The cost-effectiveness implications of suboptimal treatment for different severities of Alzheimer's disease in the UK

Darshan Zala[1] iD, Dennis Chan[2] and Paul McCrone[1]

[1]Department of Health Service and Population Research, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
Correspondence to: D. Zala, E-mail: darshanzala@hotmail.co.uk

Objective: This study aims to evaluate the impact of suboptimal treatment, defined in terms of lower population coverage (percentage of total patient population receiving optimal treatment) and delay to treatment on the cost-effectiveness of pharmacological therapies approved for the treatment of different severities of Alzheimer's disease (AD) in the UK.

Methods: A 5-year Markov model was used to simulate transition to full-time care, as delay and coverage were varied for AD patients with mild-to-moderate and moderate-to-severe dementia. The time-varying predictive equations, resource use, utilities, treatment effects and mortality were derived using published sources.

Results: For the cohort with moderate-to-severe dementia, cost-effectiveness was optimised when delay was minimised and coverage maximised. For mild-to-moderate dementia, results were similar but varied widely depending on the inputted cost of acetylcholinesterase inhibitors.

Conclusions: The average cost-effectiveness of pharmacological treatments for AD is sensitive to delays to treatment and population coverage. The results of this study can inform future healthcare policy in order to maximise cost-effectiveness of pharmacological therapies for AD. Copyright © 2017 John Wiley & Sons, Ltd.

Introduction

Alzheimer's disease (AD) accounts for 60–80% of all cases of dementia in the UK (Alzheimer's Association, 2011). At present, the number of individuals with dementia is estimated to be around 700 000 (Prince *et al.*, 2014), and, in line with the ageing population, this figure is calculated to rise to 1.5 million by 2050. This rise in numbers will be associated with a steep rise in the social and economic costs borne by patients, their caregivers and health and social care services.

The UK National Institute for Health and Care Excellence (NICE) has approved acetylcholinesterase inhibitors (AChEIs) for all severities of AD and the N-Methyl-D-aspartate (NMDA) receptor antagonist memantine for the treatment of moderate-to-severe AD (NICE, 2016). These decisions were based on a review of clinical and economic evidence (NICE, 2011). Most economic evaluations have indicated that these pharmacological treatments are cost-effective (Green *et al.*, 2005; Green, 2007; Cohen and Neumann, 2008; Rive *et al.*, 2010a), primarily as a result of their effect in delaying the requirement for full-time care (FTC) with its attendant high costs.

Studies have suggested that cost-effectiveness is sensitive to early diagnosis and initiation of therapy (Barnett *et al.*, 2014; Banerjee and Wittenberg, 2009; Weimer and Sager, 2009; Getsios *et al.*, 2012), but there has been little research on the effects of coverage. As a result of delays to diagnosis and low rates of diagnosis,

the proportion of undiagnosed AD cases has been estimated to be at least 50% (Weimer and Sager, 2009; National Audit Office, 2007), and the mean delay from onset of symptoms to diagnosis in the UK has been estimated to be around 36 months (Bond et al., 2005).

This analysis aims to assess the cost-effectiveness implications of the suboptimal treatment of AD in the UK. Suboptimal is defined as any divergence from 100% treatment coverage and/or from immediate implementation of NICE recommended pharmacological therapy from the time of diagnosis. Suboptimal treatment can occur as a result of failure to diagnose affected individuals, attribution of incorrect diagnosis to affected individuals (e.g. diagnosis of vascular dementia instead of AD) and failure to initiate treatment at the time of diagnosis.

This study differs from previous work in several ways. First, the model uses already available treatments, rather than hypothetical treatments, in contrast to other analyses (Barnett et al., 2014). Second, because it does not explicitly model a hypothetical 'real world' policy in contrast to other evaluations (Getsios et al., 2012), it allows exploration of a wider variety of scenarios in terms of treatment coverage and delay. Third, the model investigates cost-effectiveness for differing severities of AD dementia. While this study does not directly investigate the service costs associated with increasing treatment coverage and reducing treatment delay, we illustrate how these costs can be integrated with the analysis using examples.

