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An Economic Evaluation of Donepezil in Mild to Moderate Alzheimer's Disease: Results of a 1-Year, Double-Blind, Randomized Trial

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Key Words
Alzheimer's disease · Donepezil · Economic evaluation · Caregiver time · Societal costs

Abstract
The costs and consequences of donepezil versus placebo treatment in patients with mild to moderate Alzheimer's disease (AD) were evaluated as part of a 1-year prospective, double-blind, randomized, multinational clinical trial. Patients received either donepezil (n = 142; 5 mg/day for 28 days followed by 10 mg/day according to the clinician's judgement) or placebo (n = 144). Unit costs were assessed in 1999 Swedish kronas (SEK) and converted to US dollars (USD). Donepezil-treated patients gained functional benefits relative to placebo on the Progressive Deterioration Scale (p = 0.042) and Instrumental Activities of Daily Living scale (p = 0.025) at week 52. Caregivers of donepezil-treated patients spent an average of 400 h less annually providing care than caregivers of placebo-treated patients. Mean annual healthcare costs were SEK 137,752 (USD 16,438) per patient for the donepezil group and SEK 135,314 (USD 16,147) in the placebo group. With the average annual cost of donepezil at SEK 10,723 (USD 1,280) per patient, the SEK 2,438 (USD 291) cost difference represented a 77% cost offset. When caregiver time and healthcare costs were included, mean annual costs were SEK 209,244 (USD 24,969) per patient in the donepezil group and SEK 218,434 (USD 26,066) in the placebo group, a total saving associated with donepezil treatment of SEK 9,190 (USD 1,097) per patient [95% CI of SEK –43,959 (USD –5,246), SEK 25,581 (USD 3,053); p = 0.6]. The positive effects on the efficacy outcome measures combined with no additional costs from a societal perspective indicate that donepezil is a cost-effective treatment, representing an improved strategy for the management of patients with AD.

[1] See Appendix.

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Introduction

The management of Alzheimer's disease (AD) is increasingly being recognized as a major healthcare challenge. From a financial viewpoint, the costs of AD to society are enormous [1]. In the USA, for example, AD is the third most expensive disease, associated with annual direct and indirect costs of US dollars (USD) 80–100 billion [2]. The per-patient cost of care, including indirect costs, in the USA in 1996 was estimated as USD 18,408 for patients with mild AD [3]. Similarly, the total costs of caring for patients with dementia in Sweden, including both direct and indirect costs, have been estimated to be between Swedish kronas (SEK) 16 and 40 billion (USD 2–5 billion) annually [4].

The total cost of AD to society is made up from direct patient and caregiver healthcare costs (e.g., nursing home care, costs of physician services, hospital care, nursing care and medications), informal caregiver time costs (e.g., costs related to time spent caring for the patient by family member or volunteer) and patient and caregiver productivity costs (e.g., costs associated with lost or impaired ability to work) [5]. Economic evaluations have demonstrated that nursing home costs are the main determinant of the societal costs of AD [3]. In addition, the costs of unpaid caregiver support to the patient (informal care) also constitute a large proportion of the total costs [6].

Patient healthcare costs are also an important determinant of the overall societal costs of AD. Indeed, a recent study demonstrated that the symptoms of AD and related dementias increase the difficulty and costs of caring for other serious comorbid medical conditions [7]. This can lead to a disparity in costs between treating patients with and without AD. For example, the cost of caring for patients with AD and related dementias has been reported to be as much as 1.5 times greater than the cost of caring for nondemented elderly patients in the care of US-managed care organizations [7]. Furthermore, in a study conducted in the UK the societal costs of AD patients have been calculated as British pounds (GBP) 6,616–13,593 (USD 10,000–20,400) compared with GBP 387 (USD 580) for matched control subjects over a 3-month period [8]. This large cost disparity in caring for patients with AD compared with patients without AD is, in a large part, attributable to higher hospitalization costs [7]. These observations provide a significant clinical and financial incentive to improve the management of patients with AD [7].

Cholinesterase (ChE) inhibitors, such as donepezil, rivastigmine and galantamine, are the most widely used treatments for AD at present. The use of donepezil, for example, can improve the management of the symptoms of AD by slowing cognitive and functional decline [9–15]. Furthermore, ChE inhibitors may also reduce the incidence of the behavioral symptoms of AD [14, 16–18] with significant benefits versus placebo [14]. This is an important benefit since behavioral symptoms are particularly distressing to the patient and caregiver. Indeed, behavioral symptoms are correlated positively with caregiver distress [17] and are a common cause of nursing home placement [19]. Furthermore, it has also been demonstrated that treatment with donepezil can reduce caregiver burden [20] and delay nursing home placement [21]. These clinical benefits may have implications for the costs of treating AD.

