ORIGINAL RESEARCH ARTICLE

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Cost Effectiveness of Donepezil in the Treatment of Mild to Moderate Alzheimer's Disease

A UK Evaluation Using Discrete-Event Simulation

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Abstract

Background: Recommendations in the UK suggest restricting treatment of Alzheimer's disease with cholinesterase inhibitors, on cost-effectiveness grounds, to patients with moderate cognitive decline. As the economic analyses that informed these recommendations have been the subject of debate, we sought to address the potential limitations of existing models and produce estimates of donepezil treatment cost effectiveness in the UK using the most recent available data and simulation techniques.

Methods: A discrete-event simulation was developed that predicts progression of Alzheimer's disease through correlated changes in cognition, behavioural disturbance and function. Patient-level data from seven randomized, placebo-controlled donepezil trials and a 7-year follow-up registry provided the basis for modeling longitudinal outcomes. Individuals in the simulation were assigned unique demographic and clinical characteristics and then followed for 10 years, with severity of disease tracked on continuous scales. Patient mix and costs were developed from UK-specific literature. Analyses were run for severity subgroups to evaluate outcomes for sub-populations with disease of mild versus moderate severity from both a healthcare payer and societal perspective. All costs are reported in £, year 2007 values, and all outcomes are discounted at 3.5% per annum.

Results: Over 10 years, treatment of all patients with mild to moderate disease reduces overall direct medical costs by an average of over £2300 per patient. When unpaid caregiver time is also taken into consideration, savings increase to over £4700 per patient. Compared with untreated patients, patients receiving donepezil experience a discounted gain in QALYs averaging 0.11, with their caregivers gaining, on average, 0.01 QALYs. For the subset of patients starting treatment with more severe disease, savings are more modest, averaging about £1600 and £3750 from healthcare and societal perspectives, respectively.

In probabilistic sensitivity analyses, donepezil dominated no treatment between 57% and 62% of replications when only medical costs were considered, and between 74% and 79% of replications when indirect costs were included, with results more favourable for treatment initiation in the mild versus moderate severity stages of the disease.

Conclusions: Although the simulation results are not definitive, they suggest that donepezil leads to health benefits and cost savings when used to treat mild to moderately severe Alzheimer's disease in the UK. They also indicate that both benefits and savings may be greatest when treatment is started while patients are still in the mild stages of Alzheimer's disease.

Background

Alzheimer's disease is a fatal neurodegenerative disorder characterized by cognitive deterioration, impairment of daily activities and neuropsychiatric symptoms. Individuals with the disease progress from losing the ability to perform higher-level activities to losing the ability to perform basic necessities of daily living, such as eating or grooming. Behavioural symptoms commonly associated with Alzheimer's disease can progress from mood swings or apathy to psychosis or agitation.

Alzheimer's disease is the most prevalent type of dementia in older age groups. In the UK, a recent report estimated that there were over 680 000 individuals living with dementia, 417 000 of whom had Alzheimer's disease.[1] The same report estimated the annual burden of dementia at £17 billion.[1]

With no cure for Alzheimer's disease, cholinesterase inhibitors, which treat the symptoms of Alzheimer's disease, and in randomized, placebo-controlled clinical trials have been shown to improve symptoms related to cognition, behaviour and function,[2,3] currently represent the best available treatment for patients. Since becoming available in the mid 1990s, numerous studies, most based on modelling, have evaluated the cost effectiveness of treatments for Alzheimer's disease. The majority of these studies have indicated that treatment with donepezil, rivastigmine and galantamine would be cost effective, although all were based on projected benefits from short-term clinical trial data. They also depended on modelling techniques that were limited in the level of detail that could be factored into the analyses.[4-7] For example, previous models for cholinesterase inhibitors have often categorized severity of disease into aggregated health states (e.g. mild, moderate, severe), and defined disease severity using a single measure such as the Mini-Mental State Examination (MMSE) or Clinical Dementia Rating (CDR). The Assessment of Health Economics in Alzheimer's Disease (AHEAD) model[8] projected outcomes for patients based on multiple measures, including cognition and behavioural symptoms, but disease severity in that model was restricted to two health states. Furthermore, most models have been cohort based rather than individual simulations, relying on projections being made based on average patient characteristics and average treatment effects.

On the other hand, analyses conducted on behalf of the UK National Institute for Health and Clinical Excellence (NICE) suggested that treatment with cholinesterase inhibitors was not cost effective and, in 2005, NICE recommended that patients with Alzheimer's disease discontinue the use of cholinesterase inhibitors. NICE later amended their recommendation, saying that treatment should be restricted to individuals with moderate disease severity, where treatment was deemed to be cost effective.[7,9] This decision, and the economic analyses that served to inform it, have been the subject of considerable debate and legal actions.[10,11] As with other modelling studies in Alzheimer's disease, the model and methods

adopted for NICE are subject to a number of potential limitations and assumptions. These have been reviewed elsewhere,[9,10,12,13] but like the AHEAD model, the evaluation conducted for NICE used a model that restricted health outcomes and their consequent health and economic impact to two discrete health states (requiring full-time care or not requiring full-time care).

Given the ongoing debate over the NICE decision and the significant impact it has had on the treatment of patients with Alzheimer's disease in the UK, a new assessment of the economic impact of cholinesterase inhibitors is needed. Indeed, the appraisal committee for the NICE evaluation of cholinesterase inhibitors noted the limitations of the model on which it based its decision, and pointed out the need for additional research.

The current analysis uses a discrete-event simulation to evaluate the cost-effectiveness outcomes for donepezil's indication in the UK: patients with modified MMSE scores between 10 and 26. In light of NICE's decision to restrict treatment to patients with moderate disease severity, we also evaluate outcomes in patients beginning treatment with mild Alzheimer's disease (MMSE between 20 and 26) and for those initiating treatment only when MMSE scores fall below 20.

Methods

A discrete-event simulation was developed for the evaluation of donepezil's cost effectiveness in the UK. The model calculated outcomes from the perspective of both the payer responsible for all direct healthcare costs and society, tracking individuals over a period of 10 years. All costs are reported in £, year 2007 values, and all outcomes discounted at 3.5% per annum.

