Appendix B. Systematic literature review of economic models for dementia

Background

To understand the challenges associated with disease-modifying dementia treatments, a scoping search was carried out to identify published systematic literature reviews of economic models for dementia treatments. The most relevant one identified by the scoping search was a study by Nguyen et al. carried out in 2018(Nguyen et al., 2018). Therefore, a systematic literature review was carried out to identify studies published from early 2018 onwards for all treatments for dementia.

Methods

A search was carried out in June 2023 in the following databases:

- MEDLINE(R)ALL
- Embase
- Cochrane Database of Systematic Reviews
- INAHTA International HTA database

The search was limited to English language and to studies from January 2018 onwards as previous reviews evaluated economic models published before this date (Hernandez et al., 2016; Nguyen et al., 2018). Animal studies and conference abstracts were removed.

Key search terms combined terms for the target condition (Alzheimer's disease, cognitive impairment or dementia) and study design (cost-utility, cost-effectiveness, cost-benefit, cost-consequence and cost-comparison studies). The detailed search strategies are presented in Appendix B.1

Table 1. Inclusion and exclusion criteria for studies

	Inclusion criteria	**Exclusion criteria**
Population	Persons with a diagnosis of Alzheimer's disease, dementia or cognitive impairment in all settings	Studies of persons with no diagnosis of Alzheimer's disease, dementia, or cognitive impairment. Studies for interventions for caregivers only.
Interventions	Pharmacological treatments for Alzheimer's disease, cognitive impairment or dementia.	Studies assessing interventions exclusively for caregivers
Comparators	Any comparator or no intervention	None
Outcomes	Total and incremental cost and health outcomes, incremental cost-effectiveness ratios (ICERs).	Studies that do not report any of the outcomes of interest.
Type of studies	Full economic evaluations (including cost-utility, cost-effectiveness, cost-benefit and cost-consequence studies), and cost-comparison studies that include an appropriate demonstration of equal effectiveness.	Partial economic evaluations, modelling studies that predicted epidemiological outcomes over time without an economic evaluation, poster abstracts that did not provide sufficient methodological detail, letters to the editor, commentaries.

EPPI Reviewer 5 was used to export and store records from each database. Results were screened against the selection criteria based on their titles and abstracts by one reviewer, and a randomly selected 10% were reviewed by a second reviewer. Full-text review was carried out independently by both reviewers. Data extraction was completed by one reviewer and checked by another for consistency.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram is provided in Figure 1. The database searches returned 5,863 hits, after deduplication there was a total of 3,645 titles and abstracts for initial screening. After screening, 3,585 records were excluded, and 60 studies were selected for full-text review. After full-text reviewing, 17 studies meeting the inclusion criteria were included. A summary of the included studies is provided in Table 1.

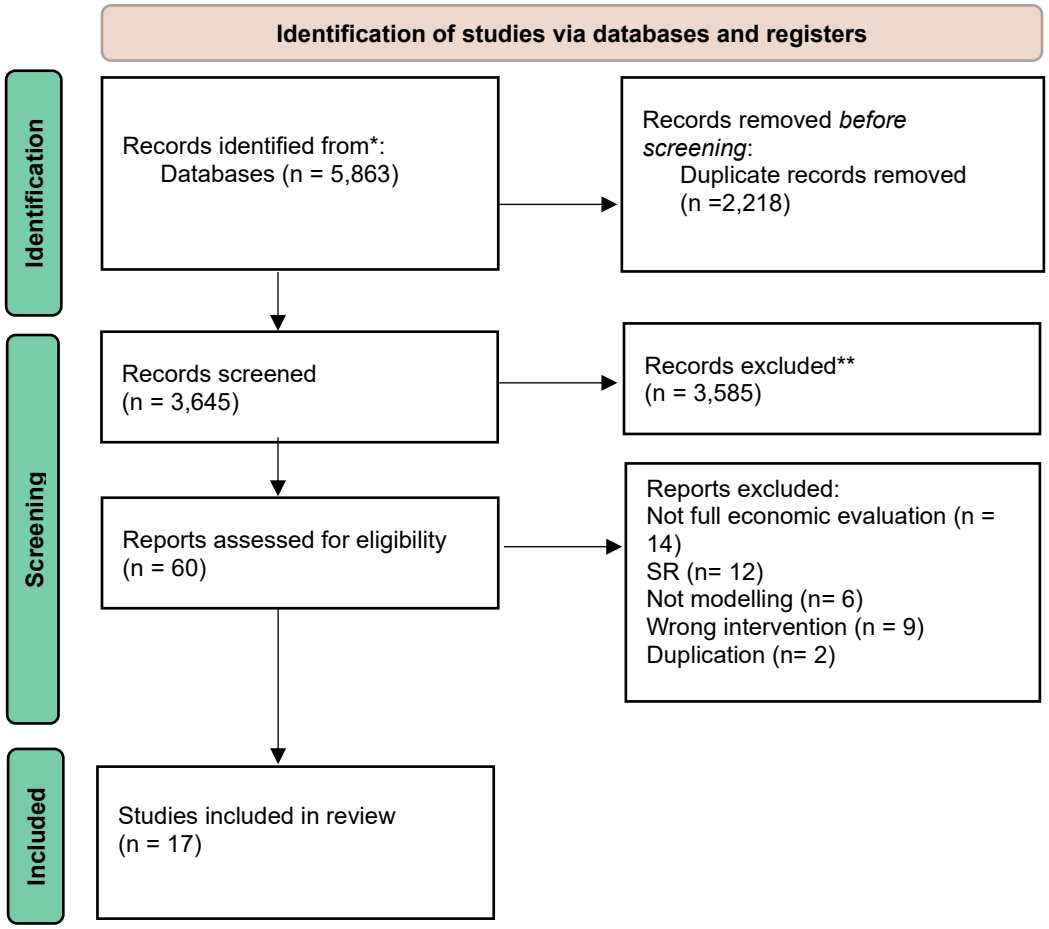

Figure 1. PRISMA diagram

Included studies

All the studies focused on Alzheimer's Disease (AD) dementia and conducted cost-utility analyses of AD treatments. Most studies were US-based (n= 9) while two studies were from the UK. A form of societal perspective was used in the majority of the studies (n=11), but the included costs and health outcomes differed. Some studies (n=4) defined the perspective as "modified societal perspective", "adjusted societal perspective" or "limited societal perspective". The healthcare perspective was used in six studies.

