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Abstract

Objective: The objective is to systematically review the literature on economic evaluations of pharmacological treatments of dementia disorders.

Methods: A systematic search of published economic evaluation studies in English was conducted using specified key words in relevant databased and websites. Data extracted included methods and empirical evidence (costs, effects, incremental cost-effectiveness ratio) and we assessed if the conclusions made in terms of cost-effectiveness were supported by the reported evidence. The included studies were also assessed for reporting quality using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Results: Fourteen studies were included in this review. There was a considerable heterogeneity in methodological approaches, use of simulation models, target populations, study time frames, and perspectives as well as comparators used. Keeping these issues in mind, we find that Cholinesterase Inhibitors (ChEIs), and especially donepezil, are dominating no treatment (*i.e.* less costly and more effective) for mild to moderate AD patients. For moderate to severe AD patients memantine is cost-effective compared to memantine or ChEIs alone. However, the effect of these drugs on survival is yet not established, which could have a major impact on the cost-effectiveness of these drugs.

Conclusion: Pharmaceutical treatments are cost-effective comparing to no treatment for dementia patients. However, more research is required on the long-term effectiveness of these drugs, especially on the effects of drugs on survival.

Key words: Dementia, pharmaceuticals, economic evaluation, Cholinesterase Inhibitors
JEL Classification: H43; I10; I18

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Background

Dementia is a syndrome with progressive deterioration in several cognitive domains that interfere with activities of daily living. Alzheimer's disease is the most common dementia disorder and accounts for 60 – 70% of dementia cases in the world [1]. Current estimates demonstrate that over 40 million people are suffering from Alzheimer's disease with the number expected to rise to over 100 million by the year 2050 [2].

Dementia affects many levels of society. Firstly, the individual suffers from impairments in cognition and functioning as well as impaired quality of life and shortened life expectancy [3]. Secondly, the relatives suffer from gradually losing a family member and in return receive a high care burden for the affected person. Indeed, the need for informal care increases when dementia progresses with deteriorating cognition and functioning [4]. Thirdly, dementia has a substantial economic impact on the society. Care for persons with dementia is very costly and resource-demanding for both the formal and informal sector [5]. The worldwide societal costs of dementia were estimated to be 604 billion US dollars in 2010, of which 252 billion for informal care (caregivers) [5]. These costs are expected to increase in the future due to population aging.

There is currently no available cure for dementia, only symptom relieving therapies. These can be either pharmacological (use of drugs) [6] and non-pharmacological [7]. However, in a context of limited resources and strained healthcare and social service budgets, it is important that every intervention is not only effective but that the effects are reasonable in relation to the cost of the intervention. That is, that the interventions are cost-effective and that the healthcare system and social services are getting the most out of their budgets in terms of patient health and quality of life. Economic evaluation assesses the cost-effectiveness of two or more alternative programs or interventions by identifying, measuring, valuing and

comparing the costs and consequences. Economic evaluations informs decision makers, allowing them to make informed decisions on how to use available resources in the best possible manner [8].

Conducting systematic reviews is a good way to identify the common characteristics of existing studies, to evaluate the studies, and to find areas where more research is required. Although there are some systematic literature reviews of economic evaluations of pharmaceutical treatment of dementia disease [9, 10], no review has been conducted after 2010. The objective of this article is therefore to study whether the pharmacological interventions for treatment of dementia disorders are cost-effective.

Methodology

We performed a systematic literature review to answer the research question in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [11]. Moreover, the Campbell and Cochrane Economics Methods Group guidelines [12] has been followed for incorporating economic evidence including search criteria, data extraction, synthesis and critical analysis.

Search strategy

A systematic search was performed to identify relevant articles published in both health economics and biomedical databases from 01.01.2000 till 31.12.2015. The databases were Medline (Pubmed), Embase and ECONbase, EconLit, Cumulative Index to Nursing and Allied Health (CINAHL), The National Bureau of Economic Research, Latin American and Caribbean Literature on Health Sciences Database (LILACS) and Popline. In addition, we searched specific economic evaluation databases: the Centre for Reviews and Dissemination database maintained by NHS (http://www.crd.york.ac.uk/CRDWeb/) and the Cost-effectiveness analysis registry

(http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx). We also searched additional articles from the reference lists of included studies. The search was performed with search/key words and the details of the search strategy and initial hits are provided in Annex 1 for the reproducibility and transparency of the work.

Inclusion and exclusion criteria

The literature search covers EEs of all types of interventions targeting patients with dementia disorders, their caregivers, and the patient-caregiver dyad. We defined pharmaceuticals intervention as interventions where the main aim was to use drugs as a treatment of dementia disorders. This means that EEs of interventions focusing on (1) non-pharmacological interventions and (2) overall management of the dementia patients in home/community/residential care, and (3) dementia screening programmes are not included. These three categories are presented in parallel publications.