Model Overview

Discrete-event simulation was selected as the modelling technique as it allows individual-level modelling, capturing heterogeneity in disease progression and other outcomes, as well as tracking correlated changes on multiple domains on continuous rather than discrete scales. The approach allows for a compact means of capturing the complexities associated with Alzheimer's disease progression and, unlike a Markov modelling approach, avoids the need to develop discrete health states. This is important for modelling outcomes in Alzheimer's disease, as it avoids the need to oversimplify the disease by, for example, restricting outcomes to requiring full-time care or not requiring full-time care, and thus masking the potential benefits of treatment, without necessitating a proliferation of intermediate health states that might make the model overly complex and development of transition matrices impractical. The discrete-event simulation approach also allows for persistence with treatment to be captured in a realistic manner. By allowing individuals to be simulated, each with their own unique attributes that are updated throughout the simulation, discrete-event simulation not only allows for more precise projections of patient experience, but is also computationally efficient, as it does not require continuous processing of patients – patients are updated only when events of relevance occur.

Figure 1 provides an overview of the model flow. Simulated patients are first created and assigned their own unique attributes. An identical copy of each patient is then created, with the original patient assigned no treatment, and the copied patient assigned to treatment with donepezil 10 mg. By creating identical copies of each patient, the simulation ensures that the treatment comparisons are not being influenced by differences in patient characteristics. Patients are then followed, with their characteristics updated over time. The simulation measures disease severity based on cognition (using the MMSE), behaviour (using the Neuropsychiatric Inventory [NPI]), activities of daily living (ADLs) and instrumental ADLs (IADLs). The simulation first begins by estimating the patient's change in MMSE score since the last time the patient's status was updated. In order to ensure the correlation amongst changes in other measures of disease severity, NPI, ADL and IADL changes are then calculated sequentially, each accounting for changes in the previously estimated scores. Based on a given patient's treatment status and current disease severity, costs, health utilities and caregiver outcomes

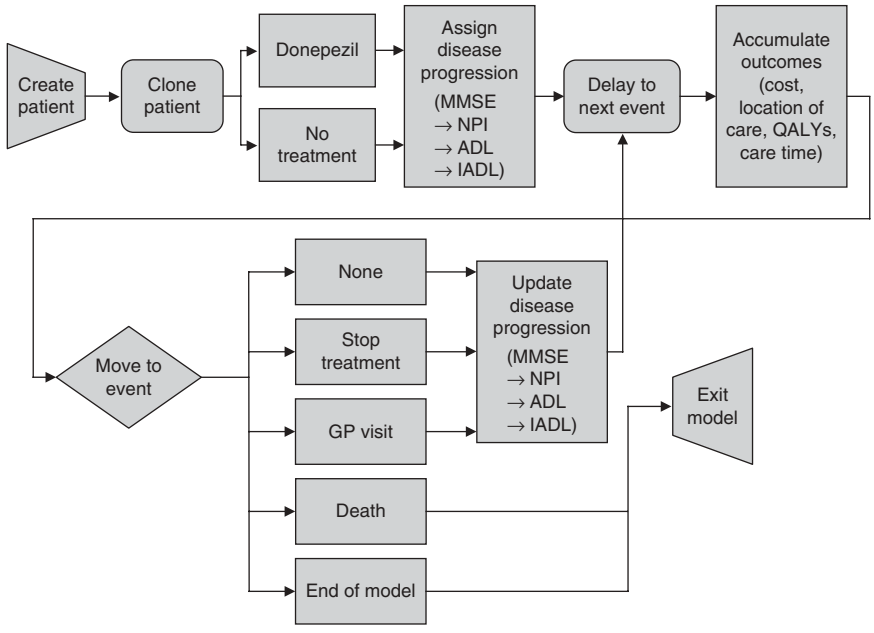

Fig. 1. Simplified representation of the Alzheimer's disease simulation flow. **ADL** = activities of daily living; **IADL** = instrumental ADLs; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory.

are calculated and accumulated over the appropriate time period. Treated patients in the simulation can discontinue treatment either as a result of pre-defined stopping rules, or for other unrelated reasons. Treatment effects are applied for up to 1 year for treated patients, after which it is assumed that any gains are maintained while the patient remains on treatment, but that no further slowing of the disease occurs. Furthermore, if patients discontinue treatment for any reason, they are assumed to lose all benefits over a 6-week period, after which their disease severity is identical to that of their untreated counterpart. Consistent with current recommendations, the only stopping rule applied in the analyses presented here is that patients discontinue therapy once their MMSE scores fall below 10. Mortality is also modelled. As cholinesterase inhibitors have not been associated with improvements in survival, time of death is assigned to each individual prior to treatment assignment, thereby ensuring that survival is identical in both groups. Finally, treated patients are assumed to receive additional physician visits beyond those that would take place regularly for patients with Alzheimer's disease for the purpose of monitoring their progress on donepezil.

Data Sources

Data for the model came from a number of sources. To ensure that the best available data were used, MEDLINE searches were performed for English language articles published in the last 10 years. The searches focused on papers in disease progression, mortality, healthcare utilization, costs, caregiver burden, treatment persistence, quality of life (QOL) and health utilities. Four separate searches were performed. All abstracts were reviewed, and any articles that reported analyses that could potentially be used as inputs into the simulation were retrieved. Key elements of each paper were abstracted and summarized, including year of publication, a description of the populations evaluated, sample sizes, measures used and methods of statistical analyses. Final selection of model parameters was made based on an assessment of both the quality

of the source data and the appropriateness of reported results as a basis for parameter estimates in the model.

Population

In order to properly capture correlations in patient characteristics, simulated patients were created by sampling from an individual patient dataset with baseline information on 826 patients from three donepezil clinical trials.[14-16] The data elements include patient age, sex, use of psychiatric medications, and MMSE, NPI, ADL and IADL scores, as well as caregiver age and sex. The trials chosen to provide the sample patients were those that had data on as many target variables as possible and taken together include all Alzheimer's disease severity levels. Baseline data on NPI for one of the studies[14] were not available and so were imputed based on a linear regression relationship to MMSE, age and sex, estimated from the other two trials.

In order that the simulated population be representative of individuals with Alzheimer's disease in the UK, the age and sex distributions of Alzheimer's disease patients in the UK as reported in *Dementia UK*[1] were used to assign sampling weights to the file.