The pharmacological treatments assessed across the studies were aducanumab (n=3), donepezil (n=3), lecanemab (n=3), combination of memantine with donepezil, galantamine and rivastigmine (n=2), roflumilast (n=1), donanemab (n=1) and a hypothetical treatment was evaluated in five studies. The comparator was supportive care (n= 3), no treatment (n=5), and standard care (n=9). In two studies, standard care included psychosocial support, alongside cholinesterase inhibitors in one and annual re-testing of cognitive and functional performance in the other while it was not defined in seven studies.

Modelling details

Model design

Markov cohort modelling was used in 9 studies while the remaining 8 studies applied patient-level simulation. Most studies included health states for mild cognitive impairment (MCI), mild, moderate, and severe AD, death. Two models were built based on the care needs of the patients, including health states pre-full-time care and full-time care states (Youn et al., 2019; Zala et al., 2018). Additionally, four models tracked the setting of care at each health state (Igarashi et al., 2023; Ito et al., 2021; Tahami Monfared et al., 2022; Whittington et al., 2022). Disease progression was defined based on disability assessment for dementia, Mini-Mental State Exam (MMSE), and neuropsychiatric inventory in one model (Kongpakwattana & Chaiyakunapruk, 2020). MMSE was used to define severity in 12 other models too (da Silva et al., 2019; Green et al., 2019; Handels, Grimm, et al., 2023; Igarashi et al., 2023; Ito et al., 2021; Tafazzoli

et al., 2018; Tahami Monfared et al., 2022, 2023; Whittington et al., 2022; Wimo et al., 2020; Youn et al., 2019; Zala et al., 2018).

Model inputs

Included costs

Included costs varied between different economic evaluations, depending on the study design and setting. From the healthcare perspective, cost of medication, lab tests, and outpatient medical follow-up were included. Additionally, the costs of treatments for depression, lung infection and femoral fracture were also included in one study (da Silva et al., 2019). Diagnostic costs were included in five studies (da Silva et al., 2019; Handels, Wesenhagen, et al., 2023; Igarashi et al., 2023; Ross et al., 2022; Wimo et al., 2020) although one of them included cerebrospinal fluid (CSF) analysis only and excluded the cost of lumbar puncture (Handels, Wesenhagen, et al., 2023). In two studies it was unclear whether the diagnostic costs were considered (Green et al., 2019; Tafazzoli et al., 2018). Direct non-medical expenses were also considered in some studies, such as transportation (Kongpakwattana & Chaiyakunapruk, 2020). The costs of treating amyloidrelated imaging abnormalities (ARIA) was considered in the base-cases of five studies while no other side effect was incorporated (Igarashi et al., 2023; Ross et al., 2022; Tahami Monfared et al., 2022, 2023; Whittington et al., 2022). Additionally, the costs of adverse events were included in the scenario analysis of one study without any specification (Kongpakwattana & Chaiyakunapruk, 2020).

The cost of formal and informal care was included in all studies except five (da Silva et al., 2019; Sinha & Barocas, 2022; Tafazzoli et al., 2018; Youn et al., 2019; Zala et al., 2018).This included both direct medical costs for caregivers (e.g., medications, hospitalizations, outpatient visits) and caregiver time and productivity costs (Green et al., 2019; Ito et al., 2021).

Health outcomes

Key outcomes of interest in the studies were survival and quality-adjusted-life-years (QALYs). Most studies (n=6) used health utilities estimated by Neumann et al (1999), those reported by Landeiro et al (2020)were used in five studies while three other

sources were used in the remaining studies (Ashizawa et al., 2021; Reed et al., 2017; Sullivan & Ghushchyan, 2006). EQ-5D was the most common measure of health utilities used in 10 studies while HUI-II was used in six studies.

Around half the studies explicitly reported including the quality-of-life (QoL) impacts on carers in the models (n=7). Two studies justified the omission of carers' QoL impacts based on previous studies which reported no difference in carers' QoL (Kongpakwattana & Chaiyakunapruk, 2020; Ross et al., 2022). The impacts of adverse events on quality of life were not considered in most studies except five (Igarashi et al., 2023; Ross et al., 2022; Tahami Monfared et al., 2022, 2023; Whittington et al., 2022). The only adverse effect considered was ARIA, which was consistent with the evidence provided in a recent meta-analysis and the disutility assumed was that of experiencing a headache which is the main symptom of ARIA (Avgerinos et al., 2021).