Studies were included if they were published between January 1st 2010 and December 31st 2015 in order to complement existing reviews in the field [10]. The inclusion criteria were: (1) pharmacological intervention either by drug including hypothetical interventions, or studies where these were one of the comparators; (2) Economic Evaluation (EE) studies such as Cost-Effectiveness Analysis (CEA), Cost-Utility analysis (CUA) and Cost-Benefit Analysis (CBA); and (3) reported in English in the scholarly literature. Studies were excluded if they were: (1) cost studies such as cost-of-illness analysis; (2) reviews, notes, commentaries, editorials related to dementia in scientific journals; and (3) study protocol or study design of interventions.

Selection and data extraction

After each search in the above-mentioned databases the initial hits were exported into EndNote and duplicates were removed. All articles were screened based on the inclusion and exclusion criteria, first based on titles and abstracts and second based on the full text. The

selection of the articles was done by one co-author while a second co-author reviewed all studies where assessment according to inclusion or exclusion criteria was challenging.

We extracted data from the selected articles along two main dimensions: the result of the study (empirical evidence) and how the results have been derived (methodology). In terms of result, we extracted the Incremental Cost Effectiveness Ratio (ICER), net monetary benefit (NMB) or Net Health Benefit (NHB) from the selected articles, as well as its components (costs and outcomes) and sensitivity measures. We also identified whether the health outcomes were measured as utility index or as other outcomes, e.g. survival years, time spent on institutional care.

Furthermore, we scrutinized whether the intervention was reported as cost-effective by the authors and whether the reported information support the conclusions, based on different scenarios presented in Table 1. We used ICER in Table 1 since ICER is more frequently used in the economic evaluation literatures than NMB or NHB [13]. However, the scenarios presented in Table 1 can be used for both incremental NMB and incremental NHB. We used the NICE threshold (£30,000 per QALY gain) to term an intervention cost-effective [14, 15]. That is, ICER higher than £30,000 per QALY was considered not cost-effective and, in NMB, the value of lambda (λ) was set to £30,000.

In the absence of any significance test, we used the information on the Cost-Effectiveness Acceptability Curve (CEAC) to judge the cost-effectiveness of the intervention, if presented. CEAC was developed as an alternative to producing CIs around the ICER which shows the probability that the intervention is cost-effective in comparison with the comparator for a range of Willingness-To-Pay (WTP) thresholds. We consider an intervention cost-effective or weakly cost-effective if the probability of the intervention being cost-effective was 90% or 80% at the NICE threshold.

In the absence of significance test and CEAC, we used the Cost-Effectiveness (CE) plane to identify whether an intervention was cost-effective or not, if presented. CE plane shows the bootstrapped incremental cost-effect pairs of two interventions with the difference in effect on the horizontal axis and the difference in costs on the vertical axis [16]. If all points are in the southeast or the northwest quadrant, the choice between the intervention is clear. In the southeast quadrant, the new intervention is both more effective and less costly than the comparator and thus dominates the comparator. The opposite is true in the northwest quadrant. We identified an intervention (weakly) dominates the comparator if (80%) 90% of the cost-effect pairs are at the southeast quadrant. In the northeast and southwest quadrants, the choice depends on the amount of money society is WTP or WTA to gain or loss, respectively for one unit of effect [17, 18]. The CE plane does not in these cases contain enough information to determine cost-effectiveness. We also considered other methods of presenting uncertainties such as intervals for ICER, intervals for net benefits and expected value of perfect information [19], if these were presented in any of the identified studies. Studies were appraised for quality of reporting using the CHEERS statement [20]. This checklist was produced with the aim of harmonizing the presentation of information, raising the quality standard of EEs. The CHEERS guideline has 24 items in six categories (title and abstract, introduction, methods, results, discussion and other). The items were scored as 'Yes' (reported in full), 'No' (not reported), and 'Not Applicable'. In order to assign a score of reporting, we assigned a score of 1 if the requirement of reporting was completely fulfilled for that item and 0 otherwise. Therefore, the maximum score was 24.

Results

The systematic literature search identified fourteen economic evaluations of pharmaceutical interventions for the treatment of dementia disorders that subsequently are included in this

review. A flow chart of the study selection procedure is presented in Figure 1. The interventions vary from use of a single drug or a combination of medications to hypothetical treatment which is not yet available on the market (i.e. immunization therapies). The comparator of the studies also varies between no treatment, standard care, best supportive treatment and other drugs. The target groups range from actual patients to hypothetical simulated patients' group. The disease stages ranged from mild cognitive impairment (MCI) to severe dementia. The perspective of analysis was healthcare or societal. The countries for evaluation are mainly from developed countries. All the studies had performed either CUA or CEA or both. In the CUA, effectiveness is measured as Quality Adjusted Life Years (QALYs) whereas in CEA, the measure of effectiveness varies and includes Life Years Gained (LYG), days of institutionalization prevented and survival. The effectiveness data derived from single randomized control trials or literature reviews of several trials from participants' country if available and otherwise from other nations. Results are presented as ICER. The discount rate varies from 3% to 6%, and the majority uses the same discount rate for both cost and effect. The main characteristics of the studies are presented in Table 2. In Table 3, we present the cost categories and the instrument for measuring the QALYs and the sources for derivation of costs and QALYs, if not collected in parallel of the trial.