Disease Progression and Treatment Effects

One goal of the project was to improve on existing economic evaluations by incorporating the effects of disease on behavioural and functional abilities of patients. To this end, data were analysed from the CERAD (Consortium to Establish A Registry for Alzheimer's Disease) registry,[17] and seven donepezil clinical trials spanning mild to severe Alzheimer's disease,[14-16,18-21] including data from open-label extensions of two of the studies.[22,23]

While MMSE data over time were available from trial data, the CERAD data offered a longer time course of data. Furthermore, the patterns of change observed in CERAD were more in line with what has been previously reported on progression of Alzheimer's disease, with progression slowest over the mildest and most severe stages of the disease.[24-26] Figure 2 plots average annual MMSE rates of change on the y-axis by previous MMSE score on the x-axis. Results are plotted for the observed CERAD data and for predicted CERAD data using the CERAD-based equation (equation 1). Observed changes are also plotted for treated and untreated patients in the donepezil clinical trials. As figure 2 indicates, the trial data showed a positive annual rate of change in MMSE (i.e. improvement) over some ranges of MMSE, even in untreated patients. Using the trial data to model the natural history of MMSE changes in an untreated population would not have been appropriate, as it would have led to predictions of improved cognition in a subgroup of untreated patients.

A piecewise linear regression model was fitted to adequately capture the relationship between rate of change of MMSE, defined as annual change in score since previous measurement, and previous MMSE in CERAD. In this approach, a different slope is allowed in different intervals of the MMSE scale, which reflects a different rate of change at different stages of the disease. The MMSE equation derived from these data has the following form:

$$Rate\ of\ change = 5.4663 - 0.4299PM_1 - 0.0042PM_2 + 0.1415PM_3 - 0.0791 PrevRate + 0.0747Age + \delta_i \quad \text{(Eq. 1)}$$

PM represents patients' previous MMSE measurement, partitioned over the scale of MMSE.

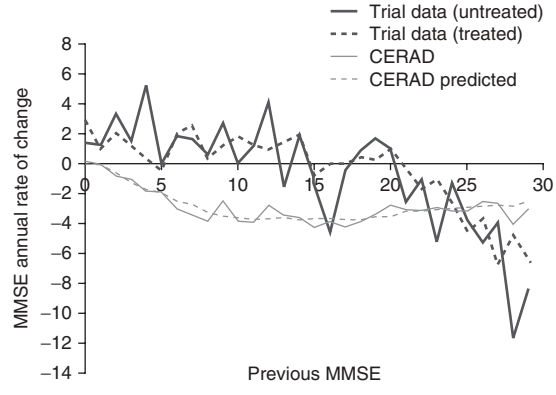

Fig. 2. Predicted and actual Mini-Mental State Examination (MMSE) rate of change in the CERAD (Consortium to Establish A Registry for Alzheimer's Disease) dataset, and actual MMSE rate of change in the donepezil trials for treated and untreated patients.

PM_1-PM_3 are calculated as: $PM_1 = \min(\text{Prev MMSE}, 9)$, $PM_2 = \max(0, \min[\text{PrevMMSE} - 9, 9])$, and $PM_3 = \max(0, \min[\text{PrevMMSE} - 18, 12])$. *PrevRate* is the patients' last known rate of decline, and age represents patients' age at baseline. δ_i represents a random intercept parameter, which allows the pattern of decline to vary from one patient to another. The MMSE scale itself ranges from 0 to 30.

A similar model to that derived from the CERAD data was fitted to the trial data[14-16,18-21] to quantify a treatment effect. Based on the observed patterns of rate of decline in treated and placebo groups, 20 weeks was identified as a changing point in effect. The estimated treatment effect size on annualized rate of change based on this model was 6.16 in the first 20 weeks of treatment and 2.47 over weeks 20–52. After week 52, continued treatment was assumed to have no further effect on the predicted rate of disease progression, and as with all treatment effects in the model, was assumed to serve to simply maintain previous gains.

NPI was predicted, based on the donepezil trials where NPI was measured,[15,16,20,21] as change from NPI at baseline. The NPI estimates for both treated and untreated patients use equation 2:

$$\begin{aligned} Rate\ of\ change_{NPI} = (&5.74 - 0.64 Donepezil + \\ &0.03 Weeks - 0.59 NPI_{base} - 0.59 NPIWeeks + \\ &0.24 NPI_{recent} - 1.74 White - 3.82 Black + \\ &2.34 PsyMed + 0.12 MMSE_{base} - \\ &0.22 MMSE_{recent} + \delta_i) \times 1.44 \end{aligned} \quad \text{(Eq. 2)}$$

Donepezil represents the treatment effect of donepezil, *Weeks* represents weeks of follow-up in the simulation, NPI_{base} is the patient's baseline NPI, NPI_{recent} is the patient's last NPI. *White* and *Black* are dummy variables for race, *PsyMed* is a dummy variable for patients on psychiatric medications at baseline, $MMSE_{base}$ represents the patient's MMSE at baseline, *Age* represents the patient's age at baseline in years, and $MMSE_{recent}$ represents the patient's previous MMSE. δ_i represents a random intercept parameter, which allows the pattern of decline to vary from one patient to another. The equation was derived based on a normalized scale of 0–100, and is therefore multiplied by 1.44 to rescale it to the standard 0–144 range for the NPI.

As the equation indicates, changes in NPI are influenced by patients' baseline and most current MMSE. Donepezil's treatment effect, therefore, comes into play not only through the treatment coefficient, but also through its influence on MMSE over time. For example, for every 1 point benefit on the MMSE due to treatment with donepezil, patients will also be predicted to experience an additional 0.22 point decline in NPI score. There is also an interaction between NPI and time (NPI_{base}Weeks explanatory variable).

The scales used to measure function (ADL and IADL) varied in the clinical trials. After selecting the trials with the most similar scales,[14-16,20,21] standardized scales ranging from 0 (best function) to 100 (worst function) were created. Six basic ADL items (toileting, feeding, dressing, grooming, ambulation, bathing) were in common amongst the ADL scales selected. These individual item responses were pulled and scored and then normalized for different response ranges to provide a 0–100 scale. Trials with IADL scales[14-16] all had items in the domains of phone, shopping, food preparation, household tasks, and finances, but only four items were exactly the same in all scales. As such, each trial's IADL scale was taken in its entirety and normalized to 0–100.