Modelling assumptions

Studies used different modelling assumptions that might have impacted on the findings. Some evaluations used important assumptions on clinical effectiveness. For instance, in one model, it was assumed that the impact of aducanumab and donanemab on relative reduction in disease progression was equal to the improvement in mean score on a cognitive and functional scale (Ross et al., 2022). Similarly, the studies made different assumptions regarding treatment discontinuation due to adverse events, progression into severe states, consent withdrawal, or other reasons. For example, one study did not model discontinuation explicitly (Yunusa et al., 2021), allowing patients to progress through disease stages but without specifying rules for stopping treatment, another one assumed treatment would stop if patients progressed into the severe AD state (Green et al., 2011) while others incorporated annual discontinuation rates which included discontinuation due to all reasons in addition to disease progression (Igarashi et al., 2023; Tahami Monfared et al., 2022, 2023; Whittington et al., 2022).

Some studies had assumptions regarding the relationship between surrogate endpoints and the key clinical outcomes. For instance, all three studies evaluating lecanemab employed amyloid level as a surrogate endpoint to predict Clinical Dementia Rating

Sum of Boxes (CDR-SB)(Igarashi et al., 2023).Additionally, the evaluation by Whittington (2022) used CDR-SB to define aducanumab's effect on health state transitions (i.e. disease progression) where evidence on health state transitions was not available. Handels et al. (2023) relied on a word learning test as an indication of the patient-relevant outcome of dementia onset. Although these assumptions were based on published literature, limitations of those studies should be considered.

A recent phase 3 trial showed that lecanemab improved CDR-SB in individuals with early AD (van Dyck et al., 2022). The studies evaluating lecanemab justified using amyloid levels as a surrogate outcome relying on two key publications; a meta-analysis by Avgerinos et al. (2021), and a longitudinal study by Fletcher et al. (2018). The meta-analysis of monoclonal antibodies against amyloid-beta showed a trend towards improvement on CDR-SB, but the effect was not statistically significant (Avgerinos et al., 2021). It did report however, that aducanumab individually resulted in a small but statistically significant improvement on CDR-SB and that bapineuzumab, gantenerumab and crenezumab did not improve any clinical outcomes. However, confidence intervals were not provided. Fletcher et al. (2018) showed that amyloid has early direct effects on medial temporal atrophy and cognition that continue into later stages, in addition to later indirect effects mediated by neocortical tau and atrophy. Thus, although reducing amyloid appears correlated with some cognitive benefits, the effects are small, suggesting other factors are also involved.

Another assumption made by most of the modelling studies of amyloid-targeting treatments was that the treatment effect is maintained as long as amyloid levels were reduced with continued treatment. However, the data available from clinical trials were limited to a couple of years.

Cost-effectiveness

The cost-effectiveness outcomes varied based on the intervention evaluated, the setting and the methods employed. The evaluated medications were found cost-effective in four studies and not cost-effective in five studies. Five studies assessed hypothetical

treatments (Green et al., 2011; Handels, Wesenhagen, et al., 2023; Ito et al., 2021; Tafazzoli et al., 2018; Wimo et al., 2020) so their results are more important in assessing factors impacting cost-effectiveness. The outcome was inconclusive in one (Tahami Monfared 2022) and mixed depending on the drug combinations in two ((Kongpakwattana & Chaiyakunapruk, 2020; Yunusa et al., 2021).

All three studies evaluating the cost-effectiveness of lecanemab reported favourable findings, one in Japan (Igarashi et al., 2023) and two in the USA (Tahami Monfared et al., 2022, 2023). However, all three studies did not include the cost of the drug hence their final findings are not clear.

As for aducanumab, three economic evaluations reported the medication as not cost-effective in US-based estimates (Ross et al., 2022; Whittington et al., 2022; Youn et al., 2019). From the healthcare perspective, the annual cost of aducanumab needed to be $270 to be considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY, and $2,560 at a WTP threshold of $100,000 per QALY (Whittington et al., 2022). Ross et al. (2022) estimated the value-based price of aducanumab to be $2,000 per year from a health care perspective and $3,000 per year from a societal perspective. Similarly, Whittington et al. reported that from the healthcare perspective, the annual cost of aducanumab should be $2,950 to be cost-effective at $100,000 WTP and $5,110 at $150,000 WTP (Whittington et al., 2022). However, this figure was estimated as $22,820/year in another evaluation for aducanumab to be deemed cost-effective compared to standard care (Sinha & Barocas, 2022). This was probably because the latter assumed that aducanumab was 100% effective in halting progression and did not use data from clinical trials while Whittington et al. (2022) used data from the trials. Additionally, Ross et al. (2022) also concluded that donanemab was not cost-effective in in the USA, with an ICER of $193,000 per QALY from a healthcare perspective and $176,000 per QALY from a societal perspective. The value-based price of donanemab was estimated at $17 000 and $22 000 per year from the healthcare and societal perspective, respectively. However, this model was based on the phase II trial data and not data from the phase III trial since it was not yet available.

In three economic evaluations, the medication donepezil was found to be cost-effective when compared to no intervention in Brazil (da Silva et al., 2019), the UK (Youn et al., 2019) and Thailand (Kongpakwattana & Chaiyakunapruk, 2020). Additionally, donepezil was shown to dominate rivastigmine (da Silva et al., 2019). Moreover, the combination therapy of donepezil and memantine was found to be superior to best supportive care in terms of both cost and effectiveness (Youn et al., 2019). Important to note that donepezil was found cost-effective in Thailand from a societal perspective although it was not cost-effective from a healthcare perspective (Kongpakwattana & Chaiyakunapruk, 2020).

Two studies evaluated the cost-effectiveness of memantine in combination with cholinesterase inhibitors (ChEIs) in the UK (Zala et al., 2018) and USA (Yunusa et al., 2021). Zala et al. (2018) found that the average patient costs were lower and QALYs higher over 5 years with Memantine in addition to acetylcholinesterase inhibitors (AChEIs) compared to monotherapy or no intervention in the UK. In the study by Yunusa et al. (2021), rivastigmine transdermal patch yielded the highest number of QALYs of 2.25 QALYs and an ICER of $93,307/QALY versus donepezil monotherapy while memantine was dominated by donepezil.