All pharmacological interventions except two focus on Cholinesterase Inhibitors (ChEIs), which are known as donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate receptor antagonist memantine. We found studies where economic evaluations have been performed for ChEIs compared to no treatment, standard care, other ChEIs, or memantine. We also found studies where ChEI monotherapy was compared with combination therapy of memantine and ChEI.

A similar DES model was used in three different studies in two countries to estimate the cost-effectiveness of ChEI over a 10-year period. In the UK [21] donepezil was compared with no

treatment, while in Germany, donepezil was compared with no treatment and memantine [22] and galantamine was compared with no treatment and Ginkgo Biloba (a herbal supplement) [23]. The severity of AD patients was measured by Mini-Mental State Examination (MMSE). For mild to moderate-severe patients, the comparator was no treatment [21] and for moderate to severe AD patients, the comparator was memantine [22, 23]. The researchers found that donepezil was the dominant option *i.e.* less costly and higher health effects (QALY) compared to no treatment for mild to moderate AD patients. Donepezil was found to dominate memantine also for patients with moderate to severe AD [22]. The beneficial effects differ on the severity level of the patients, for example, low to moderate AD patients had higher incremental QALY gain than moderate to severe AD patients. The researchers assumed that the effectiveness lasts only for 52 weeks and then the drugs had no effects on the disease, based on seven clinical trials of donepezil where the trial duration ranged from 15 to 52 weeks. Furthermore, mortality was assumed not to be affected by the treatment. Galantamine dominates both no treatment and Ginkgo Biloba [23]. Galantamine was found to reduce the time spent in institutional care by 2.34 months and also reduce costs by €3,978 compared to no treatment. Same as the donepezil, galantamine was not modelled to affect long-term survival.

Monotherapy with a ChEI compared to a combination therapy (ChEI+Memantine) has been evaluated in four studies. The same Markov model was used in three studies covering three different countries; Canada [24], Switzerland [25] and France [26] while a DES model was used in a US study [27]. The Markov model had three states (non-institutionalized, institutionalized and deceased) and the cohort was run over 5-7 years. The analyses were performed from both healthcare and societal perspectives. The combination therapy was dominating the monotherapy, which means that the cost was lower and the health effects (QALY) was higher. The effectiveness data came from clinical trials in the USA. In the USA

study [27], the effectiveness came from a phase III clinical trial of 677 randomized patients. The patients were then run in the DES model for 1,000 times in both treatment arms. The QALYs of the patient and their caregivers comes from two different trials. The researchers have considered the costs for patients living at home and for patients living in an institution. The informal caregiver costs were almost ten times higher when patients were living at home compared to patients residing at an institution. The combination therapy was dominant and would reduce complete dependence by four months although no difference was seen in the survival.

Bond et al. used ChEIs for the treatment of mild-to-moderately severe AD and memantine for the treatment of moderate-to-severe AD compared to the best supportive care (BSC) which includes treatment without AD pharmaceuticals (i.e. ChEIs or memantine) in the UK [28]. They used a three-state Markov model similar to studies by others [24-26]. The researchers found that all the ChEIs are dominant i.e. lower cost and higher effect, than BSC for mild-to-moderate AD, and among the ChEIs, donepezil is the dominant one as it produces higher QALY than galantamine. Memantine was found to increase the costs compared to BSC for moderate-severe AD, but also the health outcomes, resulting in an ICER of £32,100 per QALY. ChEIs was assumed to have no effect on survival. However, if survival is modeled as a function of the change in MMSE and ADL (activity of daily living) scores, ChEIs no longer dominate BSC (ICER £37,000/QALY) due to cost increase connected to longer time in institutionalized care. However, there is still no study that measures the effect of these drugs on survival and thus, the figure is speculative. They assume that survival is an exponential function of MMSE, Barthel score and age at the time of entry to the study. They have presented the findings of one-way sensitivity analyses by using NMB. The value per QALY gain was set to £30,000.

Markov models were used for comparing memantine with standard treatment for patients with moderate to severe AD in three different countries; the UK [29], Norway [30] and the Netherlands [31] where the UK and Norway used the same Markov model. The Markov model had three health states; pre-fulltime care, fulltime care and death. A 5-years' time frame until the patients required full-time care (FTC) was used in the UK [29] and Norway [30]. The study from the Netherlands [31] had five health states based on disease severity (moderate, independent; moderate, dependent; severe, independent; severe dependent and death). FTC is defined as patient becoming either dependent or institutionalized. The standard treatment included either no treatment [29-31] or treatment with ChEIs [29, 30]. In all these studies [29-31] memantine dominated standard treatment.

