers (Teri and Truax 1994; Dunkin and Anderson-Hanley 1998; Burns 2000). They also are more likely than non-caregivers to need physician visits and prescription medications (Baumgarten et al 1997; Dunkin and Anderson-Hanley 1998; Burns 2000). In many cases, the physical or psychological problems experienced by the caregivers are due to the stress of prolonged caregiving. Not surprisingly, caregiver burden rises with disease severity. As patients deteriorate, the emotional and physical toll of caregiving can increase health risks for the caregivers. Many caregivers become 'hidden patients' themselves.

Issues related to caregiver burden and caregiver time commitments often are further complicated as informal caregivers are most commonly spouses of the AD patients and their adult children. The spouses of AD patients often are themselves elderly and suffer from compromised health and functioning (Stone et al 1987). Second to spouses, adult children often provide care to elderly parents who are afflicted with AD. Many of these adult children are employed and have children of their own (Beach 1997). Since women have traditionally been taken up the majority of caregiving roles, the steady increase in women's labor force participation in recent decades have raised questions on the future availability of informal caregivers. Currently, 61.9% of women age 16 and older in the US are in the labor force (Szafran 2002). Among middle-aged women, who are more likely than younger women to become caregivers, labor force participation rates are even higher. Many studies documented the conflicts between women's labor force participation and informal caregiving, and showed that caregivers who were employed were more likely to withdraw from the labor market, be late or absent more often, take unpaid leave, or reduce their hours of work because of their caregiving responsibilities (Ettner 1995). Owing to absenteeism and lost productivity because of caregiving responsibilities, caregivers in the workforce cost US businesses US$36 billion annually in indirect costs (Koppel 2002).

The preference of patients and families for home care for as long as possible suggests that promoting non-institutional care for these patients should become a priority.

Psychosocial interventions, such as caregiver training, counseling, and support groups, may help reduce caregiver burden and help maintain patients in the community (Mittelman et al 1996; Hepburn et al 2003). Paid home care, including social services, home health aides, respite and adult day care also may provide relief for the caregivers, although their effects on reducing caregiver burden have not been established. Several studies have raised concerns of the possible paradoxical effects on caregivers of antidementia drugs: Delayed institutionalization may prolong informal caregiving and increase the burden of family members and caregivers (Max 1996; Wimo et al 1999). However, studies have consistently reported beneficial effects of pharmacological treatment including fewer caregiving hours (Feldman et al 2003; Wimo, Winblad, Engedal, et al 2003), and lower levels of stress and difficulty of caregiving (Fillit et al 2000; Kaufer and Sadik 2002). These studies suggest that previous reports of modest cost savings of pharmacological treatment may be underestimated. Continued home care for patients under pharmacological treatment may reduce caregiver burden and healthcare costs, and ultimately improve patient and caregiver QoL.

Discussion

Alzheimer's disease is a devastating chronic disease that significantly increases health care costs and affects the lives of the afflicted patients and their caregivers. The growing elderly population and the possible shortage of informal caregivers raise patients' healthcare needs and costs even higher. The physical and psychological toll of caregiving can increase health risks for the caregivers and increase their own medical care costs. Because caregivers are an integral part of the caring for patients with AD, management of AD needs to treat patients and caregivers as a whole. Recent developments in pharmacological therapies such as ChEIs have been shown to improve patients' cognition and function and reduce symptoms in addition to reducing informal caregiving time and caregiver burden. To better understand the cost implications of long-term treatment effects, economic analyses that use prospective, long-term data collected along with clinical data are needed. Improved pharmacological treatment and management of AD may help control healthcare costs and improve the QoL of patients and families.

Disclosure

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