Methods

Original model

The model used in this analysis is an adaptation of the Markov model used in the successful NICE submission of memantine for moderate-to-severe AD in the UK

(Rive et al., 2010a; Rive et al., 2010b). This included replicating the model for a mild-to-moderate cohort, by replacing key parameters. The definition of FTC was based on location of care and an assessment of physical and functional disability (Rive et al., 2010a). A UK cohort of AD patients, with moderate-to-severe dementia, started in pre-FTC and could either remain in this state or transition each month (Sonnenberg and Beck, 1993), from pre-FTC to FTC or from pre-FTC to death.

Populations and treatments

In view of the differing NICE recommended treatments for differing AD severity, the current study modelled two populations: (i) moderate-to-severe AD dementia, 'optimal' treatment memantine being compared with 'suboptimal' treatment (AChEIs alone or no treatment); (ii) mild-to-moderate AD dementia, 'optimal' treatment (AChEIs) compared with 'suboptimal' treatment (no AChEIs).

Adaptations to original model

Two main adaptations were made to the Rive et al., 2010a model for memantine (Figure 1). First, the 5-year time horizon was divided into a suboptimal treatment phase, characterised by ≤100% treatment coverage and/or ≥0 years of delay to optimal treatment, followed by an optimal treatment phase where all patients receive the NICE recommended treatment for their AD severity (1A). Second, the pre-FTC state was split in two: those receiving optimal treatment from the beginning and those receiving suboptimal treatment until the second (optimal) phase of the model (1B). The results from each model included the two standard base-case results. In addition, results from each combination of six levels of incomplete coverage (0%, 20%, 40%, 60%, 80%
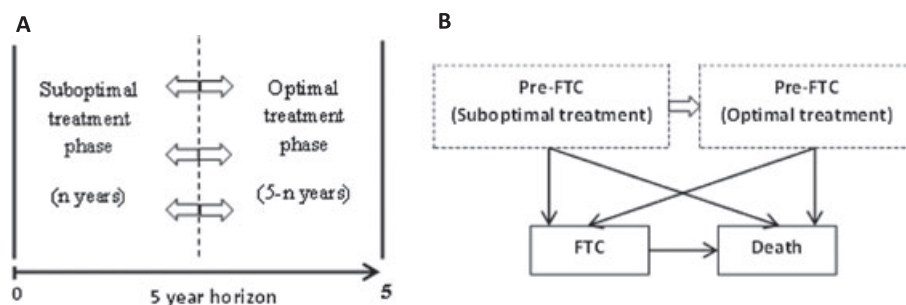
Figure 1 Model timing and schematic. Panel A model time horizon showing demarcation into suboptimal and optimal treatment phases that vary; panel B schematic that shows the transition of patients as disease progresses and movement of patients from suboptimal to optimal treatment. FTC, full-time care.

and 100%) and five different lengths of delay to optimal treatment (1, 2, 3, 4 and 5 years) were produced.

As with the original, the model ran for a total of 60 one-month cycles, and so the time horizon was 5 years. Costs were from a National Health Service (NHS) health and social care perspective and are reported in 2016 British pounds. The primary outcome for patients is the quality-adjusted life year (QALY), which is a measure of survival weighted by utilities that capture individual health-related quality of life

longitudinal epidemiological study (LASER-AD), a cohort of 224 patients comprising a roughly equal mix of mild, moderate and severe AD dementia, with dementia severity defined by scores on the Mini-Mental State Examination (Livingston *et al.*, 2004). The majority of patients were taking AChEIs at baseline (72%). A discrete version of the Cox proportional hazards model with a complimentary log–log specification was fitted (Rive *et al.*, 2010a; Rive *et al.*, 2010b).

$$P_i^{\mathrm{FTC}} = 1 - \exp[-\exp(-11.1343 + 0.0330 * \mathrm{ADAS} - \mathrm{cog_{baseline}} - 0.0877 * \mathrm{ADSC} - \mathrm{ADl_{baseline}} + 0.0377 * \mathrm{NPI_{baseline}} + 0.8122$$
$$* \mathrm{ADAS} - \mathrm{cog_{slope}} - 2.4072 * \mathrm{ADSC} - \mathrm{ADl_{slope}}) * \exp(3.3195 * \ln(\mathrm{end\ month\ of\ interval\ } i))]$$

on a scale from 1 (perfect health) to 0 (death) (Sassi, 2006). All costs and outcomes were discounted at 3.5% per annum.