Nagy et al. [32] evaluated treatment with rivastigmine patch (9.5 mg/day) and rivastigmine capsules (12 mg/day) compared to best supportive care (BSC) for AD patients in the UK. The short-term clinical benefits on MMSE score and MMSE-ADL score was extrapolated to five years to estimate the long-term benefit. Both the capsules and patches were dominating BSC while comparing between patch and capsule, the patch was the dominating one. The researchers also estimated that 22.8 days of institutional care by would be avoided by the patch and 18 days by the capsules considering MMSE score. For MMSE+ADL score 26.5 and 20.8 days would have been saved for the patch and the tablet respectively.

Skoldunger et al. [33] performed a CEA for a hypothetical disease modifying treatment (DMT) comparing to no treatment for AD patients in Sweden. According to the researchers, the DMT comprises immunization therapy or treatment with secretase inhibitors. A Markov model was used where patients move from MCI to mild dementia, moderate dementia, severe AD and death. The conversation from MCI-AD to AD-dementia does not come from meta-analysis but based on authors judgement. The effectiveness of DMT are hypothetical as there were no evidence of the efficacy of immunization therapy or treatment with secretase

inhibitors. The analysis was performed for a 20 years period with a societal perspective. The ICER for DMT was 293,002 SEK/QALY (2005 price year) and the model predicts that patients with DMT would survive 1.1 years longer and gain 0.81 QALY compared to no treatment.

Banerjee et al. [34] performed a CEA and a CUA using two antidepressant drugs, sertraline and mirtazapine comparing with placebo for dementia patients in the UK to treat depression. The CEA used Cornell Scale for Depression in Dementia (CSDD) score as the health outcome and was estimated at 13 weeks and the CUA used QALY as the outcome at 39 weeks of follow-up. Mirtazapine dominated both placebo and sertraline at 39 weeks follow-up. The researchers used both ICER and NMB where the WTP was set £30,000 per QALY gain and one-unit improvement of CSDD score.

Discussion

The economic evaluations of pharmacological treatments for dementia disorders differ in several areas such as in comparators, efficacy of different drugs or technologies, target groups, methods, costs and outcomes included, and used instruments to measure the outcomes. This makes general comparison across all the studies difficult. Differences may also arise from differences in healthcare systems, time to transfer a patient to institutional care, time to send them back to homecare or vice versa, incentives to healthcare professionals and institutions, clinical practices, population values, availability and accessibility of drugs or technologies, reimbursement and currency purchasing power, etc. We agree with the previous reviews that the comparability of the results of different EE studies is limited due to differences in studies specially differences in the assumption made in the simulation models [9, 10]. Keeping these differences in mind, we found that most of the pharmaceutical treatments evaluated in the included studies are cost-effective.

Cost-effectiveness is at its heart a normative concept as it refers to if an intervention is worth its costs, *i.e.* the decision-maker WTP for the outcome under study. This will differ between settings but also between individuals, and it is therefore essential that the authors of EE are clear about the valuation of the outcomes when determining an intervention's cost-effectiveness. Preferably a societal valuation should be used when reporting cost-effectiveness although this value is generally unknown for most outcomes such as MMSE score, time spent in institutional care, or years of survival. An exception is the value of a QALY where NICE in the UK uses a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained [14, 15]. There are no official guidelines for the USA and Australia although 50,000 US$/QALY is frequently employed as a threshold in the USA [35] and 50,000 AUS$/Disability Adjusted Life Year (DALY) in Australia [36]. For all other outcome measure, each study needs to establish the societal valuation of the used outcome in order to, potentially, claim cost-effectiveness. A few special situations exist however; if the intervention is both better (worse) and less (more) costly than the comparator (scenarios 2 and 4 in the Table 1), it is (not) preferred irrespective of the valuation of the outcome measure. For simplicity, we will term all clearly preferred alternatives as cost-effective in the continued discussion.

In Table 4, we presented the cost-effectiveness of the included articles as reported by the authors as well as our own assessment based on the reported information. It is foremost important to establish that there is a difference in costs and/or outcomes between the intervention and the comparator before calculating the ICER or NMB, for example by reporting Confidence Intervals (CIs). If CIs or corresponding test were not available, we take a conservative approach and assess the cost-effectiveness as "unknown due to lack of information" as it cannot be established if the intervention is different from the comparator.