As with the NPI, ADL and IADL equations predict change from baseline with the resulting equations (equations 3 and 4):

$$\begin{aligned} Rate\ of\ change_{ADL} = &1.35 - 0.81 Donepezil + \\ &0.06 Weeks - 0.79 ADL_{base} + 0.71 ADL_{previous} \\ &+ 0.12 MMSE_{base} + 0.09 Age + 0.81 PsyMed - \\ &3.05 Black - 0.49 MMSE_{recent} + \delta_i \end{aligned} \quad \text{(Eq. 3)}$$

$$\begin{aligned} Rate\ of\ change_{IADL} = &1.27 + 0.63 Donepezil + \\ &0.17 Weeks - 0.06 DoneWeek - 0.84 IADL_{base} + \\ &0.002 IADLWeek + 0.84 IDAL_{previous} - \\ &0.67 Male + 0.20 MMSE_{base} - 0.28 MMSE_{recent} - \\ &0.16 ADL_{base} + 0.18 ADL_{recent} + \delta_i \end{aligned} \quad \text{(Eq. 4)}$$

Although the NPI was tested as an independent variable, it was not found to be a significant predictor of changes in function, given the other variables already in the model. For ADL scores, donepezil's effect was modelled directly through the treatment effect term and the terms for patients' most recent MMSE. For IADLs, donepezil's treatment effect comes into play through the treatment term, as well as patients' most recent MMSE and ADL scores. Unlike the other equations, the IADL equation also contains an interaction term between donepezil and time to reflect an increasing effect over time.

Additional details on derivation of the prediction equations are provided in the technical appendix (see the Supplemental Digital Content 1, http://links.adisonline.com/PCZ/A69).

Persistence

Patients can stop treatment for three reasons in the simulation: reaching the end of the user-specified treatment duration (10 years in the base case), clinical stopping rules (MMSE falling below 10 in the base case) and other reasons. Patients who stop treatment are assumed to lose all treatment benefits over the course of the subsequent 6 weeks.[27]

Premature treatment discontinuation is applied using data from a UK study of 88 Alzheimer's disease patients receiving donepezil (table I).[28] In addition, hazard ratios for treatment discontinuation are applied to the baseline discontinuation rates based on equations derived from the donepezil clinical trial data. Baseline rates from the UK study[28] are adjusted in the model using the trial-derived hazard ratios to account for simulated patients' disease severity (baseline and current) as well as changes in disease severity over the course of the simulation, both measured using the MMSE. A Cox regression model in which MMSE and the rate of decline in MMSE were updated over time was used for the discontinuation hazard ratio analysis. Patient demographics were also tested as predictors of discontinuation but were not significant and thus not retained. Based on the baseline hazard and hazard ratios, a time to treatment discontinuation is calculated for each patient actively receiving treatment.

Table I. Unadjusted discontinuation rates for patients with Alzheimer's disease receiving donepezil[28]

	Months			Annual risk after 12 mo
	0–3	0–6	6–12	
Stopping over interval (%)	5.1	5.1	10.2	10.3

Table II. Power function parameters for prediction of survival in years[29]a

Age (y)	Females		Males	
	A	B	A	B
65–69	11.719	0.544	15.301	0.375
70–79	10.096	0.753	10.170	0.922
80–89	8.401	0.814	7.356	0.812
≥90	6.360	0.703	7.724	1.182

a Survival (years) = A × (percent surviving)^B.

Mortality

Age and sex-specific survival data from the MRC CFAS (Medical Research Council Cognitive Function and Ageing Study)[29] were used to estimate survival patterns for the population. While these data were based on patients with all forms of dementia, rather than just Alzheimer's disease, they represented recent estimates, with follow-up ending in 2005, on a large sample (n = 438) of patients in England and Wales. As mentioned, treatment with donepezil was assumed to have no influence on patient survival, so estimates of time to death in the model were assumed to be identical for treated and untreated patients. Time to death was estimated by fitting power functions for different age and sex subgroups (table II).

Medical Costs

Current *British National Formulary* costs were used to assign a daily treatment cost of £3.18 for donepezil 10 mg. In addition, patients receiving active therapy were assumed to incur costs associated with biannual visits to their physician. A £50 cost per visit was assigned based on GP costs reported in *Unit Costs of Health and Social Care 2007*.[30]

Direct patient care costs were taken from the *Dementia UK* report,[1] and inflated to £, year

2007 values. For patients living in the community, the *Dementia UK* report provided cost estimates for mild, moderate and severe disease. These costs were interpolated to fit the following severity ranges: mild (MMSE ≥25), mild-moderate (MMSE ≥20 and <25), moderate (MMSE ≥15 and <20), moderate-severe (MMSE ≥10 and <15), and severe (MMSE <10) [table III]. For institutionalized patients, *Dementia UK* only provided a single cost estimate, and as such, the model applies the same monthly care cost for all patients in institutions regardless of disease severity.

Costs and time by location of care are accumulated based on the severity of disease that patients experience over the course of the simulation. For example, if 50% of patients with MMSE scores below 10 are institutionalized, then patient care costs for a patient with an MMSE score below 10 would be calculated as 50% × £2645 and 50% × £904 for any given month. Similarly, institutionalization is not modelled as an explicit event. Rather, time spent by patients in institutions in the example above would be allotted as 50% of the time that the patient was alive.

As the *Dementia UK* report only provided an overall rate of institutionalization (36.5%),[1] it was necessary to combine this information with other data to get severity-specific institutionalization percentages. A UK study,[31] reporting that, in a sample of 445 nursing home residents, 43.8% had dementia with MMSE scores of ≤17, and 21.6% had dementia with MMSE scores between 18 and 23, was used in combination with the severity distribution of Alzheimer's disease patients in the UK from *Dementia UK* to derive the proportion of patients institutionalized in each severity category that would yield an overall proportion of 36.5% (table III).