Various studies have attempted to measure the financial impact of treatment with ChE inhibitors of AD [22–28]. Modeling studies with donepezil have indicated that the drug costs for donepezil are a small constituent of total costs (3–8%) of the management of patients with AD and are offset 1–2 years after beginning treatment with donepezil, with potential cost savings beginning at 2–5 years [26–28]. Furthermore, observational studies have suggested that the costs of treatment with donepezil are offset by a reduction in the direct healthcare costs in donepezil-treated patients [29] and suggest that treatment with donepezil is cost neutral or results in cost savings [30]. While these studies are useful in the absence of large and costly prospective economic evaluations that are logistically and ethically difficult to perform, the most accurate way to assess healthcare costs is using actual health resource utilization data [1]. This task is complicated by the slow progression of AD, which means that studies must be of sufficient duration to enable the cost consequences of treatment success to be realized.

A double-blind, multinational, 1-year clinical study evaluating donepezil versus placebo in patients with mild to moderate AD (described elsewhere) [12] was therefore designed to include pharmacoeconomic outcomes. This analysis evaluated the impact of treatment on the direct and indirect costs of caring for an AD patient, including the informal costs for care time provided by the caregiver. This is the first study to evaluate prospectively the impact of treatment with a ChE inhibitor on the societal costs of AD over a 1-year period.

Materials and Methods

Patients

Eligible patients were required to have a diagnosis of AD consistent with the *Diagnostic and Statistical Manual of Mental Health Disorders*, 4th edition (DSM-IV) criteria [31] and National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for possible or probable AD [32]. Patients also had to have mild to moderate AD confirmed by a Mini-Mental Status Examination (MMSE) [33] score of ≥ 10 and ≤ 26. Patients were required to meet a number of other inclusion criteria and none of the exclusion criteria [12]. In particular, all patients were required to have a reliable caregiver, defined as one who would report to the clinic, contribute to patient assessments, ensure treatment compliance and clinic visits, and who would contact the patient at least twice weekly, one of which would be a personal visit. Patients living in nursing homes at screening were excluded from the study.

The study was carried out in accordance with the Declaration of Helsinki and its amendments. Written informed consent was obtained from the patient (if possible), the caregiver and the patient's representative (if applicable) prior to beginning detailed screening activities. The patient's assent to participate was required in all cases.

Study Design

This was a 52-week, randomized, multicentre, double-blind, placebo-controlled, parallel-group study involving 28 study centers in five Northern European countries: Denmark, Finland, The Netherlands, Norway and Sweden.

Eligible patients were randomized to treatment with either donepezil or placebo. Donepezil was administered orally at a dose of 5 mg once daily for the first 28 days. At week 4, the clinician could adjust the patient's dose of donepezil to 10 mg once daily to complete 52 weeks of treatment. At any subsequent visit, the clinician had the option to reduce a patient's daily dose of donepezil to 5 mg once daily, as necessary. The dose could also be increased again to 10 mg once daily following a dose reduction.

Efficacy Measures

The results obtained using the Gottfries-Bråne-Steen (GBS) scale [34, 35], the MMSE, the Global Deterioration Scale (GDS) [36] and the Progressive Deterioration Scale (PDS) [37] are described in detail elsewhere [12]. The results obtained using the Instrumental Activities of Daily Living (IADL) scale [38] and the Physical Self-Maintenance Scale (PSMS) [39] are described here using the intent-to-treat population.

Economic Measures

The impact of treatment on the caregiver and on the direct and indirect costs of care was determined using the Resource Utilization in Dementia (RUD) questionnaire [40].

The RUD questionnaire contains questions concerning the utilization of the following resources: study medication (patients only), frequency and duration of hospitalization (patients and caregivers), visits to healthcare professionals (patients and caregivers), use of concomitant medications (patients and caregivers), living accommodation (patients only), use of social services (patients only) and time caring for patients or missed work (caregivers only).

The RUD questionnaire was completed by caregivers at baseline and at Weeks 12, 24, 36 and 52. Caregivers were asked to provide data for 1 month prior to the start of medication (baseline visit) and the period since their last economic assessment (all other visits).

Economic Evaluation

The methods employed in the economic evaluation were consistent with the principles contained in guidelines for the economic evaluation of pharmaceutical products [41]. The analysis was performed from a societal perspective.

The intent-to-treat population, equivalent to the observed case cohort for cognitive and functional outcomes, was used in the analyses of the economic data. The total cost in each treatment group was calculated by adding the costs for each resource. The average cost per patient in each treatment group was then calculated by dividing the total cost by the number of randomized patients. Sensitivity analyses, in which costs were imputed for patients after they withdrew from the study, were also undertaken (see below).