Our assessments are in line with the reported conclusions in many studies [26, 27, 29-32, 34] which were based on the criteria of Table 1 and CEAC and CE-plane as described in the method section. Many studies do not report the 95% CIs (or corresponding test) for either costs or outcomes (Table 4) [21-28, 30, 32, 33]. We acknowledge that, in EE, costs and effects are very disperse and it may be difficult to find significant differences between two comparators [37]. However, 95% CIs (or corresponding tests) of the differences in costs and effects should always be included. Many studies handle the uncertainties around costs and effects by presenting Cost-Effectiveness Acceptability Curve (CEAC) (Table 4) [21, 22, 26, 28, 32, 34] which is a good practice that should be included in all EE. CEAC was developed as an alternative to producing CIs around the ICER. However, there is no agreement on when to claim an intervention cost-effective based on the findings from the CEAC. For ease of comparison, we termed an intervention "cost-effective" (weakly cost-effective) if the intervention had 90% (80%) probability to be cost-effective at the NICE threshold.

We also found some studies where uncertainties are presented using CE without providing a CEAC [27, 29, 30]. The CE plane it is helpful to identify whether an intervention is cost-effective or not if all (most of) the cost and effects pairs are in the dominating quadrants. However, if most of the pairs are in the northeast/southwest quadrants, then the WTP threshold comes into play and it is difficult to determine the actual probability of being cost-effective at the NICE threshold by looking at the CE plane only. For example, Hartz et al.[22] showed that 99% of all the incremental cost-effect pairs are on the southeast quadrant, which clearly shows that donepezil dominates no treatment for mild to moderate AD patients. However, in the same article they showed that only 70% of the pairs are on the southeast quadrant while comparing donepezil to memantine for moderate to severe AD patients. Thus, without access to the data it is not possible for the reader to assess the probability of donepezil being cost-effective compared to memantine at a specific threshold, even though

the CE plane suggest that this might be the case, at least on the 80% level. We therefore consider the cost-effectiveness in this case to be unknown due to lack of information (Table 4). CE plane and CEAC provide different information regarding the uncertainties around cost-effectiveness and should be viewed as complement rather than substitute.

For outcomes other than QALY, such as Cornell Scale for Depression in Dementia (CSDD) [34], survival [27] and delay to admit in the institutional care [23] it falls upon the authors to try to establish the societal valuation of the used outcome, for example by comparing to the value that the society has been willing to pay in the past. Only in those cases where the intervention is better but not more expensive, cheaper but not worse, or better and cheaper than the alternative (or the other way around) is the cost-effectiveness argument clear. However, all included studies failed to make a convincing case for the societal valuation of an outcome other than QALY. For example, Banerjee et al. showed that there is an 80% chance of mirtazapine to be cost-effective at £30,000 for one-point improvement of CSDD score. However, it is not discussed whether the societal WTP for one-point improvement is £30,000. It is therefore not possible, with any certainty, to make any conclusions regarding the cost-effectiveness of the intervention and labelling such interventions as "cost-effective" is inappropriate. In these cases, we consider the cost-effectiveness "unknown due to no agreed cost-effective threshold value" (Table 4). Future research is needed to reach an agreement among researchers and policymakers regarding the valuation of outcome measures other than QALY.

However, it is worth to state that neither the cost-effectiveness threshold nor the inference drawn from the CEAC or CE plane should be used as the only decision-making tool for implementations of these interventions. Instead, a country and context-specific process for decision making should be considered, reflecting legislation and involving patients' group, caregivers and civil society organizations [38, 39].

Effectiveness data

All authors used data from trials to determine the efficacy of (non-hypothetical) treatments on AD patients. The efficacy data from one country is often used for another country's population. For the ChEIs studies in Germany [22, 23], the efficacy data came from a clinical trial performed in the UK. For memantine [29-31], the efficacy data came from a single observational study from Canada which has been criticized for selection bias of AD patients [40]. Therefore, the extrapolation of efficacy data performed in a specific country to general AD patients may provide a biased estimation. Moreover, the treatment pattern for AD is country specific regarding standard care, insurance coverage, nursing home placement, access to healthcare, drug reimbursement, etc. Therefore, the cost-effectiveness of these studies might be over or underestimated. There are good guidelines on the transferability of data from one country to another for EE which might be helpful [41, 42].

The evidence on the efficacy of drugs is limited, for example, there are no clinical studies on the effectiveness of Donepezil for a period longer than 1 year, *i.e.* the efficacy of the drug on survival is not known. In that case, some researchers assume that the drugs had no effect on survival [21-23] or that the survival did not differ while comparing two different ChEIs [24-26]. This affects the ICER, as Bond et al. suggested, as a positive effect of survival may make ChEIs less cost-effective compared to standard care [28]. More QALYs are gained when a treatment effect of ChEIs on survival is assumed, owing to additional life, but this gain is spent in a more expensive state *i.e.* institutional care.

In the memantine studies [21-23], the efficacy data came from a trail with a 24-week period which was extrapolated in the cost-effectiveness study to 52 weeks although the timeframe in the studies was 10 years. The assumption was that drug has no effect on disease after 52 weeks. The same assumption was used in studies [29-31] where the efficacy comes from

RCTs with the highest duration of six months and the duration of analysis was 5-years. If the long-term clinical efficacy of a drug is not available, the explicit way of exploring the efficacy by modeling should be considered a strength of modeling, not a weakness [43]. However, the long-term efficacy assumptions should benefit from some consensus and harmonization, apart from the recommendation to perform relevant sensitivity analyses. Reliable data was also missing, for example the transition from MCI to AD was hypothetical [33], and the database for resource calculation was based on dementia patients instead of AD patients in Sweden [33] which might have an effect on the cost-effectiveness in these studies.

