The Challenge of Demonstrating Cost Effectiveness in Alzheimer's Disease in England: Case Study of a Hypothetical Emerging Treatment

Treharne C, Spencer C
Mtech Access, Bicester, UK

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Introduction

- Alzheimer's disease (AD) is a progressive neurological disease, characterised by deterioration in patient cognition, function and behaviour (1)
- Dementia and AD are the leading cause of death in England, UK, accounting for 11.6% of all registered deaths in February 2022 (2)
- The risk of AD and other types of dementia increases with age, affecting 1 in 14 people over the age of 65, and 1 in every 6 people over the age of 80 (1); it is estimated that there are currently 944,000 people in the UK living with dementia (3)
- The total cost of dementia is approximately £25 billion in the UK, of which £1.7 billion are healthcare costs, £12.5 billion are social care costs, and £10.2 billion are informal care costs (4)
- Currently, the treatments available for AD do not slow or stop the progression of the disease (they are not disease-modifying), but, rather, are focused on symptom management
- Current National Institute for Health and Care Excellence (NICE, 2018) guidelines recommend the use of donepezil, galantamine, rivastigmine for mild to moderate AD, and memantine for moderate to severe AD in adults (5)

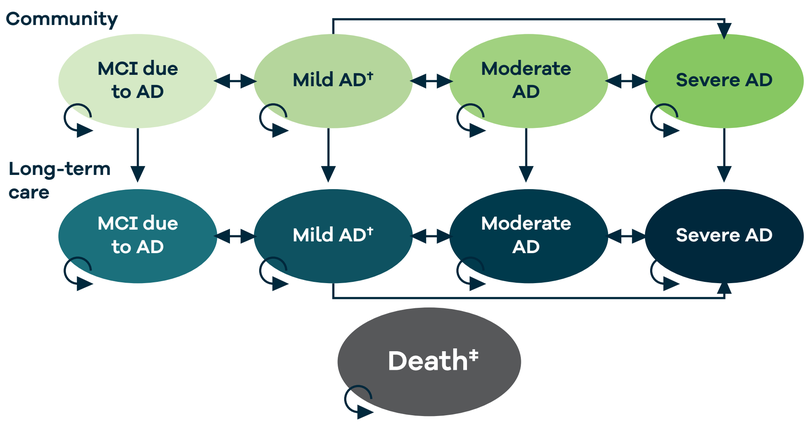
Objectives

- This analysis aimed to identify cost-effective treatment profiles for a hypothetical emerging treatment (HET) for patients with mild AD, from an English NHS perspective
- This analysis further aimed to understand the key drivers of cost effectiveness in AD

Methods

- A lifetime Markov model was developed to estimate costs and health outcomes for patients with mild AD treated with current standard of care (SoC [donepezil and memantine]) versus a HET
- The model structure was based on the Institute for Clinical and Economic Review evidence review for aducanumab, with five health states representing increasing AD severity (mild cognitive impairment [MCI] due to AD, mild AD, moderate AD, severe AD and death) (6) (Figure 1)

Figure 1: Markov model structure



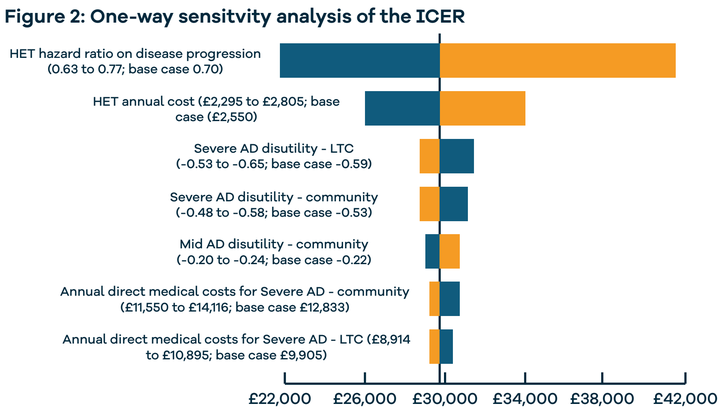
Abbreviations: AD, Alzheimer's Disease; MCI, mild cognitive impairment.
†Model entry. ‡Patients can die from any health state. Death is an absorbing state.