The primary economic analytical technique used was a cost-consequence analysis with a list of multiple, clinically important patient outcomes and the cost differences between the two treatments. No discounting was necessary since the economic evaluation had a time horizon of 1 year. Living accommodation was classified into five categories based upon the level of professional and medical care available in each setting. These categories were: living at home, service house, home for the aged, group living and nursing home.

Costs are given in SEK and USD using a conversion rate of 8.38, the mean value for 1999. Unit prices were obtained from Swedish national statistics and scientific publications. All costs are reported in 1999 values, using wage and price indices from county councils or the consumer price index to adjust data to 1999 values.

Sensitivity Analyses

The following sensitivity analyses were conducted:

To account for patients withdrawing from the study prematurely, annualized costs were calculated by adding the sum of the observed costs (before withdrawal), the costs for donepezil taken after withdrawal, and the inputted costs for the time after discontinuation (using least-squares mean daily costs matched for treatment, baseline MMSE, patient age, caregiver gender and country).

The potential effects of accommodation cost imbalances at baseline were investigated by adjusting costs by baseline accommodation costs and number of study days.

Patient hospitalization data were subjected to a sensitivity analysis in which hospitalizations categorized as unrelated to AD (e.g., those associated with angina, cancer and kidney disease) were excluded.

The effects on caregiver time costs were tested by the use of an alternative cost per hour [SEK 51 (USD 6) per hour instead of SEK 102 (USD 12) per hour].

The effects of caregiver gender on caregiver time costs were evaluated using an analysis of variance (ANOVA), including factors for treatment and caregiver gender.

Statistical Analysis

All statistical tests were two-sided and performed at the 0.05 significance level.

Sample Size

The study was powered according to the primary clinical efficacy variable (the GBS scale). A target sample size of approximately 150

Table 1. Summary of patient and caregiver characteristics at baseline

	Placebo (n = 144)	Donepezil (n = 142)	p value
Patients			
Age (mean ± SD), years	72.9 ± 8.0	72.1 ± 8.6	
Female patients	85 (59.0)	99 (69.7)	0.065
Country of residence			
Sweden	39 (27.1)	40 (28.2)	
Norway	28 (19.4)	27 (19.0)	
Finland	45 (31.3)	44 (31.0)	
Denmark	24 (16.7)	23 (16.2)	
The Netherlands	8 (5.5)	8 (5.6)	
MMSE score (mean ± SD)	19.26 ± 4.54	19.37 ± 4.37	
PDS score (mean ± SD)	52.93 ± 20.45	52.77 ± 20.58	
IADL score (mean ± SD)	18.90 ± 6.26	18.69 ± 6.09	
PSMS score (mean ± SD)	8.56 ± 3.08	8.41 ± 2.92	
Caregivers			
Age (mean ± SD), years	63.0 ± 13.3	61.0 ± 14.7	0.26
Male caregivers	52 (36.1)	71 (50.0)	0.02
Relationship to patient			
Husband	40 (27.8)	55 (38.7)	0.04
Wife	54 (37.5)	34 (23.9)	
Child	30 (20.8)	40 (28.2)	
Friend	6 (4.2)	4 (2.8)	
Other	14 (9.7)	9 (6.3)	
Marital status			
Married/cohabiting	125 (86.8)	125 (88.0)	0.81
Never married	8 (5.6)	6 (4.2)	
Divorced/separated	6 (4.2)	8 (5.6)	
Widowed	5 (3.5)	3 (2.1)	
Cohabiting children (mean ± SD)	0.31 ± 0.71	0.42 ± 0.78	0.19
Caregiver lives with patient	101 (70.1)	94 (66.2)	0.53

Figures in parentheses represent percentage.

patients per treatment group was determined using the primary efficacy variable to achieve a power of 0.8 ($\alpha = 0.05$) [12].

Baseline Characteristics

The similarity of treatment groups with regard to patient and caregiver characteristics at baseline was evaluated using ANOVA models containing treatment and country effects for continuous variables and Cochran-Mantel-Haenszel statistics for categorical variables using countries as strata. Baseline data are presented as mean ± standard deviation (SD).

Clinical Efficacy

Secondary analyses of the PDS, IADL and PSMS were performed using linear categorical models to ascertain the percentage of patients in each treatment group showing a decline for individual items of these scales.

Economics

The mean cost and standard error of each variable were reported by the treatment group. The cost difference between treatment groups and the 95% confidence interval (CI) were calculated. The difference between the cost difference and zero was tested using the Wilcoxon rank sum test to minimize the influence of extreme observed costs.