Sensitivity analysis

The sensitivity analyses conducted in the economic models have provided valuable insights into the robustness of the findings and the potential impact of various uncertainties. The studies employed different methods, including probabilistic sensitivity analysis (PSA), one-way sensitivity analysis, and scenario analyses, to explore the influence of specific parameters on the outcomes. Uncertainties around the estimates were explored in all studies except one (Youn et al., 2019).

Overall, the studies indicate that cost of the medications, clinical effectiveness, time horizon and the analysis perspective had considerable impacts on the cost-effectiveness outcomes. For example, Sinha et al. (2022) reported that the ICER ranged from $128,520/QALY at a time horizon of 30 years to $731,660/QALY at a time horizon of 3 years in the sensitivity analyses. Similarly, Tahami Monfared et al. (2023)

demonstrated that changing the time horizon from lifetime to 5 years significantly reduced the value-based price estimates by 84% and 75% from the healthcare and societal perspectives, respectively.

Discussion

The systematic review examined 17 economic evaluations of medications targeting mild cognitive impairment (MCI) or dementia for AD, evaluating their cost-effectiveness based on various interventions and methodologies. All the included studies conducted cost-utility analyses, and the most common perspective was the societal perspective.

The cost-effectiveness outcomes varied based on the interventions evaluated and the methods employed. Donepezil, lecanemab and memantine in combination with cholinesterase inhibitors were found to be cost-effective in some studies. Aducanumab, on the other hand, was mostly reported as not cost-effective in US-based estimates.

The assumptions made in the economic models could impact the cost-effectiveness outcomes. Some studies made key assumptions regarding clinical effectiveness, such as the impact of medications on disease progression and surrogate endpoints predicting clinical outcomes. For example, Sinha et al. assumed that aducanumab completely halts progression (i.e. effectiveness of 100%), which led to a substantially lower ICER per QALY estimate compared to the evaluation conducted by Whittington et al (2022). Assumptions about the continuation of benefits of treatments beyond the duration of clinical trials were also prevalent.

Sensitivity analyses showed that parameters such as the cost of medications, clinical effectiveness, time horizon, and analysis perspective had considerable impacts on the cost-effectiveness outcomes.

Similar to our findings, the previous systematic reviews of economic models identified some issues including justification of key model components, data selection, comprehensive assessment of uncertainty, model validation, and consistency (Green et al., 2011; Nguyen et al., 2018). Most studies in the previous review of dementia

treatments focussed on AD (n= 42) except one that evaluated treatments for vascular dementia (Nguyen et al., 2018). This was paralleled in our review since all the studies focussed on dementia caused by AD. It was also mentioned that most models rely solely on cognitive function to characterise progression, ignoring impacts of functional and behavioural symptoms on care needs and costs (Green et al., 2011). In comparison, there is a greater focus on the care needs of dementia patients in the models identified in this review in addition to the use of MMSE scores. As highlighted in the previous reviews, the relationship between short-term surrogate outcomes and long-term outcomes is uncertain and relying on surrogate outcomes makes it challenging to reach a clear conclusion about the cost-effectiveness estimates.

In conclusion, the findings highlight the importance of considering various factors, such as categories of costs to include, assumptions around clinical effectiveness, and choice of perspective, when evaluating the cost-effectiveness of interventions. Sensitivity and scenario analyses also play a crucial role in characterising the uncertainties and their potential impact on the outcomes.

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Table 2 Summary of included studies

Author, year, country	Perspective, discounting, cost year, currency	Model type, cycle length, time horizon	Population	Intervention and comparator	Costs included	Data sources	ICER
da Silva, 2019, Brazil	Healthcare, 5%, 2016, BRL	Markov cohort, 1 year, 10 years	Hypothetical cohort of individuals aged 65 years and older diagnosed with AD according to the PCDT criteria	Donepezil compared to Natural history (not defined), and rivastigmine	Medications. Diagnostic tests (as recommended by Brazilian AD PCDT11): complete blood count, electrolytes, blood glucose, urea, creatinine, thyroid stimulating hormone (TSH), computed tomography, magnetic resonance imaging, and neuropsychological tests. Additional tests and treatments: Tests and treatments for depression, lung infection, and femoral fracture. Outpatient medical follow-up costs. The costs did not include institutionalization.	Published literature	BRL3,342/QALY (Donepezil vs no intervention)
Green, 2019, USA	Costs include societal, 3%, 2017, USD	Markov cohort,1 year, Lifetime (20 years)	Patients with MCI	Hypothetical treatment compared to Usual care (not defined)	Not all reported, just states that costs of informal care and productivity loss were included	Uniform Data Set (UDS) from the US National Alzheimer's Coordinating Center (NACC) and published literature	$50,542/QALY