Cost inclusion

The cost included in the analysis has drastic effects on the cost-effectiveness and it varies from study to study (Table 3). In studies with ChEIs [21-23], the costs for medication was relatively small but the cost of institutionalized care contributed to a great extent, thus the more days of institutionalized care avoided the higher the savings and the lower the ICER. A clear description of all the costs items, including unit costs and source, would have been helpful. For example, instead of mentioning physician visits [25], specifying general [21, 22, 31] or specialist physician [30] would have been helpful as specialist physician costs more than a general physician. For inpatient care, intensive care costs more than just hospitalization, therefore the inclusion of intensive care [30] is likely to make the intervention costlier. We found that most of the studies used country-specific cost data (Table 3) which is a good practice instead of using cost data from another country and should be followed in the future EE studies of dementia medications. However, it is not uncommon in EE to collect cost data from studies performed in other countries. For example, in the Norwegian study [30] the cost of informal care was based on information from the OECD

countries and not specific to Norway. It requires a clear description of the sources, transformation procedures and inflation adjustment.

Informal care

Dementia is expected to affect people close to the patient directly and indirectly through the burden of informal care. In the World Alzheimer Report, the cost of informal care contributed 42% of total cost worldwide [5] for Alzheimer care. Informal care plays an important role in cost-effectiveness analysis and most studies included in this review have included caregivers to some extent. However, it is difficult to estimate the cost of informal care for a number of reasons. First, it is debatable what types of activities need to be considered as caregiving. Second, it is difficult over a long period of time to monitor each activity of caregivers which may lead to recall and interpolation bias. Third, there is much controversy regarding the valuation of time for informal care [44]. For example, Rive et al [30] has included different valuation for caregivers' time based on productivity loss ($55.34/hour), or leisure time loss ($8.61/hour) while most of the other included studies did not differentiate this way[1]. Furthermore, the value of, as well as the principal for determining, one hour of informal care varies from study to study (Table 3). For example, two studies from the UK [21, 32] used minimum wage in the UK as caregiver's time cost whereas in the Swedish study [33] cost of a professional home service was used.

Regarding the effect on caregivers' health (e.g. QALY, see Table 3), we find only three studies where this has been included in the analysis and all three studies used a DES model [21, 22, 27]. Moreover, for the same study, different instruments were used to measure QALY for the patient (EQ-5D) and the caregiver (SF-36) [21, 22]. Readers need to be cautious when comparing QALYs derived from various instruments as the QALY varies

[1] Costs in parentheses are converted to 2015 USD using consumer price index and purchasing power parity

depending on the instrument used [45]. Although the QALY gain for caregivers in the above studies was very negligible, we think that caregivers' QALY needs to be included in the analysis as caregivers play a significant role in dementia care and constitutes a substantial part of the cost of dementia.

Issues with simulation models

It is suggested that the outcomes of dementia disorders should capture as many health-related variables as possible including cognition, behaviors and functioning instead of a single outcome such as overall health-related quality of life since dementia disorders are multifaceted [46]. The DES models [21-23] have captured more health states and related outcome than the Markov models [24-26]. Moreover, Markov models have a limitation on managing individual level characteristics which can be overcome by DES model. However, these processes make the model complex and reduce transparency. The included Markov models has only three health states; pre-institutionalized, institutionalized and death [29-31] whereas the DES models [21-23] are more complicated in structure and can be judged as more accurate than Markov models. However, in 2012 Oremus et al. [46] pointed out that the assumptions in DES models used for estimating the cost-effectiveness of pharmaceutical interventions for AD were generally not clearly described. Unfortunately, this is still the case for the studies included in this review [21-23], for example how patients have been stimulated and how patient characteristics have been assigned.

Good practice guidelines for modelling studies recommend that the modelers should present a technical note of the model so that others can understand all the assumptions behind the model [47, 48]. Except for one study [28], there was no technical report available for the models. Since the space of a journal is less likely to be a problem nowadays, attaching a technical note as supplementary materials would be helpful.

Another important issue in modeling is the validity of the model itself which shows the robustness of the findings. Authors should consider variations using internal, external and structural validation of the models. Although all authors have performed sensitivity analyses (Table 2) to test the robustness of their results, the structural assumptions were untested in all studies. In case of probabilistic sensitivity analyses, the distribution of the parameters and sources were missing.