Caregiver Time Costs

The relationship of caregiver time to disease severity parameters was developed from two of the donepezil clinical trials where these data were available[15,16] using a linear repeated measures, fixed effects model (equation 5).

$$Care\ Minutes\ Per\ Day = 76.41 + 1.8Age_{cc} + 93.02Male_{cc} + 85.56Male_{patient} - 6.47MMSE + 0.58NPI + 2.66ADL + 2.61IADL + 20.55PsyMed \quad \text{(Eq. 5)}$$

Age_{CG} represents the caregiver's age, $Male_{CG}$ is a dummy variable for the caregiver's sex, and $Male_{patient}$ for the patient's sex. *PsyMed* is a dummy variable for whether the patient was receiving psychiatric medications at baseline (see the Supplemental Digital Content for additional details).

Caregiver time was valued at the UK minimum wage of £5.30 per hour.[32]

Health Utilities

Health utilities for patients were estimated based on a published regression equation.[33] The study on which the published equation is based used the EQ-5D to derive health utilities for 272 Alzheimer's disease patients in Sweden, Denmark, Finland and Norway. Patients across the spectrum of cognitive function were included in the study. The mean age in the study was 76 years, with 38% of the population being male, which is consistent with patient demographics for the UK reported in *Dementia UK,* where males

Table III. Monthly medical per-patient care costs (£, year 2007 values) by disease severity and location of care[1,31]

MMSE score	Institutionalized		Living in the community	
	% patients	cost	% patients	cost
Mild (≥25)	12.9	2645	87.1	649
Mild-moderate (≥20 and <25)	25.6	2645	74.4	701
Moderate (≥15 and <20)	38.3	2645	61.7	754
Moderate-severe (≥10 and <15)	51.0	2645	49.0	829
Severe (<10)	70.0	2645	30.0	904

MMSE = Mini-Mental State Examination.

were estimated to make up roughly one-third of the dementia patients in the UK, and the age group with the largest number of dementia patients was 75–84 years.[1] As the utility study used the brief, rather than the full NPI, the published coefficient for the NPI term was modified to correspond to the full NPI scale. The final equation took the form of equation 6:

$$Utility = 0.408 + 0.010MMSE - 0.004NPI - 0.159Institutionalized + 0.051Caregiver \quad \text{(Eq. 6)}$$

MMSE represents the patient's current MMSE, *NPI* represents the patient's current NPI, *Institutionalized* and *Caregiver* are dummy variables for whether the patient is institutionalized or lives with their caregiver.

Caregiver utilities were based on analysis of the data from donepezil trials where caregivers completed the SF-36.[14-16] The scores were transformed to health utilities[34] and then related with a linear repeated measures model to other trial outcomes to develop equation 7 (see the Supplemental Digital Content for additional details).

$$Caregiver\ Utility = 0.90 - 0.003Age_{CG} + 0.03Male_{CG} + 0.001Male_{patient} + 0.00MMSE - 0.001NPI - 0.001ADL - 0.0004IADL - 0.01PsyMed \quad \text{(Eq. 7)}$$

Analyses

Base-case analyses and deterministic sensitivity analyses are based on 20 replications of 1000 patients in each treatment arm. For probabilistic sensitivity analyses, the model was run 500 times based on runs of 5000 patients per treatment arm. Base-case and deterministic sensitivity analyses required approximately 10 minutes of computing time. Probabilistic sensitivity analyses required just over 2 hours of computing time.

Probabilistic sensitivity analyses varied the following parameters:

- treatment effects on MMSE, NPI, ADL and IADL;
- patient care costs;
- caregiver time regression parameters;
- patient utility regression parameters;
- caregiver utility regression parameters;
- percentage of patients living in the community by disease severity;
- treatment discontinuation rates;
- intercept terms for equations of changes in MMSE, NPI, ADL and IADL.

For many parameters, standard errors were available from the parameter source data, reflecting the study sampling error. When available, standard errors were used to measure parameter uncertainty. Where a standard error was not available, we used 25% of the parameter as an assumed standard error. Parameters on continuous variables were assumed to be Normally distributed, while proportion parameters on discrete variables were assumed to be Beta distributed. Of note, we did not take into consideration correlations amongst input variables in conducting the probabilistic analyses. As a consequence, some of the parameter estimates from the disease progression equations were not varied in the probabilistic sensitivity analyses in order to avoid nonsensical scenarios. Besides the treatment effect and intercept terms, parameter estimates for the disease progression equations (e.g. the effect of age on rate of MMSE change) were not varied in the probabilistic analyses. Other parameters not varied in the analyses included the decision to stop treatment when MMSE scores fall below 10 (100% discontinuation was assumed), and the parameter estimates for mortality predictions.

Results

For the overall population of patients, MMSE scores between 10 and 26, as well as for the mild and moderate population subgroups, donepezil 10 mg dominated the 'no treatment' strategy, with savings from the healthcare payer perspective ranging from almost £1600 per patient starting treatment in the moderate stages of the disease to over £4000 per patient starting treatment in the mild stages of the disease (table IV). When caregiver time costs are included, these savings are even greater, ranging from about £3750 to almost £7100 per patient depending

on when treatment is started. At the same time, QALYs for patients starting treatment with disease of mild severity increase by an average of 0.132, while for those starting treatment with disease of moderate severity, gains are somewhat smaller, averaging 0.098 per patient. Gains in caregiver QALYs are relatively small, averaging 0.012 per caregiver for the population as a whole.