Results

A total of 286 patients enrolled in the trial, and 142 were randomized to treatment with donepezil and 144 to treatment with placebo. Ninety-five (66.9%) of donepezil patients and 97 (67.4%) of placebo patients completed the study. The dose of medication was increased from 5 to 10 mg/day in 91.5% of donepezil-treated patients compared with 97.2% of placebo-treated patients over the course of the trial. Mean overall compliance was 94.6% in the donepezil group and 94.9% in the placebo group.

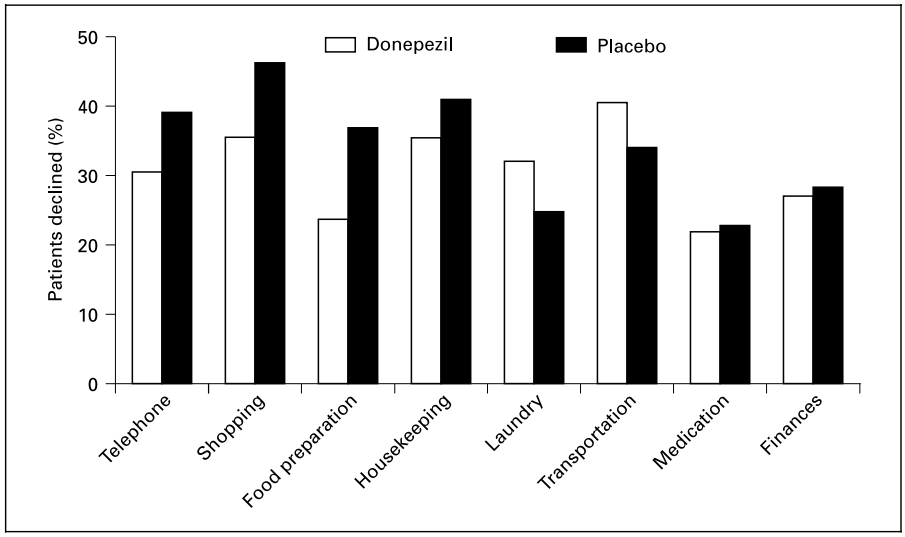

Fig. 1. Percentage of donepezil- and placebo-treated patients deteriorating on individual items of the IADL scale at week 52. Donepezil vs. placebo: overall p = 0.025. Data were available for 135–136 donepezil-treated and 138–140 placebo-treated patients. The exact number of patients depended on the specific item of the IADL.

Patient and Caregiver Characteristics at Baseline

Patients in the two treatment groups were comparable with respect to age and baseline MMSE score (table 1). There was a slight imbalance in gender distribution between the two groups, although this did not reach statistical significance. The majority of the patients enrolled in this study were residents of Finland and Sweden, with smaller proportions residing in Norway, Denmark and the Netherlands (table 1). Abnormal medical history findings prior to, or at screening (defined as clinically significant diseases or conditions other than AD), were reported by 82.4% of donepezil- and 88.2% of placebo-treated patients. Psychiatric disorders, such as phobic disorders, anxiety states and neurotic depression, were the most commonly reported comorbid illnesses in both the donepezil (30.3%) and placebo (27.8%) groups [12].

Caregivers in the two treatment groups were similar with respect to age, marital status, number of cohabiting children and the proportion living with the patient (table 1). Caregivers of patients in the donepezil group were significantly more likely to be male and the husband of the patient than the caregivers in the placebo group. Therefore, caregiver gender was included in the statistical models to assess any effect on the dependent variable. Since in no case was the caregiver gender term significant, the term was removed from the final models.

Clinical Efficacy

Significant differences in favor of donepezil over placebo were demonstrated on the GBS and MMSE at weeks 24, 36 and 52 [12]. Furthermore, subdomain analyses of the PDS at week 52 demonstrated that donepezil-treated patients showed benefits in 9 of the 10 domains on the PDS relative to placebo-treated patients and the treatment difference reached statistical significance for the telephone (p = 0.009), memory (p = 0.003), and self-care (p = 0.042) items [12]. Treatment response to donepezil was not predicted by the *APOE* genotype or gender in this population [12].

Analyses of the percentage of patients in decline for individual items of the IADL scale demonstrated that treatment with donepezil significantly reduced the deterioration of IADL in individual patients compared with placebo. Overall, significantly fewer patients in the donepezil group deteriorated in individual IADL items at week 52 compared with placebo-treated patients (fig. 1). Similarly, donepezil-treated patients experienced less deterioration in their ability to perform basic activities of daily living (ADL) compared with placebo-treated patients as assessed by the PSMS. Analyses of the percentage of patients in decline for individual items of the PSMS demonstrated that fewer donepezil patients experienced an overall decline in ADL than placebo-treated patients at weeks 24 (p = 0.011) and 36 (p = 0.032).