Data sources

Disease progression and transition to full-time care. The key advantage of this modelling framework is that the covariates in the equation determining the pre-FTC to FTC transition include all of the well-established AD domains (cognition, function, behaviour), as measured by the total scores on the following clinical scales: AD Assessment Scale cognitive sub-score (ADAS-cog), AD Cooperative Study Activities of Daily Living scale (ADCS-ADL) and the Neuropsychiatric Inventory (NPI) total score. The equation was fit to data from the London and South-East Region

Fixed covariates include the baseline values of all three scales and the average monthly rates of change (i.e. slopes) of ADAS-cog and ADCS-ADL. Probabilities of movement to FTC varied with interval *i* and were converted into monthly (per cycle) transition probabilities before being entered into the model.

Baseline scale, slope and treatment effects for the moderate-to-severe model were taken from the original model, and inputting these gave the standard care transition probabilities to FTC (Rive *et al.*, 2010a). Baseline and slope statistics were calculated using moderate-to-severe patients from LASER-AD (Table 1). Baseline statistics for the mild-to-moderate model were taken from the control arm (202 patients with 70% AChEI use) of a 24-week, double-blind trial comparing memantine with AChEIs in a mild-to-moderate AD population (Peskind *et al.*, 2006). Given

Table 1 Predictive equation parameters and treatment effects

Parameters		Model 1: moderate-to-severe AD Mean (SE)	Model 2: mild-to-moderate AD Mean (SE)
Standard care	ADAS-cog baseline	36.30 (1.70)	27.3 (0.69)
	ADCS-ADL baseline	45.00 (1.87)	56.2 (0.93)
	NPI baseline	18.54 (1.86)	12.2 (0.92)
	ADAS-cog slope[a]	0.6116 (0.0809)	0.1667 (0.1033)
	ADCS-ADL slope[b]	−0.7503 (0.0876)	−0.3833 (0.1400)
Treatment effects	ADAS-cog[a]	−1.54 (0.31)	−2.67 (1.22)
	ADCS-AD[b]	1.53 (0.62)	0.9 (0.36)
	NPI[a]	−1.34 (0.93)	−3.51 (0.45)

AD, Alzheimer's disease; ADAS-cog, AD Assessment Scale cognitive sub-score; ADCS-ADL, AD Cooperative Study Activities of Daily Living scale; NPI, Neuropsychiatric Inventory.
[a]Negative change or treatment effect indicates improvement.
[b]Positive change or treatment effect indicates improvement.

that most of the patients were treated with ACHEIs in the LASER-AD cohort that was used to fit the predictive equation, by entering these scale statistics, we obtained time-varying transition probabilities for the optimal treatment arm.

Treatment effects. As in Rive *et al.* (2010a), the transition probabilities for the other treatment arm were obtained by applying a treatment effect additively to the baseline scale parameters but not to the slopes and so assumed there is no disease modifying effect. This is consistent with previous literature and the original published framework (Green *et al.*, 2005; Green, 2007; Cohen and Neumann, 2008; Rive *et al.*, 2010a; Rive *et al.*, 2010b). For the moderate-to-severe AD cohort, treatment effects were weighted mean differences taken from a meta-analysis of 6-month randomised controlled trials most of which compared memantine monotherapy to AChEIs (Rive *et al.*, 2010a; Winblad *et al.*, 2007).