To minimize uncertainty in parameter estimates, researchers have suggested using data from meta-analyses or systematic reviews [18, 46]. However, data in reviews or meta-analysis are often not country specific, and may thus introduce a bias, especially for costs. One option would be to combine country-specific data with meta-analysis or systematic reviews in sensitivity analyses to ensure the robustness of the results. In the case of lack of valid data, such as health utilities for patients and caregiver and the efficacy of drugs, we suggest considering these uncertainties in sensitivity analyses and discussing the results extensively.

Quality assessment

We find that most of studies have high score on the CHEERS (table 2) especially comparing to studies on non-pharmaceutical interventions [49] or screening interventions [50]. However, it should be kept in mind that these guidelines are to ensure the quality of the reporting and not the quality of the study as such. For example, some studies have performed an economic evaluation of a hypothetical treatment [33], therefore, without the efficacy of a drug/technology, the cost-effectiveness of these hypothetical treatments may have limited value to the policy makers. Another example is “no treatment” as a comparator for several drugs for severe AD patients [21-23]. From a methodological point of view, there is no problem using “no treatment” as a comparator, but from a clinical perspective, it is questionable if this is a valid treatment option for severe AD patient. If so, the estimated

ICER cannot be used for decision making. A high CHEERS score therefore does not imply a well-performed study, just as poor reporting not necessarily imply poor quality and biased results.

Role of funding source

A majority of studies were funded by pharmaceutical companies (Table 2) as expected due to the requirement of presenting cost-effectiveness information. Previously have concerns been raised about studies funded by industry as they have been shown to be more likely to report favorable cost-effectiveness ratios [51], and especially in modeling studies [52]. The latter is considered to be due to the complex mathematical equations and many assumptions in the models, referred to as a "black box" [53], which allows modelers to choose assumptions that enhances cost-effectiveness. The results of the included studies should therefore be interpreted with some caution.

Strength and Limitation

This review poses particular strengths. In line with recommendations, we searched key electronic bibliographic databases and other sources. Manual searching of reference lists of the reviewed articles was carried out to identify relevant studies. Identified studies were independently assessed for inclusion against a set of predetermined criteria. No restrictions were applied on types of economic evaluation or country of origin including both trials- and model-based economic evaluation.

There are also particular limitations to our study. First, the quality of reporting based on CHEERS scoring is based on the interpretation of the reviewers and disagreement may arise. Second, we have not assessed the methodological quality of the articles or the different models. An evaluation of the modeling quality using different checklists for different models would have been interesting [54] but beyond the scope of this broad literature review. Third,

we did not perform a systematic quantitative assessment to identify key drivers of cost the effectiveness.

Conclusion

We found that for mild to moderate AD patients, ChEIs is cost-effective comparing to no treatment while for moderate to severe AD patients memantine is cost-effective comparing with ChEIs. However, long-term data on the effectiveness of drugs, especially survival, is scarce and the use of registers could be helpful in the future.

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Table 1: Decision rules for economic evaluations (new intervention vs. comparator)

Scenarios	Cost	Outcome	Interpretation
1	↑	↑	**Cost-effective** if the willingness-to-pay exceeds the ICER
2	↓	↑	**Cost-effective** (new intervention dominates the comparator)
3	≈	↑	**Cost-effective** (new intervention dominates the comparator)
4	↑	↓	**Not cost-effective** (comparator dominates the new intervention)
5	↓	↓	**Cost-effective** if the ICER exceeds the willingness-to-accept
6	≈	↓	**Not cost-effective** (comparator dominates the new intervention)
7	↑	≈	**Not cost-effective** (comparator dominates the new intervention)
8	↓	≈	**Cost-effective** (new intervention dominates the comparator *i.e.* cost-saving)
9	≈	≈	**Not cost-effective** (new intervention and comparator are equal)

Abbreviation: **↑:** statistically significantly higher; **↓:** statistically significantly lower; **≈:** no statistically significant differences

Table 2: Characteristics of the studies with pharmaceuticals treatments for dementia disorders