Total Costs

The economic evaluation investigated three main cost areas: patient healthcare costs, caregiver healthcare costs and caregiver time costs. These three areas were added together to give a total cost.

The total cost (all patient and caregiver costs) per patient over 1 year was SEK 209,244 (USD 24,969) for

Table 2. Total costs per patient in the month before and after 1 year of treatment with donepezil or placebo

	Prestudy (1 month)		In-study (12 months)		
	donepezil	placebo	donepezil	placebo	cost saving[1]
Study medication			10,723 (1,280)		
Patient hospitalization	2,049 (245)	1,186 (142)	6,476 (773)	4,662 (556)	–1,814 (–216)
Patient emergency room	137 (16)	49 (6)	398 (47)	208 (25)	–190 (–23)
Patient healthcare professionals	684 (82)	611 (73)	2,286 (273)	2,332 (278)	46 (5)
Patient concomitant medications			352 (42)	352 (42)	0
Patient social services	2,704 (323)	3,050 (364)	21,528 (2,569)	31,230 (3,727)	9,702 (1,158)
Patient accommodation[2]	8,831 (1,054)	8,738 (1,043)	95,989 (11,454)	96,530 (11,519)	541 (65)
Total patient direct costs	14,405 (1,719)	13,634 (1,627)	137,752 (16,438)	135,314 (16,147)	–2,438 (–291)
Caregiver hospitalization	369 (44)	153 (18)	1,793 (214)	3,006 (359)	1,213 (145)
Caregiver emergency room	99 (12)	86 (10)	484 (58)	392 (47)	–92 (–11)
Caregiver healthcare professionals	758 (90)	827 (99)	2,826 (337)	4,636 (553)	1,810 (216)
Caregiver medications			582 (69)	624 (74)	42 (5)
Total caregiver direct costs	1,226 (146)	1,066 (127)	5,685 (678)	8,658 (1,033)	2,973 (355)
Caregiver patient care	6,610 (789)	5,821 (695)	64,736 (7,725)	73,265 (8,743)	8,529 (1,018)
Caregiver missed work	461 (55)	287 (34)	1,071 (128)	1,197 (143)	126 (15)
Total caregiver time costs	7,071 (844)	6,108 (729)	65,807 (7,853)	74,462 (8,886)	8,655 (1,033)
Overall total patient and caregiver costs	22,702 (2,709)	20,808 (2,483)	209,244 (24,969)	218,434 (26,066)	9,190 (1,097)

Values represent SEK with the USD given in parentheses.

[1] Cost saving per patient = placebo – donepezil.

[2] Patients were housed in the following classes of living accommodation: living at home, service house, home for the aged, group living and nursing home. Costs included the cost of living and care in each of these settings.

the donepezil group and SEK 218,434 (USD 26,066) for the placebo group (table 2), resulting in a cost saving for donepezil treatment compared with placebo treatment of SEK 9,190 (USD 1,097) with 95% CI of SEK –43,959 (USD –5,246), SEK 25,581 (USD 3,053). This saving was not significantly different from zero (p = 0.60).

Patient healthcare accounted for over 60% of total costs for each treatment group, with caregiver time representing over 30% of the total costs (table 2). The differences in the total per-patient costs between patients residing in different countries were minimal and an ANOVA model including a factor to take account of the country demonstrated that there was no relationship between the patients' countries and total costs.

Patient Costs

Patient costs were provided for all patients. Patient-related costs for the donepezil group were SEK 137,752 (USD 16,438) per patient compared with SEK 135,314 (USD 16,147) per patient for the placebo group (table 2), resulting in an additional, but nonsignificant, cost per patient of SEK 2,438 (USD 291) with 95% CI of SEK –22,166 (USD –2,645), SEK 27,042 (USD 3,227), which was not significant (p = 0.85) in the donepezil group. This additional cost (SEK 2,438; USD 291) was 77% lower than the additional per-patient annual cost of donepezil (SEK 10,723; USD 1,280), indicating that the cost of donepezil treatment was offset by savings in other patient-related costs. The annual cost of study medication (donepezil) represented 7.8% of the patient costs in the donepezil group.

The main elements driving the costs of patient care in this study were accommodation and social service costs, representing approximately 70 and 20% of the patient costs, respectively.