Figure 3 shows gains in other health outcomes with donepezil for the mild and moderate subgroups. For those initiating treatment when their disease is in the mild stages, time alive with MMSE scores above 10 increases by an average of 3.4 months, time with NPI scores above 28, which has been identified as the threshold for serious behavioural disturbances,[35] falls by 1.2 months, and time institutionalized falls by

Table IV. Base-case results by disease severity for the 10 years following treatment initiation

Parameter	Untreated[a]	Donepezil[a]	Net difference[a]
MMSE score ≥ 10 and ≤ 26			
Drug costs	0.00	2 185	2185
Direct costs (excluding drug costs)	91 212	86 690	–4522
Total direct costs	91 212	88 875	–2337
Indirect costs	79 734	77 302	–2432
Total costs	170 947	166 178	–4769
QALYs (patient)	1.269	1.378	0.108
QALYs (caregiver)	2.909	2.920	0.012
QALYS (patient + caregiver)	4.178	4.298	0.120
Total healthcare cost per QALY (patient + caregiver)			Dominant
Societal total cost per QALY (patient + caregiver)			Dominant
MMSE score ≥ 20 and ≤ 26			
Drug costs	0.00	2 411	2411
Direct costs (excluding drug costs)	76 943	70 473	–6470
Total direct costs	76 943	72 884	–4059
Indirect costs	67 389	64 362	–3027
Total costs	144 332	137 246	–7086
QALYs (patient)	1.364	1.496	0.132
QALYs (caregiver)	2.728	2.743	0.015
QALYS (patient + caregiver)	4.092	4.239	0.147
Total healthcare cost per QALY (patient + caregiver)			Dominant
Total societal cost per QALY (patient + caregiver)			Dominant
MMSE score ≥ 10 and <20			
Drug costs	0.00	2 095	2095
Direct costs (excluding drug costs)	97 218	93 544	–3674
Total direct costs	97 218	95 639	–1579
Indirect costs	84 983	82 796	–2187
Total costs	182 201	178 435	–3766
QALYs (patient)	1.228	1.326	0.098
QALYs (caregiver)	2.984	2.995	0.011
QALYS (patient + caregiver)	4.212	4.321	0.109
Total healthcare cost per QALY (patient + caregiver)			Dominant
Total societal cost per QALY (patient + caregiver)			Dominant

a Presented as £ unless otherwise indicated, year 2007 values.

MMSE = Mini-Mental State Examination.

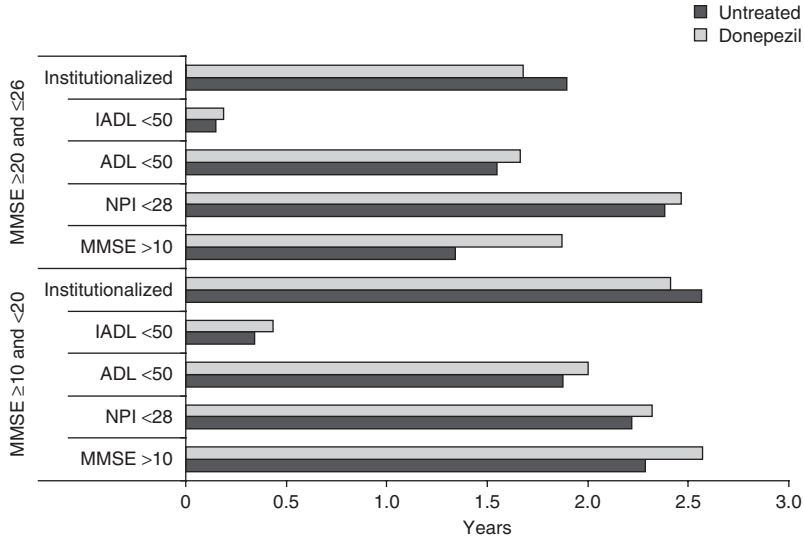

Fig. 3. Disease severity outcomes for patients in the two disease severity subgroups: base-case results. **ADL** = activities of daily living; **IADL** = instrumental ADLs; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory.

2.6 months. For those initiating treatment only when their disease has advanced to the moderate stages, benefits are also significant. Time with MMSE scores maintained above 10 increases by >6 months, largely because a significant number of patients initiate treatment close to this threshold. Time with NPI scores above 28 falls by almost 1 month, while institutionalization time falls by an average of almost 1.9 months.

One-way sensitivity analyses (table V) show that donepezil's position of dominance held in both population subgroups in all but two analyses. For the group with mild severity, results were most strongly influenced by changes in patient care costs, allowing treatment to continue after MMSE scores fell below 10, changes in treatment effectiveness, changes in discontinuation rates, and reducing the duration of treatment to 1 year. Only when treatment effects were reduced by 50% did savings in direct costs fall below £1000 per patient, although even in this case, savings from the societal perspective exceeded £1000 per patient. Allowing treatment to continue when MMSE scores fell below 10 led to an increase in QALYs gained, but because of minimal cost offsets over this stage of the disease, overall savings per patient fell. Results for the group starting treatment when their disease was of moderate severity were broadly similar. However, in two cases donepezil was no longer dominant from the healthcare perspective. When treatment effects with donepezil were reduced by 50%, donepezil was associated with small incremental direct costs, averaging £136 per patient over 10 years, and an incremental cost-effectiveness ratio (ICER) of £2897 per QALY gained. Donepezil remained dominant from the societal perspective in this analysis although per-patient savings averaged less than £450. When the proportion of patients institutionalized was reduced by 25% for patients in the moderate-severe and severe states only, then donepezil was associated with a cost per QALY of £1222 from the healthcare perspective, although again, remained dominant from the societal perspective.

Probabilistic sensitivity analyses yielded considerably more variability in outcomes, although donepezil remained the dominant therapeutic option in most replications. Figure 4 shows the cost-effectiveness acceptability curve for the subgroup of patients starting treatment with mild disease severity. From the healthcare payer perspective, donepezil dominated treatment in 62% of replications, with incremental cost per

Table V. One-way sensitivity analysis results by disease severity at treatment initiation