- Setting of care was also tracked. Patients had an annual health-state-specific probability of transitioning from the community to long-term care (LTC). It was assumed that once in LTC, patients remained there until death
- Treatment was assumed to slow disease progression, modelled via a hazard ratio (HR) applied to natural history data from Potashman et al (7)
- Patients were assumed to discontinue treatment when they reached severe AD in line with the aducanumab Institute for Clinical and Economic Review analysis (6). No other discontinuation was modelled
- We obtained clinical data, cost (direct medical) and utility inputs from literature and UK data sources (3,6,8,9)
- The model incorporated age-adjusted utility based on the published Ara and Brazier algorithm (10)
- Standardised mortality ratios (SMR) were applied to the general population mortality in each health state. More severe health states were associated with higher mortality (11)
- We used two-way sensitivity analysis to explore cost-effective treatment profiles at willingness-to-pay thresholds of £20,000 and £30,000, and one-way sensitivity analysis was used to determine drivers of cost effectiveness
- Costs and outcomes were discounted at an annual rate of 3.5% in line with NICE methods (12)

Results

For an emerging treatment with HRs on disease progression of 0.9, 0.7, and 0.5 versus SoC, the maximum annual treatment costs at a willingness-to-pay threshold of £30,000 were £825, £2,550, and £4,400, respectively (Table 1). At a maximum willingness-to-pay threshold of £20,000, the corresponding maximum annual treatment costs were £590, £1,800, and £3,100, respectively

Figure 2: One-way sensitvity analysis of the ICER



Abbreviations: AD, Alzheimer's Disease; HET, hypothetical emerging treatment; LTC, long-term care.

Table 1: Two-way sensitivity analysis of the ICER for hypothetical AD treatment profiles

Annual HET cost	Hazard ratio versus natural history: 0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
£1,000	Dominant	Dominant	£124	£1,218	£2,666	£4,803	£8,365	£15,526	£37,116
£2,000	£2,656	£4,130	£5,769	£7,835	£10,681	£14,953	£22,109	£36,504	£79,866
£3,000	£7,111	£9,080	£11,414	£14,451	£18,697	£25,102	£35,853	£57,481	£122,615
£4,000	£11,566	£14,030	£17,059	£21,068	£26,713	£35,252	£49,598	£78,458	£165,365
£5,000	£16,021	£18,980	£22,704	£27,685	£34,728	£45,402	£63,342	£99,436	£208,115
£6,000	£20,476	£23,929	£28,349	£34,302	£42,744	£55,552	£77,086	£120,413	£250,865
£7,000	£24,931	£28,879	£33,993	£40,918	£50,760	£65,702	£90,830	£141,390	£293,615
£8,000	£29,386	£33,829	£39,638	£47,535	£58,775	£75,852	£104,575	£162,368	£336,365
£9,000	£33,841	£38,779	£45,283	£54,152	£66,791	£86,002	£118,319	£183,345	£379,114
£10,000	£38,296	£43,729	£50,928	£60,769	£74,807	£96,152	£132,063	£204,322	£421,864

Abbreviations: AD, Alzheimer's Disease; HET, hypothetical emerging treatment; ICER, incremental cost-effectiveness ratio.

- A one-way sensitivity analysis was conducted for a HET profile with a HR of 0.7 and a cost of £2,550 (Figure 2). All relevant input parameters were varied ±10%
- Apart from the HET efficacy (HR on disease progression) and annual treatment cost parameters, the biggest drivers of the analysis were the disutility values applied to the severe AD and mild AD health states and the severe AD health state costs. However, the impact of these parameters on the incremental cost-effectiveness ratio (ICER) was much smaller (<4%) than that of the HR on disease progression (up to 38%) or the annual treatment cost (12%)
- For the same HET profile, the impact on the ICER when considering different perspectives on costs and outcomes was further explored. This included incorporating social care costs, caregiver productivity losses and caregiver disutility (Table 2)
- When all these elements were included within the base case, the ICER reduced by 13%. The inclusion of social care costs had the biggest individual impact on the ICER

Table 2: Scenario analysis varying the perspective on costs and outcomes

Scenario #	Scenario	ICER	Change in ICER from baseline (£29,669/QALY)
1	Inclusion of social care costs	£26,523	-10.6%
2	Inclusion of caregiver productivity losses	£29,047	-2.1%
3	Inclusion of caregiver disutility	£29,543	-0.4%
4	1 + 2	£25,901	-12.7%
5	1 + 2 + 3	£25,791	-13.1%

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Conclusion

- Using established AD modelling approaches, a range of cost-effective profiles for a HET for the treatment of early AD were identified. The analysis suggests that a commercial arrangement would likely be required for a HET to be considered cost effective from an English NHS perspective. Any diagnostic cost associated with identifying eligible patients would also impact the economically justifiable price; this was not considered as part of the current analysis, but may be significant (e.g. positron emission tomography or magnetic resonance brain imaging or cerebrospinal fluid sampling)
- Perhaps unsurprisingly, the biggest drivers of cost effectiveness were treatment efficacy (defined as a HR on disease progression) and annual treatment cost for a HET. The inclusion of social care costs reduced the ICER by 10%, while the inclusion of caregiver disutility only had a minimal impact on the ICER (-0.4%)

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Abbreviations

AD, Alzheimer's disease; HET, Hypothetical emerging treatment; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; LTC, Long-term care; MCI, Mild cognitive impairment; NICE, National Institute for Health and Care Excellence; SMR, Standardised mortality ratio; SOC, Standard of care

(Stand No. X2-304)

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