At study entry, 132 (93.0%) donepezil-treated patients and 133 (92.4%) placebo-treated patients lived at home (either alone or with a companion). Of these patients, 9 and 10 patients, respectively, moved into alternative, more expensive accommodation (service house, home for the aged, group living, nursing home or other accommodation). Fewer patients in the donepezil group than in the

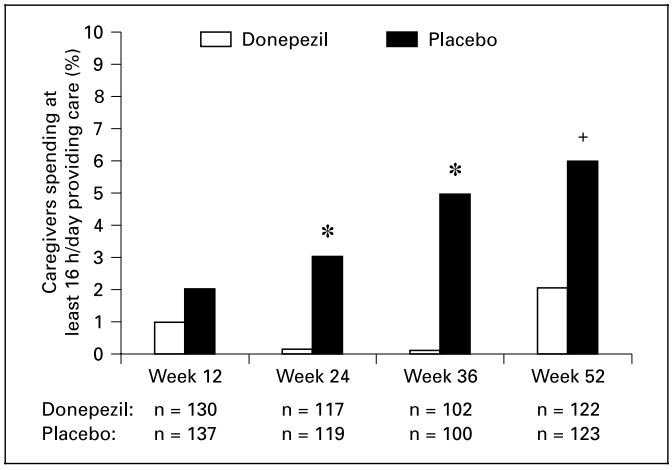

Fig. 2. Percentage of caregivers of donepezil- and placebo-treated patients spending at least 16 h each day providing care. * $p < 0.05$; + $p = 0.1$ vs. placebo.

placebo group moved into a nursing home (3 patients vs. 8 patients, $p = 0.13$).

Spending on social services represented a cost saving for the donepezil treatment group compared with the placebo cohort. The per-patient cost of social services (e.g., visiting nurse, home health aid, meals-on-wheels, day care and transportation) among donepezil-treated patients was 68.9% of that among patients receiving placebo (table 2). However, this difference between the treatment groups was not significant ($p = 0.19$).

The ratio of per-patient costs for patient hospitalization in the donepezil versus the placebo group during the month before the start of the study was 1.73. The corresponding ratio during the study was 1.39, indicating that donepezil treatment yielded a reduction in the cost of patient hospitalization compared with placebo treatment. Patient hospitalization still represented an area of additional expense among donepezil-treated patients compared with placebo-treated patients (table 2). Donepezil-treated patients were hospitalized 35 times during the study and spent a total of 276 days in hospital compared with 16 hospitalizations and 254 days hospitalized in the placebo group. However, the average length of hospital stay per visit was lower in the donepezil group than in the placebo group at 7.9 versus 15.9 nights per hospital stay for donepezil- and placebo-treated patients, respectively. Geriatric and surgical wards accounted for 43.1 and 30.0% of hospitalization time for the donepezil group and 66.9 and 9.4% of hospitalization time for the placebo group, respectively.

There was little difference between treatment groups in the patient costs of visits to healthcare professionals. Donepezil-treated patients made 374 visits (2.6 per patient) compared with 481 by placebo-treated patients (3.3 per patient). Patients most frequently visited general practitioners (donepezil: 149 visits, placebo: 168 visits) or physiotherapists (117 and 105 visits, respectively).

The per-patient cost of concomitant medications were identical for patients in the two treatment groups (table 2). The most costly agents in the donepezil group were antidepressants (34.5% of total), antibacterials (14.2%) and hypnotics/sedatives and anxiolytics (11.2%). The most costly agents in the placebo group were drugs used in psychoses and related disorders (23.8%), antibacterials (17.7%) and antidepressants (15.5%).

Caregiver Costs

Caregiver costs were categorized as either time- or health-related costs. The total caregiver costs were SEK 71,492 (USD 8,531) per patient in the donepezil group and SEK 83,120 (USD 9,919) per patient in the placebo group. This represents a saving of SEK 11,628 (USD 1,388) per patient for the donepezil versus the placebo group for caregiver costs. The main element driving the caregiver costs in this study was the amount of time spent caring for the patient and, in particular, assisting the patients with ADL.

Patient care accounted for nearly all of the caregiver costs (table 2). Indeed, 92 and 89.6% of overall caregiver costs (time- and health-related costs combined) were made up of time-related costs in the donepezil and placebo groups, respectively. Donepezil treatment yielded a per-patient cost saving of SEK 8,655 (USD 1,033) with 95% CI of SEK −32,111 (USD −3,832), SEK 14,802 (USD 1,766) with respect to caregiver time ($p = 0.47$).