Analysis	Net QALYs	Net direct cost (£)	Net indirect costs (£)	Net total costs (£)	Cost per QALY
MMSE score ≥ 20 and ≤ 26					
Base case	0.147	−4059	−3 027	−7 086	Dominant
Caregiver time effects of disease severity ↓ 25%[a]	0.147	−4059	−2 271	−6 329	Dominant
Patient care cost ↓ 25%[b]	0.147	−2392	−3 027	−5 419	Dominant
Institutional care costs ↓ 30%	0.147	−1870	−3 027	−4 897	Dominant
Proportion of all patients institutionalized ↓ 25%	0.136	−2890	−3 027	−5 917	Dominant
Proportion of only moderate-severe and severe patients institutionalized ↓ 25%	0.132	−2507	−3 027	−5 534	Dominant
Patient utility effects of disease severity ↓ 25%[a]	0.125	−4059	−3 027	−7 086	Dominant
No stopping rules	0.154	−3648	−3 209	−6 856	Dominant
Stop treatment if MMSE deteriorates on any scale after 6 mo	0.146	−4042	−3 000	−7 041	Dominant
5 y time horizon	0.142	−3949	−2 945	−6 894	Dominant
Treatment effects ↓ 25%[a]	0.106	−2125	−2 088	−4 213	Dominant
Treatment effects ↓ 50%[a]	0.067	−273	−1 098	−1 372	Dominant
MMSE change intercept ↑ 25%	0.179	−7124	−3 695	−10 820	Dominant
MMSE change intercept ↓ 25%	0.117	−2470	−2 453	−4 923	Dominant
No discontinuation	0.212	−5653	−4 322	−9 975	Dominant
Double discontinuation	0.102	−2977	−2 113	−5 090	Dominant
Treatment duration 5 y	0.142	−3950	−2 942	−6 892	Dominant
Treatment duration 1 y	0.041	−1700	−719	−2 419	Dominant
MMSE score ≥ 10 and ≤ 20					
Base case	0.109	−1579	−2 187	−3 766	Dominant
Caregiver time effects of disease severity ↓ 25%[a]	0.109	−1579	−1 641	−3 220	Dominant
Patient care cost ↓ 25%[b]	0.109	−617	−2 187	−2 805	Dominant
Institutional care costs ↓ 30%	0.109	−71	−2 187	−2 259	Dominant
Proportion of all patients institutionalized ↓ 25%	0.101	−838	−2 187	−3 025	Dominant
Proportion of only moderate-severe and severe patients institutionalized ↓ 25%	0.092	112	−2 187	−2 075	Dominant (societal) £1222 (healthcare)
Patient utility effects of disease severity ↓ 25%[a]	0.093	−1579	−2 187	−3 766	Dominant
No stopping rules	0.127	−364	−2 643	−3 007	Dominant
Stop treatment if MMSE deteriorates on any scale after 6 mo	0.107	−1533	−2 130	−3 663	Dominant
5 y time horizon	0.109	−1574	−2 183	−3 757	Dominant
Treatment effects ↓ 25%[a]	0.077	−726	−1 394	−2 120	Dominant
Treatment effects ↓ 50%[a]	0.047	136	−579	−442	Dominant (societal) £2897 (healthcare)
MMSE change intercept ↑ 25%	0.143	−2337	−2 866	−5 203	Dominant
MMSE change intercept ↓ 25%	0.086	−1183	−1 698	−2 881	Dominant
No discontinuation	0.143	−2212	−2 865	−5 076	Dominant

Continued next page

Table V. Contd

Analysis	Net QALYs	Net direct cost (£)	Net indirect costs (£)	Net total costs (£)	Cost per QALY
Double discontinuation	0.084	–1113	–1665	–2778	Dominant
Treatment duration 5 y	0.109	–1574	–2181	–3756	Dominant
Treatment duration 1 y	0.040	–180	–757	–937	Dominant

a Coefficients in regression equations relating to disease severity (MMSE, NPI, ADL and IADL) were reduced by 25%/50%.

b All patient care costs were reduced by 25%.

ADL = activities of daily living; **IADL** = instrumental ADLs; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; ↓ indicates decrease; ↑ indicates increase.

discounted QALY estimates falling below £30 000 in >78% of replications. From the societal perspective, 79% of replications resulted in donepezil dominating no treatment, with ICERs falling below £30 000 per QALY in 87% of replications. For patients initiating treatment with disease of moderate severity (figure 4), 57% of replications results in donepezil being dominant from the healthcare perspective, and 74% from the societal perspective. Seventy-four percent of replications resulted in cost-per-QALY estimates below £30 000 from the healthcare payer perspective, and 85% from the societal perspective.

Discussion

Current recommendations in the UK restrict treatment to patients in the moderate stage of Alzheimer's disease based in large part on analyses that suggested that treatment of patients in the milder stages of the disease is not cost effective. In those analyses, the cost effectiveness of cholinesterase inhibitors for treatment initiated in patients with moderate Alzheimer's disease was estimated at between £23 000 and £35 000 per QALY, while the cost effectiveness of treatment initiated while patients were still in the mild stages of the disease was estimated at between £56 000 and £72 000.[7] Our analyses indicate donepezil would not only dominate treatment without pharmacotherapy in both subgroups, but also that treatment of patients with mild disease offers additional health benefits and savings relative to initiating therapy only once patients enter the moderate stages of the disease. With roughly 425 000 patients with Alzheimer's disease in the UK,[1] and assuming that at least 75% of these patients are in the mild to moderate stages of the disease,[1] if all patients were treated with donepezil, the base-case results of our simulation

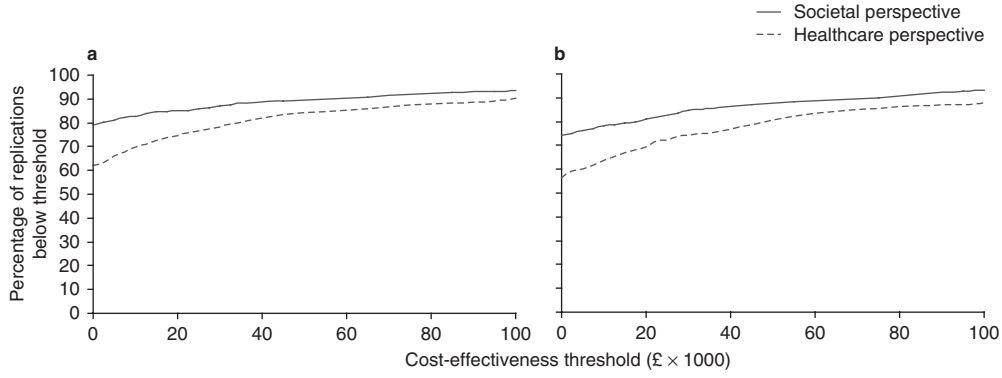

Fig. 4. Cost-effectiveness acceptability curve for patients starting treatment with (**a**) Mini-Mental State Examination (MMSE) scores ≥20 and ≤26 and (**b**) MMSE ≥10 and <20.

would indicate savings in healthcare costs of over £75 million per year, with annual societal savings of over £150 million.