Handels, 2023b, Netherlands	Adjusted societal perspective, 4% for costs and 1.5% for effects, 2020, Euros	Markov cohort, 1 year, Lifetime	Persons with MCI and abnormal CSF amyloid beta1-42, who visited a memory clinic in the Netherlands, aged 70.	Hypothetical disease modifying treatment for patients underwent a lumbar puncture. In strategy A the treatment was provided to all and In strategy B, it was provided to a subgroup based on the CSF-subtype test result compared to Standard care including psychosocial support and cholinesterase inhibitors	Medical, social and informal care costs. Cost of care and treatment costs were included. The costs of the CSF proteomics analysis were included. It was assumed that lumbar puncture was carried out in usual care and therefore, its costs were not included.	Published literature	€36000/QALY (Strategy A vs no intervention) €22000/QALY (Strategy B vs no intervention)
Handels, 2023c, Netherlands	Societal, 4% for costs and 1.5% for effects, 2020, Euros	Patient level simulation, 1 year, 50 years	Patients with a diagnosis of MCI20 without major comorbidities in a Dutch memory clinic setting	Roflumilast compared to Standard care including psychosocial support and annual retesting of cognitive and functional performance	Medical, social and informal care costs. Treatment costs, side effects, and additional required diagnostics were not considered for both fictive strategies. It was assumed MRI is performed in all patients with MCI in the roflumilast arm.	Published literature	€33941/QALY
Igarashi, 2023, Japan	Narrow healthcare, broader healthcare, and societal, 2%, Not reported, JPY (¥)	Patient level simulation, Not reported, Lifetime	Patients aged between 50 and 85 years, an MMSE score of at least 22, and a 1.1 amyloid PET standardized uptake value ratio (SUVr)	Lecanemab plus standard of care (SoC) compared to Standard of care (not defined)	Direct medical costs, formal and informal care costs. The study included the cost of screening and diagnostics: CSF and PET scans.	Phase III CLARITY AD trial and published literature	Narrow healthcare - ¥1,331,305 to ¥3,939,399, Broader healthcare - ¥1,636,827 to ¥4,249,702, Societal - ¥1,938,740 to ¥4,675,818

Ito, 2021, USA	Healthcare, limited societal and full societal, 3%, Not reported, USD	Patient level simulation, Not reported - probably 1 year, Lifetime	A hypothetical cohort of patients selected from the Alzheimer Disease Neuroimaging Initiative database who received the diagnosis of MCI and scored 24-30 on the Mini-Mental State Examination and had a global Clinical Dementia Rating scale of 0.5	A hypothetical disease-modifying AD drug compared to Usual care (not defined)	Patient health care costs: Medications, hospitalizations, emergency department visits, outpatient visits, and neuropsychological assessments. Patient non-health care costs: Dependent living accommodations, community services, consumable goods, and financial support received. Caregiver health care costs: Medications, hospitalizations, emergency department visits, and outpatient visits. Caregiver productivity costs: Value of caregiver time spent caring for the patient or work hours lost due to caregiving, whichever was higher.	Published literature	Healthcare - $192000/QALY, Healthcare with carer QoL - $107000 Full societal - $74000/QALY

Kongpakwattana, 2020, Thailand	Societal and healthcare, 3%, 2017, THB and USD (34 THB= 1 USD)	Discrete event simulation, N/A,10 years	A simulated cohort of 50000 persons, based on a data set of Thai AD patients	Donepezil, Galantamine, Rivastigmine, and Memantine compared to No treatment	Direct medical costs: outpatient, inpatient, and emergency visits; medications; and out-of-pocket payments Direct non-medical costs: transportation, formal caregiving, and unpaid caregiving time.	Published literature and Thai AD dataset	Societal perspective - Donepezil 138, 524 THB [4,062 USD]; Galantamine dominated; Rivastigmine 11,029,657 THB [323,443 USD]; Memantine less effective (ICER not estimated) Healthcare perspective Healthcare perspective - Donepezil 504,804 THB; Galantamine dominated ; Rivastigmine 13,908,491 THB ; Memantine dominated
Ross, 2022, USA	Healthcare and societal, 3%, 2020, USD	Markov cohort, 1 month, Lifetime	Simulated cohort of persons with a mean (SD) age of 75.2 (5.5) years; 65% had mild cognitive impairment and 35% had mild dementia	Aducanumab and donanemab compared to Standard of care (not defined)	Medication, MRI twice a year for monitoring both treatments, PET scans for monitoring donanemab, materials and services costs per infusion, hospitalisation, outpatient visits, unpaid caregiving	Published literature. Efficacy of aducanumab and donanemab using primary outcome data was from phase 3 and phase 2 trials (EMERGE and ENGAGE)	Aducanumab - Health care $981000/QALY and societal $964000/QALY, Donanemab - Health care $193000/QALY and societal $176000/QALY
Sinha, 2022, USA	Healthcare, 3%, Not reported, USD	Markov cohort, 1 year, 5 years	Hypothetical cohort of persons aged 65 years with mild AD	Aducanumab compared to Standard of care (not defined)	Annual healthcare costs (breakdown not provided)	National Alzheimer's Coordinating Center Uniform Data Set and published literature	$383,080/QALY (95% CI: 14,110–1,082,060)
Taffazoli, 2018, USA	Health system, Not reported, Not reported, USD	Individual patient simulation, N/A 10 years	Simulated 1,000 AD patients with mild, moderate, or severe disease and an average MMSE of 19	Hypothetical symptomatic treatment compared to Placebo	Care and medication costs.	Published literature along with clinical trial data-insufficient details around trials used	344,425/QALY