More caregivers of placebo-treated patients compared with those of donepezil-treated patients reported spending most of each day (at least 16 h a day) caring for patients at weeks 12, 24 ($p < 0.05$), 36 ($p < 0.05$) and 52 (fig. 2). When the amount of time spent assisting patients with basic and instrumental ADL was added and truncated at 16 h/day, it was calculated that caregivers in the donepezil group spent an average of 9.9 h/day assisting the patient compared with 11.0 h/day in the placebo group. Thus, caregivers in the donepezil group spent an average of 400 h less (11.0–9.9 = 1.1 × 365 days) providing care compared with caregivers in the placebo group over the 52 weeks of the study, which is equivalent to 10 weeks of work. In addition, caregivers of patients receiving donepezil, compared with those receiving placebo,

spent less time assisting patients with both basic [2.4 vs. 3.7 h/day (p = nonsignificant)] and instrumental [7.7 vs. 8.3 h/day (p = nonsignificant)] ADLs.

Donepezil treatment yielded a per-patient cost saving of SEK 2,973 (USD 355) with 95% CI of SEK –6,651 (USD –794), SEK 706 (USD 84) for caregiver health-related costs (p = 0.11; table 2). In the month before the start of the study, the ratio of per-patient costs of caregiver hospitalization for the donepezil and placebo groups was 2.41 (table 2). However, the corresponding ratio during the study was 0.60, demonstrating that donepezil treatment produced cost savings for caregiver hospitalizations over the study period.

The cost of medications was similar for caregivers in the two treatment groups (table 2). In the donepezil group, antihypertensive, antihyperlipidemic and antidepressant drugs were responsible for most of the expenditure on drug treatments for caregivers, with these classes accounting for 27.0, 22.3 and 12.1% of concomitant medication costs, respectively. In the placebo group, the main contributors to caregiver medication costs were antihypertensive (37.4%), antihyperlipidemic (10.3%) and diuretic (8.4%) agents.

Sensitivity Analyses

When costs were imputed for patients withdrawing from the study, the total per-patient costs were SEK 272,808 (USD 32,555) in the donepezil group and SEK 277,336 (USD 33,095) in the placebo group, thus resulting in an incremental saving in the donepezil group of SEK 4,528 (USD 540) with 95% CI of SEK –34,351 (USD –4,099), SEK 25,295 (USD 3,018). This difference was not significant (p = 0.77). The removal of hospitalization costs categorized as not associated with AD reduced the per-patient costs of hospitalization to SEK 4,911 (USD 586) in the donepezil group and SEK 3,614 (USD 431) in the placebo group during the study. Adjustment of patient accommodation costs using an ANOVA, with treatment, baseline costs and accommodation as covariates, resulted in an increase in the per-patient savings in accommodation cost in the donepezil versus the placebo groups from SEK 541 (USD 65) (table 2) to SEK 1,529 (USD 182), although this treatment difference was not significant (p = 0.69). Sensitivity analysis of caregiver time costs reduced the total per-patient cost saving of donepezil treatment from SEK 9,190 (USD 1,097) (table 2) to SEK 4,924 (USD 588). Adjustment of caregiver time costs to account for caregiver gender (but using the original value for caregiver time) resulted in a per-patient cost saving of SEK 10,463 (USD 1,259) in the donepezil versus the placebo group (p = 0.47). The magnitude of the treatment differences obtained using these sensitivity analyses differed from the main analysis, but the direction of the results did not alter. These sensitivity analyses, therefore, confirm the findings of the main economic evaluation.

Discussion

This economic evaluation performed as an adjunct to a 1-year, placebo-controlled clinical trial of donepezil [12] is unique in determining prospectively the impact of a ChE inhibitor compared with placebo for the treatment of AD patients. The results have demonstrated that the cognitive and functional benefits of donepezil treatment are realized with no increase of costs to society compared with placebo treatment over 1 year.

The difficulties inherent in performing dedicated long-term economic studies are well recognized [42]. Adequate powering for economic variables requires a large number of patients due to the wide variations in cost outcomes and would almost certainly equate to overpowering for clinical variables. Further, current ethical committee guidelines suggest that continuation of a trial beyond the point where clinical superiority is determined is ethically questionable [42]. Therefore, an economic 'piggyback' evaluation that provides an indication of areas where cost savings might be realized is a reasonable alternative to large-scale and long-term dedicated cost analyses of drugs, particularly in the AD patient population.

The beneficial effects of donepezil on patient function observed in this study are consistent with the results of two previous clinical studies with donepezil [11, 13]. One of these studies demonstrated that the time to a clinically evident decline in function was at least 72% longer in patients treated with donepezil compared with placebo over a 1-year period [13]. This slowing in the deterioration of the ability to perform ADL in donepezil- versus placebo-treated patients [12] may have translated to a reduction in the amount of time caregivers in the donepezil group spent assisting patients compared with caregivers in the placebo group. Indeed, caregivers in the donepezil group reported spending less time assisting with both instrumental and basic ADL than caregivers in the placebo group. Furthermore, significantly more caregivers of placebo- compared with donepezil-treated patients reported spending most of each day (at least 16 h a day) caring for patients at weeks 24 and 36. This is consistent with the findings of recent studies that have demonstrated

that donepezil treatment can reduce caregiver burden [17, 20].