For the mild-to-moderate cohort, meta-analyses for obtaining treatment effects were sought from the published literature in order to satisfy the following conditions: treatment effects combined were around 24 weeks; most of the patients in the combined studies were mild-to-moderate severity; treatment was donepezil, and treatment effects were on their original scales (weighted mean differences). The treatment effect for donepezil on ADAS-cog was taken from a meta-analysis of mainly 6-month randomised controlled trials that compared AChEIs in mild-to-moderate AD patients (Hansen *et al.*, 2008). The treatment effect for donepezil on the NPI was taken from a similar meta-analysis of four trials (Lockhart *et al.*, 2011). No recently published meta-analyses (Hansen *et al.*, 2008; Lockhart *et al.*, 2011; Di Santo *et al.*, 2013; Kobayashi *et al.*, 2015) or trials within these satisfied the conditions for a treatment effect for donepezil on the ADCS-ADL. Therefore, a treatment effect for galantamine from a large 5-month trial was inputted for this scale instead (Tariot *et al.*, 2000). These treatment effects were then 'reversed' (placebo versus AChEI) before being additively applied to scale baselines to produce the transition probabilities for the standard care arm.

Switching to optimal treatment. Depending on the scenario, there will be some patients who are in that proportion of the modelled cohort with treatment coverage and experiencing no delays. These receive the NICE recommended treatment from the beginning and are unaffected by the change in phase; they transition for the 5 years with treatment effects applied from time 0. When patients starting suboptimal treatment reached the second phase and switched to optimal treatment, the assumption was that they continue in the same way as those who received optimal treatment from the beginning— prognosis is independent of previous experience.

Two other assumptions were evaluated during sensitivity analyses. First, at point of switching, treatment effects were applied to baseline scales that had been updated using the monthly rates of change (slopes), and the time variable in the predictive equation was reset to zero. This did not capture the disease progression that occurs independent of any treatment effect and that is so important in modelling AD. In fact, this approach actively 'punished' patients in terms of QALYs and time in pre-FTC for having the optimal treatment from the beginning. Second, treatment effects were again applied to updated baseline scales, but the time variable was not reset. This also implied unrealistic disease progression; over 5 years, switchers were worse off in QALY and time in pre-FTC terms relative to people who received suboptimal treatment from time 0 (standard care arm).

Mortality. As in the original Rive *et al.* (2010a) model, the second transition patients can experience—from pre-FTC or FTC to death—was determined by a survival analysis using a Weibull parameterisation. The assumption of no treatment effect on mortality was maintained. The full LASER-AD cohort not divided by severity was used to fit the equation, and so probabilities of death do not vary by severity model.

Costs. For both models, the mean (SE) monthly costs of care for pre-FTC and FTC were £805 (£217) and £3634 (£284), respectively. The resources used for these states were collected from the LASER-AD study. In each model, monitoring costs associated with the optimal treatments were applied: initial consultation with a specialist at the start of treatment (£139) followed by general practitioner visits every half year (£36). Health state and monitoring costs were updated or adjusted using the hospital and community health services index to reflect 2016 prices (Curtis, 2016). The daily cost of memantine was inputted as £0.053. The assumption that treatments stop when patients enter FTC or death is also continued. For the mild-to-moderate model, the daily cost of donepezil was inputted (£0.055) because this is the most widely prescribed AChEI in the UK (Cooper *et al.*, 2016). These drug costs account for the recent expiration of patents and reflect the current daily costs of these drugs as listed in the British National Formulary

(BNF, 2016). They are substantially lower than previously reported drug costs: memantine at £2.16 (Rive *et al.*, 2010a) and donepezil at £3.18 per day (Getsios *et al.*, 2012). No treatment cost was incurred in standard care in either severity model because it is background therapy for all patients and so makes no difference to incremental costs.