Tahami Monfared, 2022, USA	Healthcare and societal, 3%, Not reported, USD	Individual patient level simulation, 1 month, Lifetime	2000 individuals with early AD, ages 50–90 years, Mini-Mental State Examination C 22, and amyloid PET SUVr level C 1.1	Lecanemab + standard of care (not defined) compared to Standard of care (not defined)	Medication, monitoring, MRI,amyloid-related imaging abnormalities-edema/effusion, residential and community care costs.	National Alzheimer's Coordinating Center-Uniform Data Set and Efficacy data for lecanemab was informed by the phase IIb proof-of-concept trial - BAN2401-G000-201 trial (Study 201; NCT01767311)	Not estimated (it cannot be calculated based on the figures provided because the cost of drugs not included)
Tahami Monfared, 2023, USA	Healthcare and societal, 3%,2022 USD	Individual patient level simulation, 1 month, Lifetime	Hypothetical patients (based on CLARITY trial) aged 50–85 years, with an MMSE score greater than or equal to 22, and an amyloid PET standardized uptake value ratio (SUVr) of 1.1.	Lecanemab + standard of care (not defined) compared to Standard of care (not defined)	Healthcare, social care, formal and informal caregiving costs.	The CLARITY AD trial and the published literature	Healthcare perspective – US$18,709–35,678 per QALY societal perspective$19,710–37,351 per QALY
Whittington, 2022, USA	Health system and modified societal perspective, 3%, Not reported, USD	Markov cohort,1 year, Lifetime	Hypothetical cohort of adults with AD, aged 65 years and older	Aducanumab compared to Supportive care	Aducanumab acquisition costs, administration costs, monitoring costs, adverse event costs, long-term care costs, and other patient medical and pharmacy costs.	Published literature and National Alzheimer's Coordinating Center database	Healthcare - $1.33 million per QALY; Modified societal $1.27 million per QALY

Wimo, 2020, Sweden	Societal ,3%, 2016, SEK	Markov cohort,1 year, 40 years	People with AD-MCI, aged 60 years and older	Hypothetical disease modifying treatment compared to No intervention	Long term institutional care, hospital care, home services, informal care, medication.	Data from the SveDem Swedish dementia registry, which started in 2007 and currently comprises over 90,000 people with different dementia disorders from the time of dementia diagnosis to annual follow-ups was used to estimate the natural progression in dementia and AD. Data of 91,371 observations from 53,880 individuals with AD was used. Costs were from a population-based costing database.	532,519 per QALY
Youn, 2019, UK	NHS and PSS ,3.5%, 2011/2012 GBP	Discrete event simulation, N/A, Lifetime	UK population aged 45 years and above, some of which have AD. This study examined modelling approaches for three different diseases in a linked model, with and without assumed correlation	Donepezil: patients with a Mini-Mental State Examination (MMSE) score between 10 and 26 at diagnosis (i.e. 10≤ MMSE ≤26) ; Memantine was assumed for patients with MMSE < 10. compared to Best supportive care	Not reported	Review of NICE TA111: The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model.	Donepezil and memantine therapy dominated BSC (cost saving £14 with 0.001 QALY gain)

Yunusa, 2021, USA	Healthcare, 3%, 2020, USD	Markov cohort,1 year, Lifetime	Persons with moderate-to-severe AD aged 65	combination of memantine with each ChEI (donepezil, galantamine and rivastigmine) compared to Best supportive care or monotherapy with Chel or memantamine	Antipsychotic medications, monitoring, physician visits and home care	Data from National Alzheimer's Coordinating Center (NACC) database and published literature. Costs from 2016 Medicare Provider Utilization and Payment Data from the US Centers for Medicare & Medicaid Services (CMS).	Rivastigmine oral and galantamine monotherapy were strongly dominated by galantamine-memantine. Memantine was dominated by donepezil and rivastigmine-memantine was extendedly dominated by rivastigmine transdermal patch. rivastigmine transdermal patch yielded the highest number of QALYs of 2.25 QALYs and an ICER of $93,307/QALY [versus donepezil monotherapy]
Zala, 2018, UK	NHS and PSS, 3.5%, 2016, GBP	Markov cohort, 1 month, 5 years	(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)	AChEIs+Memantine, Monotherapy compared to (i) moderate-to-severe AD dementia: memantine being compared with AChEIs alone or no treatment; (ii) mild-to-moderate AD dementia AChEIs compared with no AChEIs	Monitoring costs: Initial consultation with a specialist (£139) followed by general practitioner visits every 6 months (£36). Drug costs: Daily cost of memantine (£0.053) and donepezil (£0.055) for mild-moderate Alzheimer's disease. Health state costs: Updated to 2016 prices using a health services index. Care costs: Included but not specified.	Data from the London and South-East Region longitudinal epidemiological study (LASER-AD) and published clinical trials and network meta-analyses. Costs from NHS reference costs and PSSRU.	The optimal treatment in both models dominates standard care—average patient costs are lower and QALYs higher over 5 years.
Abbreviations: AChel, acetylcholinesterase inhibitor; AD, Alzheimer's disease; BSC, best supportive care; Chel, cholinesterase inhibitor; CSF, cerebrospinal fluid; ICER, incremental cost-effectiveness ratio; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PET, positron emission tomography; QALY, quality-adjusted life-year; SoC, standard of care; sUVR, standardized uptake value ratio.							

Appendix B.1 Search strategies

Medline ALL

Search date: 7th June 2023

Ovid MEDLINE(R) ALL <1946 to June 06, 2023>

Search Strategy:

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1 exp Dementia/ (203622)

2 (dementi* or pseudodementi*).tw. (137153)

3 (alzheimer* or alzeimer* or (cortical adj4 sclerosis)).tw. (181580)

4 ((encephalopath* or cogniti* or neurocogniti*) adj4 (aids or hiv)).tw. (4459)

5 ((aphasi* adj4 (primary or progress*)) or mesulam* or ppa or (ftd adj4 temporal)).tw. (6755)

6 (((creutzfeldt or ja?ob*) adj4 (disease or syndrome)) or cjd or vcjd or (spongiform adj4 encephalopath*) or "corticostriatospinal degeneration" or (pseudosclerosis adj4 spastic)).tw. (11670)