It is noteworthy that caregiver time-related costs represented approximately one third of the total cost in each treatment group. This observation emphasizes the importance of including costs of informal care in economic evaluations of AD treatments, particularly when considering a population of patients with mild to moderate disease who generally reside within the community. It is also interesting that the two largest cost savings associated with donepezil were in the areas of social services and caregiver time spent on patient care. These savings are consistent with a reduction in the deterioration of ADL.

Overall, this economic evaluation suggested that patient and caregiver benefits were achieved without a significant difference between donepezil and placebo treatment in total costs and its constituents, patient costs, caregiver time and caregiver health-related costs. Comparisons of the total costs for the donepezil and placebo groups revealed a per-patient cost saving of SEK 9,190 (USD 1,097) in favor of donepezil over the 52-week study period. This difference was not significant. However, statistically significant differences in primary economic variables were not expected as the study was powered to detect a significant difference in a clinical variable (GBS total score) [12]. Nevertheless, the results suggest that the clinical benefits associated with donepezil treatment are achieved with no additional cost to society. Trends towards savings were reported in the donepezil versus the placebo treatment group for caregiver health and caregiver time costs. When patient costs alone are considered, costs are slightly higher [SEK 2,438 (USD 291) per patient] in the donepezil compared with the placebo group. However, this represents a substantial offset of the cost of donepezil treatment since this difference is 77% less than the annual per-patient cost of donepezil treatment (SEK 10,723; USD 1,280).

The small differences in costs for patient accommodation and hospitalization between the treatment groups may be related to the inclusion criterion of community patients with mild to moderate AD and the evaluation window of 1 year. Only a small proportion of patients in each group was transferred to alternative, more expensive accommodation during the treatment period. However, more than twice as many placebo- compared with donepezil-treated patients moved into a nursing home during the study. These trends are in line with the predictions of modeling studies, which suggested that treatment with donepezil delays institutionalization [26–28]. Furthermore, observational studies have confirmed that donepezil treatment is associated with delays in nursing home placement [21, 22]. A substantial proportion of the accommodation costs included in this study were made up of 'hotel costs', i.e. costs for housing, food and heating, which were equal for all patients, irrespective of the category of living accommodation (living at home, service house, home for aged, group living or nursing home). However, for sheltered living, there are additional costs linked to care. For example, the daily cost of accommodation in the patient's own home, living with their spouse or a relative, was SEK 251 (USD 30) compared with SEK 1,197 (USD 143) for a nursing home.

Prestudy costs of patient hospitalization differed between the treatment groups suggesting that for rare events such as hospitalization, randomization does not always distribute these events evenly. Nonetheless, comparison of the prestudy cost ratio with the in-study cost ratio showed that donepezil yielded a reduction in hospitalization compared with placebo.

Previous economic modeling studies predicted that donepezil treatment may offer cost savings compared with no treatment and would represent a cost-effective alternative to no treatment [26–28]. For example, one modeling study concluded that the costs of donepezil acquisition, preparation and administration might be offset by cost savings in patient care after 2 years [27]. Moreover, observational studies have demonstrated that treatment with donepezil may result in savings, or the costs of donepezil are at least offset, after 6–12 months of treatment [22, 29, 30]. The present prospective, placebo-controlled study, involving mild to moderate AD patients, supports these findings.

The cost data obtained in this study are likely to be relevant to other healthcare systems and countries beyond the five Northern European countries included in this study. It has been noted previously that the costs of caring for patients with dementia in Sweden are similar to those in Canada and the USA [4]. In addition, despite differences in the healthcare systems of the five countries included in this study, there were only minimal differences in total per-patient costs between the countries.

Donepezil treatment versus placebo was associated with clinically beneficial effects in conjunction with minimal incremental additional resource utilization, when patient costs alone were considered. This therefore suggests that donepezil improves the care of AD patients and may help reduce the substantial cost disparity in caring for patients with AD compared with elderly patients without AD, described previously [7]. Evidence concerning the beneficial effects of donepezil in patients with more

advanced AD [14] and the observation that treatment with donepezil is associated with a delay in nursing home placement [21, 22] support the importance of this therapy in the management of AD. Furthermore, the findings of the current study suggest that the clinical benefits of donepezil are attained at no additional cost compared with placebo treatment, and thus support the view that treatment with donepezil is a cost-effective treatment option for the management of patients with AD.

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Appendix

The Donepezil Nordic Study Group

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