Outcomes. As in the original model, pre-FTC (EQ-5D) utilities were time varying and determined by a generalised linear model fitted to the LASER-AD cohort data (Rive *et al.*, 2010a). As with the predictive equation, treatment effects were applied to baselines and the same assumption about patients that switch was made. The utilities in the FTC state for moderate-to-severe and mild-to-moderate models were means calculated from patient cohorts in FTC with the relevant severity AD: 0.336 and 0.340, respectively (Rive *et al.*, 2010a; Caro *et al.*, 2002).

Net monetary benefit (NMB) is the monetary value of average QALY benefits net of the average costs of treatment, assuming the willingness-to-pay for a QALY is the NICE specified £30 000: NMB = QALYs × £30 000 − costs. Incremental NMB was calculated for optimal care and each scenario as the difference in NMB relative to the NMB for (base-case) standard care.

Results

Base-case results

Table 2 shows base-case deterministic results and the uncertainty around these estimates in terms of standard errors from the probabilistic sensitivity analysis. The optimal treatment in both models dominates standard care—average patient costs are lower and QALYs higher over 5 years. When the costs

inputted were identical to the original publication (Rive *et al.*, 2010a), results in the moderate-to-severe model were also the same. However, with the updated (and higher) input costs, total costs increase in both arms. The difference in costs also increases because of the drop in the price of memantine.

When the previous price of donepezil was inputted, the results for the mild-to-moderate model were similar to the results produced by the models that informed NICE guidance for mild-to-moderate AD (NICE, 2011; Bond *et al.*, 2012): AChEI therapy saved around £600 and increased QALYs by 0.035. With updated costs, AChEI therapy continues to dominate standard care, but cost savings are substantially higher.

Moderate-to-severe scenario results

Figures 2 and 3 show the results for all coverage-delay scenarios (see Appendix A of the Supporting Information). The dashed lines represent the fixed base-case results from Table 2. The relationship between delay and outcomes, with fixed coverage, is non-linear. This is because the predictive equation moves patients to FTC at a non-linear rate, and so the marginal effect of delay on outcomes will vary by level of delay. Coverage has a linear relationship with all outcomes, which can be seen by noting the equal spacing between curves; indeed, when the horizontal axis is coverage instead of delay, the figures yield straight lines. Changing coverage has an additive impact because it involves swapping patients between defined pathways. As coverage increases or delay decreases, beyond a year outcome values tend towards the base-case optimal value.

For the moderate-to-severe cohort, optimal treatment (memantine) for all patients from the beginning provides lowest costs and highest benefits. Delaying treatment increases costs and decreases

Table 2 Five-year (per patient) base-case results

|	Standard care	Optimal	Difference
Model 1: moderate to severe[a] (mean ± SE)			
Total costs (£)	£105 420 ± 9346	£102 020 ± 9313	−£3400 ± 1121
QALYs	1.502 ± 0.092	1.533 ± 0.089	0.031 ± 0.013
Time in pre-FTC (months)	19.8 ± 1.6	21.1 ± 1.7	1.3 ± 0.4
Model 2: mild to moderate (mean ± SE)			
Total costs (£)	£62 988 ± 6170	£58 545 ± 5599	−£4443 ± 1030
QALYs	1.958 ± 0.108	2.004 ± 0.110	0.047 ± 0.014
Time in pre-FTC (months)	34.8 ± 2.2	36.5 ± 2.0	1.7 ± 0.4