7 (binswanger* or ((subcortic* or "sub cortic*" or arteriosclerotic) adj4 (encephalopath* or leukoencephalopath*)) or cadasil*).tw. (2556)

8 ((kosaka adj2 shibayama) or (neurofibrillary adj1 tangle*) or dntc).tw. (9820)

9 (((frontotemporal or (fronto adj temporal) or (corticobasal or (cortico adj basal) or (frontal adj lobe))) adj4 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)) or ftld or ftlds or ftd or ftds).tw. (11189)

10 ((pick* adj1 (complex or disease* or syndrome)) or (wilhemsen adj1 lynch) or ddpac or (lob* adj4 atroph*)).tw. (5833)

11 (huntington* or ((progressive or major or juvenile or hereditary) adj4 chorea)).tw. (20717)

12 (((kluver or kluever) adj4 bu?y) or (("temporal lobectomy" adj4 behavi*) or ("temporal lobe" adj4 dysfunction*))).tw. (636)

13 ("lewy bod*" or dlb or lbd or dlbd).tw. (14200)

14 ("senile confusion" or "senile psychosis" or senilit*).tw. (862)

15 Tauopathies/ (2541)

16 tauopath*.tw. (4972)

17 cerad.tw. (903)

18 (Posterior adj cortic* adj atroph*).tw. (534)

19 sivd.tw. (177)

20 Cognitive Dysfunction/ (35210)

21 ((cognitive or mental) adj2 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)).tw. (140677)

22 or/1-21 (430921)

23 exp "Costs and Cost Analysis"/ (264651)

24 exp Models, Economic/ (16212)

25 Markov Chains/ (15960)

26 Monte Carlo Method/ (32169)

27 Decision Trees/ (12082)

28 (cost adj (comparison* or consequence* or benefit* or minimisation or minimization or effectiv* or utility or per)).tw. (195573)

29 (cca or cba or cma or cea or cua).tw. (54604)

30 ((economic or pharmacoeconomic or marginal or cost*) adj2 (evaluation* or analys* or model*)).tw. (69243)

31 markov.tw. (27669)

32 "monte carlo".tw. (58264)

33 decision tree*.tw. (14251)

34 "discrete event".tw. (1337)

35 ((quality or disability) adj adjusted).tw. (22911)

36 (qaly or qalys).tw. (13939)

37 (daly or dalys).tw. (4508)

38 "incremental cost".tw. (15266)

39 icer*.tw. (6993)

40 or/23-39 (575938)

41 22 and 40 (7125)

42 limit 41 to (english language and yr="2018 -Current") (2441)

43 animals/ not (humans/ and animals/) (5093573)

44 42 not 43 (2388)

45 limit 44 to (comment or letter) (31)

46 44 not 45 (2357)

Embase

Search date: 7th June 2023

Saved as: *Alzheimers - dementia - cognitive decline - Embase*

Embase <1974 to 2023 June 06>

Search Strategy:

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1 exp dementia/ (444333)

2 (dementi* or pseudodementi*).tw. (201588)

3 (alzheimer* or alzeimer* or (cortical adj4 sclerosis)).tw. (251509)

4 ((encephalopath* or cogniti* or neurocogniti*) adj4 (aids or hiv)).tw. (6708)

5 ((aphasi* adj4 (primary or progress*)) or mesulam* or ppa or (ftd adj4 temporal)).tw. (10006)

6 (((creutzfeldt or ja?ob*) adj4 (disease or syndrome)) or cjd or vcjd or (spongiform adj4 encephalopath*) or "corticostriatospinal degeneration" or (pseudosclerosis adj4 spastic)).tw. (14752)

7 Binswanger encephalopathy/ (503)

8 (binswanger* or ((subcortic* or "sub cortic*" or arteriosclerotic) adj4 (encephalopath* or leukoencephalopath*)) or cadasil*).tw. (3731)

9 ((kosaka adj2 shibayama) or (neurofibrillary adj1 tangle*) or dntc).tw. (13399)

10 (((frontotemporal or (fronto adj temporal) or (corticobasal or (cortico adj basal) or (frontal adj lobe))) adj4 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)) or ftld or ftlds or ftd or ftds).tw. (19060)

11 ((pick* adj1 (complex or disease* or syndrome)) or (wilhemsen adj1 lynch) or ddpac or (lob* adj4 atroph*)).tw. (7852)

12 (huntington* or ((progressive or major or juvenile or hereditary) adj4 chorea)).tw. (28497)

13 (((kluver or kluever) adj4 bu?y) or (("temporal lobectomy" adj4 behavi*) or ("temporal lobe" adj4 dysfunction*))).tw. (832)

14 ("lewy bod*" or dlb or lbd or dlbd).tw. (21617)

15 ("senile confusion" or "senile psychosis" or senilit*).tw. (938)

16 tauopath*.tw. (8075)

17 cerad.tw. (1741)

18 brain cortex atrophy/ (3455)

19 (Posterior adj cortic* adj atroph*).tw. (963)

20 sivd.tw. (246)

21 cognitive defect/ (213451)

22 ((cognitive or mental) adj2 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)).tw. (215962)

23 or/1-22 (742284)

24 exp economic evaluation/ (353694)

25 exp economic model/ (3727)

26 exp markov chain/ (15640)

27 exp monte carlo method/ (52098)

28 "decision tree"/ (21529)

29 discrete event simulation/ (381)

30 (cost adj (comparison* or consequence* or benefit* or minimisation or minimization or effectiv* or utility or per)).tw. (273461)

31 (cca or cba or cma or cea or cua).tw. (80317)

32 ((economic or pharmacoeconomic or marginal or cost*) adj2 (evaluation* or analys* or model*)).tw. (104190)