There are a number of reasons why the results presented here differ so significantly from those conducted on behalf of NICE. One of the important differences is that our analyses apply measurements of disease progression on a series of continuous scales – MMSE, NPI, ADL and IADL – as opposed to the model used by NICE, which dichotomized Alzheimer's disease into requiring full-time care and not requiring full-time care. Accordingly, in our analyses, both health utilities and costs are applied on a much finer gradient. This has important implications as the discrete-event simulation allows us to capture benefits over the full course of the disease. While our results are not directly comparable to those conducted on behalf of NICE, both models predict delays in reaching severe stages of the disease of roughly 1.5 to 3 months,[7] while total cost and benefit results differ significantly, suggesting that the ability to capture finer gradients of benefit over the course of the disease has a large impact. In the NICE model, the mean delay to requiring full-time care for donepezil was approximately 2 months. In our analyses, the requirement for full-time care is not modelled as an outcome, but the reduction in time that patients spend institutionalized is roughly 2.5 months. These estimates are in line with previous modelling efforts, which suggest that the delay to institutionalization or full-time care is less than 6 months. The difference in ability to capture benefits over the entire course of the disease has implications not only for the assignment of costs in the model, but also for health utilities. QALY gains for patients receiving donepezil averaged 0.11 per patient. In both the NICE and AHEAD models used to evaluate the cost effectiveness of galantamine,[7,36] QALY gains per patient were significantly lower, averaging about 0.06 per patient.

Another important difference between the models is the incorporation of longitudinal multivariate analyses of disease progression and treatment effects, with treatment effects based on up to 1 year of placebo-controlled data in our model. The analyses conducted on behalf of NICE applied only a fixed mean treatment effect across patients over a single time interval. Unlike the NICE model, our model does not apply an undifferentiated and constant mortality risk, includes stopping rules, considers less than perfect persistence with treatment, and integrates caregiver health directly into the model rather than applying it *post hoc* based on calculations largely external to the model. By using discrete-event simulation and sampling from patient-level data sets to create simulated patients, we were also able to create a much more realistic sample of individuals with demographic and disease characteristics that reflect observed data, rather than sampling from a selection of uncorrelated distributions.

Our simulation also used different data sources from those used in the NICE evaluation, which could also explain differences in results between the two models. Data for health utilities, costs of care, institutionalization and patient profile inputs, all differ between the two models. However, the results of our sensitivity analyses, which indicate that varying these inputs over wide ranges does not substantively alter findings, suggest that it is the differences in modelling techniques and assumptions that has a far greater impact on results than differences in the selection of input data. For example, the NICE evaluation assumed that only 70% of costs associated with institutionalization would be covered by the NHS, and therefore only included 70% of institutional care costs in their analysis. We used the full cost of institutional care in our base-case analyses, but in sensitivity analyses where we reduced this cost by 30%, donepezil remained dominant from both healthcare and societal perspectives.

The results of our simulations suggest that donepezil is cost effective in the treatment of Alzheimer's disease patients if treatment is initiated before patients reach the severe stages of Alzheimer's disease. In deterministic analyses, donepezil dominated no treatment in the base-case analyses and in each of the one-way sensitivity analyses. Probabilistic analyses incorporating parameter uncertainty also yielded favourable results.

As with any model, our simulation does have its limitations, the most important related to availability of data. One of these data restrictions is that the longest duration of head-to-head clinical trial data available was for 1 year.[15] Consistent with many other modelling studies in this area, we have adopted a conservative approach, by assuming that after 1 year, continued treatment serves a maintenance function only, and no further benefits of treatment in terms of slowing disease progression are experienced. Furthermore, we assume that if treatment is discontinued, all benefits are lost within 6 weeks.

Other limitations of the data revolve around assigning costs and utilities associated with different degrees of disease severity. In particular, the cost data for the UK are based entirely on MMSE ranges and do not consider behaviour or function. Furthermore, in order to achieve a finer gradient of costs, we interpolated the cost of care for patients living in the community, creating costs for five severity ranges, based on source data for three ranges. Whether there is a linear relationship between costs and severity for patients with mild, moderate and severe cognitive decline could not be evaluated from the available data, and therefore introduces uncertainty in our estimates. Institutionalization costs are assumed to be the same across all patients. Additional research on direct medical costs for patients living in the community and in institutional care in the UK would be of considerable value and would allow for a more precise assignment of costs in the simulation.

The predictive equations developed for this model have not been validated against external data sets. The model predictions for untreated patients have been compared to expected cognitive outcomes in the CERAD population and provide good fits. Similarly, treatment effect sizes at 24 weeks, the duration of most of the clinical trials, in the simulated population were very close to those observed in the trials, although the simulation does seem to underestimate the treatment effect on IADLs (see the Supplemental Digital Content). However, the CERAD and trial data were used to develop the equations themselves, and therefore do not provide the strongest test of the validity of the equations. In sensitivity analyses, even when treatment effect terms were reduced by 50%, donepezil remained dominant in patients with mild disease, and highly cost effective in patients with disease of moderate severity. Furthermore, sensitivity analyses on key parameters, including the overall rate of change for MMSE using the CERAD equations, indicated that results were consistently favourable for donepezil. Nevertheless validation against a dataset not used to develop the equations would be required for more robust testing and refinement of the equations. The predicted effects of donepezil are based on clinical trial data and it is possible that treatment effectiveness would be different in actual practice.

The probabilistic sensitivity analyses were also subject to a number of limitations. In some cases, variance figures around estimates were unavailable, and a standard error of 25% of the mean was assumed. The analyses also did not consider potential correlations between parameters in the disease progression equations.

Finally, the current analyses conducted only a limited number of scenarios in terms of treatment decisions. Additional analyses evaluating the most efficient use of cholinesterase inhibitors in terms of when, and for how long, treatment should be continued would be valuable.

Conclusion

Despite limitations of the data, these analyses suggest that donepezil is highly cost effective in the treatment of mild to moderate Alzheimer's disease in the UK. The results indicate that to restrict treatment to patients with moderate Alzheimer's disease may not only limit the potential health gains associated with earlier treatment, but also increase the overall cost of caring for patients with Alzheimer's disease. While our model and analyses can undoubtedly be refined, the methodology adopted for these analyses advances on previous work in this area and provides a flexible framework for the economic evaluation of interventions in Alzheimer's disease.

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