QALY, quality-adjusted life years; FTC, full-time care.
[a]The deterministic and probabilistic results are virtually identical with the Rive *et al.* (2010a) model when cost inputs are the same. The results presented here are shown for the updated cost inputs and drug costs that reflect modern prices.
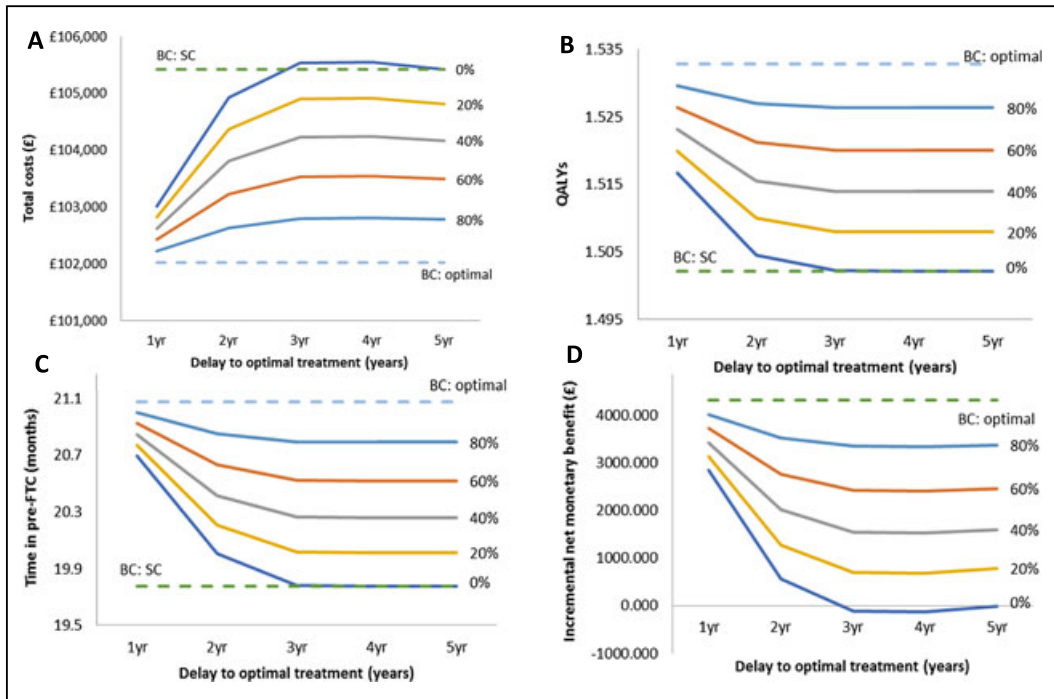
Figure 2 Moderate-to-severe model (per patient) results: coverage and delay in treatment scenarios. Panel A average total costs over 5 years; panel B average quality-adjusted life years (QALYs); panel C average time (months) spent in pre-full-time care (FTC) state; panel D average incremental net monetary benefit relative to base-case (BC) standard care (SC). [Colour figure can be viewed at wileyonlinelibrary.com]
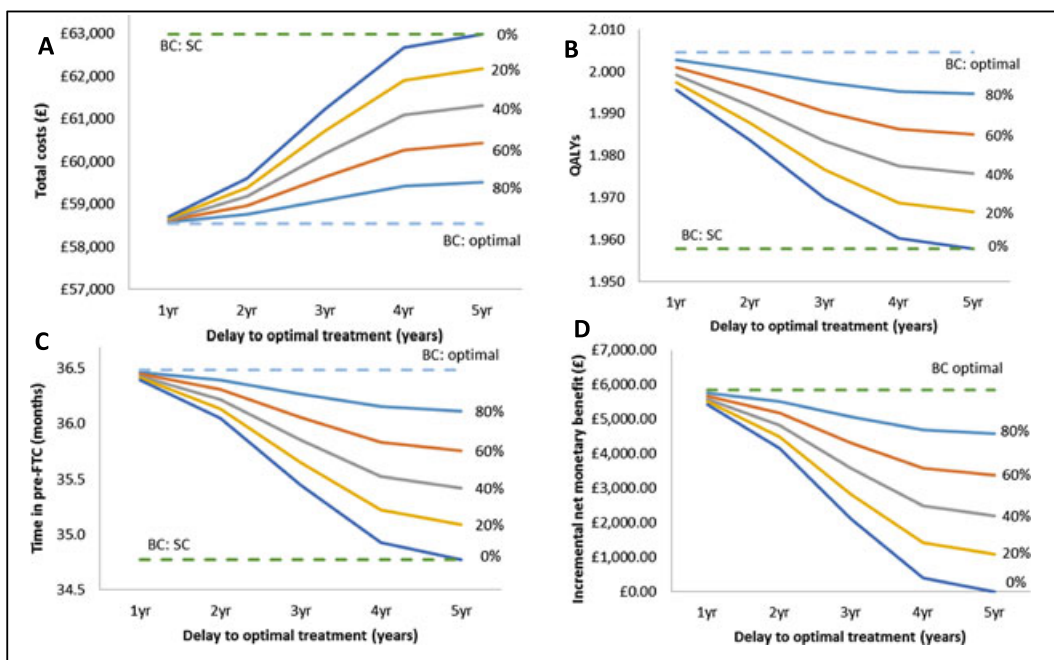
Figure 3 Mild-to-moderate model (per patient) results: coverage and delay in treatment scenarios. Panel A average total costs over 5 years; panel B average quality-adjusted life years (QALYs); panel C average time (months) spent in pre-full-time care (FTC) state; panel D average incremental net monetary benefit relative to base-case (BC) standard care (SC). [Colour figure can be viewed at wileyonlinelibrary.com]