33 markov.tw. (36614)

34 "monte carlo".tw. (61228)

35 decision tree*.tw. (20510)

36 "discrete event".tw. (1912)

37 ((quality or disability) adj adjusted).tw. (34174)

38 (qaly or qalys).tw. (26471)

39 (daly or dalys).tw. (6005)

40 "incremental cost".tw. (25321)

41 icer*.tw. (14482)

42 or/24-41 (708176)

43 23 and 42 (10722)

44 limit 43 to yr="2018 -Current" (4056)

45 nonhuman/ not (human/ and nonhuman/) (5317063)

46 44 not 45 (3875)

47 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. (5558650)

48 46 not 47 (3091)

49 limit 48 to (editorial or letter) (114)

50 48 not 49 (2977)

51 limit 50 to english language (2936)

Cochrane Database of Systematic Reviews

Search date: 7th June 2023

Saved as: *Alzheimers - dementia - cognitive decline*

Issue 6 of 12, 2023

ID Search Hits

1 [mh Dementia] 9173

2 (dementi* or pseudodementi*):ti,ab 15185

3 (alzheimer* or alzeimer* or (cortical NEAR/4 sclerosis)):ti,ab 12645

4 ((encephalopath* or cogniti* or neurocogniti*) NEAR/4 (aids or hiv)):ti,ab 453

5 ((aphasi* NEAR/4 (primary or progress*)) or mesulam* or ppa or (ftd NEAR/4 temporal)) 929

6 (((creutzfeldt or ja?ob*) NEAR/4 (disease or syndrome)) or cjd or vcjd or (spongiform NEAR/4 encephalopath*) or "corticostriatospinal degeneration" or (pseudosclerosis NEAR/4 spastic)):ti,ab 64

7 (binswanger* or ((subcortic* or (sub NEXT cortic*) or arteriosclerotic) NEAR/4 (encephalopath* or leukoencephalopath*)) or cadasil*):ti,ab 44

8 ((kosaka NEAR/2 shibayama) or (neurofibrillary NEAR/1 tangle*) or dntc):ti,ab 81

9 (((frontotemporal or (fronto NEAR/1 temporal) or (corticobasal or (cortico NEAR/1 basal) or (frontal NEAR/1 lobe))) NEAR/4 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)) or ftld or ftlds or ftd or ftds):ti,ab 396

10 ((pick* NEAR/1 (complex or disease* or syndrome)) or (wilhemsen NEAR/1 lynch) or ddpac or (lob* NEAR/4 atroph*)):ti,ab 117

11 (huntington* or ((progressive or major or juvenile or hereditary) NEAR/4 chorea)):ti,ab 747

12 (((kluver or kluever) NEAR/4 bu?y) or (("temporal lobectomy" NEAR/4 behavi*) or ("temporal lobe" NEAR/4 dysfunction*))):ti,ab 14

13 ((lewy NEXT bod*) or dlb or lbd or dlbd):ti,ab 523

14 ("senile confusion" or "senile psychosis" or senilit*):ti,ab 52

15 [mh ^Tauopathies]14

16 tauopath*:ti,ab 54

17 cerad:ti,ab144

18 (Posterior NEAR/1 cortic* NEAR/1 atroph*):ti,ab 16

19 sivd:ti,ab 16

20 [mh ^"cognitive dysfunction"] 2896

21 ((cognitive or mental) NEAR/2 (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)):ti,ab 18742

22 {OR #1-#21} with Cochrane Library publication date Between Jan 2018 and Dec 2023, in Cochrane Reviews 136

INAHTA International HTA database

Search date: 7th June 2023

Saved as: not applicable – saved to personal account without option to name strategy

Database version: not applicable

On-screen limits applied for English-language only and publication date from 2018-2024. 56 results retrieved after limits applied.

Line , Query , Hits

22 #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 434

21 (cognitive or mental) AND (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*) 170

20 "Cognitive Dysfunction"[mh] 15

19 sivd 0

18 posterior and cortic* and atroph* 0

17 cerad 0

16 tauopath* 0

15 "Tauopathies"[mh] 0

14 "senile confusion" or "senile psychosis" or senilit* 0

13 (lewy or dlb or lbd or dlbd) 6

12 (kluver or kluever) or ("temporal lobectomy" and behavi*) or ("temporal lobe" and dysfunction*) 1

11 huntington* or ((progressive or major or juvenile or hereditary) and chorea) 9

10 (pick* and (complex or disease* or syndrome)) or (wilhemsen and lynch) or ddpac or (lob* and atroph*) 13

9 ((frontotemporal or "fronto temporal" or (corticobasal or "cortico basal" or "frontal lobe")) and (decline* or dysfunction* or deteriorat* or degenerati* or loss* or impair*)) or ftld or ftlds or ftd or ftds 1

8 (kosaka and shibayama) or (neurofibrillary and tangle*) or dntc 1

7 binswanger* or ((subcortic* or "sub cortic*" or arteriosclerotic) and (encephalopath* or leukoencephalopath*)) or cadasil* 3

6 ((creutzfeldt or jakob* or jacob*) AND (disease or syndrome)) or cjd or vcjd or (spongiform and encephalopath*) or "corticostriatospinal degeneration" or (pseudosclerosis and spastic) 23

5 (aphasi* and (primary or progress*)) or mesulam* or ppa or (ftd and temporal) 3

4 (encephalopath* or cogniti* or neurocogniti*) and (aids or hiv) 11

3 (alzheimer* or alzeimer* or (cortical and sclerosis)) 127

2 dementi* or pseudodementi* 188

1 "Dementia"[mhe] 208