benefits but at a decreasing rate. Leaving patients without optimal treatment also increases costs and decreases benefits.

Published estimates place untreated AD at around 50% (Getsios *et al.*, 2012; National Audit Office, 2007) and average delays to diagnosis at 3 years (Bond *et al.*, 2005). Assuming this as the status quo, pursuing a strategy of early diagnosis with all patients receiving optimal treatment immediately, we would expect an average saving of up to £1856 over 5 years. We would also expect average NMB to increase by up to £1893. As another example, if delay was 3 years for the typical patient and a programme increased coverage from 50% to 55%, incremental NMB would increase by £175. This would be an upper limit; an average cost figure associated with the programme, true negative cases and false positive cases would have to be subtracted.

Mild-to-moderate scenario results

For the mild-to-moderate cohort, all results are similar to the moderate-to-severe cohort—average benefits decrease and costs increase with delays to treatment (AChEIs) and proportion left untreated (3B and 3C). Relative to the moderate-to-severe model, these outcomes changed more slowly and did not level off with later delays. Assuming that at present 50% of cases go undiagnosed and average delay is 3 years, if all patients were to receive treatment without delay, we would expect cost savings of up to £1375 and an increase in NMB of around £1902.

When the older price for donepezil is inputted, coverage-delay scenarios are drastically different (see Appendix B of the Supporting Information). Increasing coverage is actually punished in cost terms for delays up to around 3 years, and after this turning point, the relationship between coverage and cost is reversed. Any proportion of patients left untreated for delays to AChEI treatment up to 3 years will yield lower average costs than the scenario where all patient receive AChEI treatment from time 0. The most cost-effective strategy was a delay in AChEI treatment for everyone for some point up to 1 year. Inputting the older price for memantine did not change the results of the moderate-to-severe model a great deal.

Discussion

This study aimed to investigate how changes in delay, coverage and disease severity determine the cost-effectiveness of pharmacological treatments for AD. Cost results are different for each severity cohort,

despite treatment costs being very similar and monitoring, pre-FTC and FTC input costs being identical. Total costs are a balance between two processes: direct treatment (drug and monitoring) costs increase with lower delays and higher coverage, but these increases are offset by lower health state costs as patients move more slowly into expensive FTC. The balance between these processes is determined by the equation that predicts movement to FTC, and it predicts very different rates of movement over time for each cohort (Appendix C of the Supporting Information).

Getsios *et al.* (2012) evaluated early assessment in the UK for suspected mild-to-moderate AD, defined as more frequent reassessment within the current diagnostic pathway. In the Getsios *et al.* base-case, the time to diagnosis (and donepezil treatment) was set at 36 months in the latter strategy. Both Figure 3 and the analysis in which the price of donepezil is set to the higher price reported in Getsios *et al.* (Appendix B of the Supporting Information) suggest that when starting from a delay of 3 years (at any coverage), there are gains in cost-effectiveness from any combination of decrease in delay and increase in coverage. Therefore, this study is consistent with previous work: early assessment—as defined in Getsios *et al.*—increases cost-effectiveness.

The main limitation of the framework—as with almost all models in AD—was the assumption that the (6-month) treatment effects were maintained over the model duration. The LASER-AD cohort was composed of only patients residing in urban areas, and so there may be some issue with generalising the results to the entire UK population. In the moderate-to-severe model, both the original model publication (Rive *et al.*, 2010a) and this study are suggesting that memantine monotherapy is the active treatment being modelled. There is some concern that the applied treatment effect may be biased because two of the six trials used in the relevant meta-analysis (Winblad *et al.*, 2007) included background treatment with donepezil. However, there is little clinical evidence that monotherapy and combination therapy differ in efficacy (NICE, 2011). A more general criticism is that other modelling approaches (e.g. discrete event simulation) are better at capturing the heterogeneous nature of AD progression. However, the use of time-varying probabilities (and utilities) based on predictive equations fit to individual-level data can compensate for the disadvantages of Markov modelling.

More caution needs to be taken in interpreting the outputs for the mild-to-moderate AD model. First, the LASER-AD cohort contained AD patients of all severities, but the fitted equation was used separately

in the two differing severity cohorts to predict movement to FTC. Second, the modelled trial cohort (Peskind *et al.*, 2006) was based in the USA and may not be entirely representative of the UK population (Herrmann *et al.*, 2015; Dodel *et al.*, 2015). Third, the cohort used to fit the predictive equation (LASER-AD) is different from this modelled cohort, unlike in the moderate-to-severe analysis. Fourth, the calculated scale slopes were based on 24-week change, which may misrepresent disease progression. However, as suggested, the results for the mild-to-moderate model are in line with previous work.

In final conclusion, QALYs would be increased in both severity groups by programmes designed to improve coverage and reduce delay to optimal treatment. Such programmes and the related technology (Blackwell *et al.*, 2004; IXICO, 2014; Heister *et al.*, 2011) also have good potential to be cost saving by reducing delay to NICE recommended treatment. This conclusion has been strengthened by the recent expiration of patents and subsequent low cost of approved pharmacological treatments for AD in the UK.

Ethics statement

Ethical approval was not required. This study did not involve research on human subjects, and so no ethics approval was sought.

Conflict of interest

None declared.

Key points

- The suboptimal pharmacological treatment of AD in the UK can be defined in terms of low coverage (percentage of total patient population receiving treatment) and excessive delay to treatment.
- Quality of life was maximised and costs minimised in both severity groups (mild-to-moderate and moderate-to-severe AD) when delay was minimised and coverage maximised.
- For the mild-to-moderate AD group, these results were highly sensitive to the inputted cost of approved treatment (AChEIs).
- When the previous (higher) price of donepezil was used for the mild-to-moderate AD group, cost-effectiveness was no longer maximised by minimising delay and maximising coverage.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table A.1. Results for all coverage-delay scenarios and both severities

Figure B.1. Moderate-to-severe model (per patient) results with previous drug price: coverage and delay in treatment scenarios with Memantine at £2.16 per day. Panel A average total costs over 5 years; Panel B average QALYs; Panel C average time (months) spent in pre-FTC state; Panel D average incremental net monetary benefit relative to BC standard care (BC = base-case, SC = standard care)

Figure B.2. Mild-to-moderate model (per patient) results with previous drug price: coverage and delay in treatment scenarios with Donepezil at £3.18 per day. Panel A average total costs over 5 years; Panel B average QALYs; Panel C average time (months) spent in pre-FTC state; Panel D average incremental net monetary benefit relative to BC standard care (BC = base-case, SC = standard care)

Figure C.1. Probability of movement to FTC for moderate-to-severe AD patients

Figure C.2. Probability of movement to FTC for mild-to-moderate AD patients

Figure C.3. Proportion of patient cohort in pre-FTC (moderate-to-severe AD patients)

Figure C.4. Proportion of patient cohort in pre-FTC (mild-to-moderate AD patients)