First author, year, country	Analysis	Intervention	Comparator	Target population; Sample size	Perspective; time horizon	Currency, price year	Outcomes measures	Discount rate	Incremental cost-effectiveness ratio (ICER)	Sensitivity analysis	Model	CHEERS	Funding source
Getsios, 2010, UK [21]	CUA	ChEI (Donepezil)	No treatment	Mild to moderate Alzheimer patients	Health care payer and societal; 10 years	GBP, 2007	QALY	3.5%	Donepezil dominates, gains 0.111 QALY and saves £4,700 per patient	PSA	DES	22	Industry
Hartz, 2012, Germany [22]	CUA	ChEI (Donepezil)	Memantine and no treatment	Mild-to-moderate and moderate – to-severe Alzheimer patients	Health care and societal; 10 years	Euro, 2008	QALY	3%	Donepezil dominates no treatment; gains 0.131 QALY and saves €7,007 and €9,893 from healthcare and societal perspective for Mild-to-moderate patients; Donepezil dominates memantine, gains 0.01 QALY and saves €1,960 and €2,825 from healthcare and societal perspective for moderate-to-severe patients	DSA and PSA	DES	22	Industry
Guo, 2010, Germany [23]	CEA	ChEI (Galantamine)	No treatment or ginkgo	Alzheimer patients	Third party payer (insurance); 10 years	Euro, 2009	LY, days of institutionalized delayed	5%	Glantamine dominates, gains 0.298 yrs and 0.280 yrs not in severe health state and saves €3,978 and €3, and 972 per patients comparing to no drug and Gingko, respectively	DSA	DES	22	Industry
Lachaine, 2011, Canada [24]	CUA	Memantine + ChEI	ChEI	Alzheimer patients	Health care and societal; 7 years	Can$, 2010	QALY	5%	Memantine+ ChEI dominates, gains 0.26 QALY and saves Can$ 21,391 and Can$ 30,512 per patient form societal and health care perspective	DSA and PSA	Markov	20	Industry
Pfeil, 2012, Switzerland [25]	CUA	Memantine + ChEI	ChEI (Donepezil)	Alzheimer patients	Health care and societal; 5 years	CHF, 2011	QALY	3%	Memantine+ ChEI dominates, gains 0.12 QALY and saves CHF 4,780 and CHF 27,656 per patient from societal and healthcare perspective	DSA	Markov	20	Industry
Touchon, 2014, France [26]	CUA	Memantine + ChEI	ChEI	Alzheimer patients	Health care and societal; 7 years	Euro, 2010	QALY	3%	Memantine+ ChEI dominates, gains 0.25 QALY and saves €3,318 and €8,341 per patient from societal and health care perspective	DSA and PSA	Markov	20	Industry

Thibault, 2015, USA [27]	CUA, CEA	Memantine (extended release) + ChEI	ChEI	Alzheimer patients	Health care and Societal; 3 years	US$, 2013	QALY, survival	3%	Memantine+ ChEI dominates, gains 0.12 QALY and saves $18,355 and $20,947 per patient from societal and health care perspective	DSA and PSA	DES	23	Industry
Bond, UK, 2012 [28]	CUA	Donepezil, galantamine, rivastigmine capsules and patches, memantine	Standard care	Mild-to-moderate and moderate – to-severe Alzheimer patients	NHS and PSS; 20 years	GBP, 2009	QALY	3.5%	£35,300/QALY for donepezil for moderate AD patients and £26,500/QALY for memantine for severe AD patients	DSA and PSA	Survival partition model	24	Government
Rive, 2010, UK [29]	CUA	Memantine	Standard care	Moderate-to-severe Alzheimer patients	Health care; 5 years	GBP, 2009	QALY	3.5%	Memantine dominates; saves £1,711 and gains 0.031 QALY also delays 6 weeks of admission to fulltime care	DSA and PSA	Markov	23	Industry
Rive, 2012, Norway [30]	CUA	Memantine	Standard care	Moderate-to-severe Alzheimer patients	Societal; 5 years	NOK, 2009	QALY	3%	Memantine dominates; saves NOK 30,041 and gains 0.025 QALY also delays 4.4 weeks of admission to fulltime care	DSA and PSA	Markov	23	Industry
Hoogveldt, 2011, The Netherlands [31]	CUA	Memantine	Standard care	Moderate-to-severe Alzheimer patients	Societal; 5 years	Euro, 2008	QALY	4% on health outcomes and 1.5% on cost	Memantine dominates; saves €3,830 and gains 0.058 QALY also increases 0.149 years of independence state	DSA and PSA	Markov	20	Not reported
Nagy, 2010, UK [32]	CUA	Rivastigmine patch and capsule	Best supportive treatment	Alzheimer patients	Societal; 5 years	GBP, 2008	QALY	3.5%	£10,579/QALY for patch and £15,154 /QALY for capsule	DSA and PSA	Not clear	20	Industry
Skoldunger, 2013, Sweden [33]	CUA	Disease modifying treatment (immunization therapy/secretase inhibitors)	No treatment	Alzheimer patients	Societal; 20 years	SEK, 2005	QALY	3%	293,002 SEK/QALY	DSA and PSA	Markov	21	Government & non-governmental organization
Banerjee, 2013, UK [34]	CEA, CUA	Sertraline and mirtazapine for reducing depression in dementia	Placebo	Dementia patient; Sertraline=107, Nirtazapine=108, Placebo=111	Health care; 13 and 39 weeks	GBP, 2009-2010	Cornell scale for depression in dementia, QALY	Not applicable	Mirtazapine dominates placebo; saves £1,106 and gains 0.05 QALY. Mirtazapine dominates Sertraline; saves £1,811 and gains 0.02 QALY	DSA	No model	20	Government & Industry

Abbreviations: CEA, cost-effectiveness analysis; ChEI, Acetylcholinesterase inhibitor; CHF, Swiss franc; CUA, cost utility analysis; DES, discrete event stimulation; DSA, deterministic sensitivity analysis; GBP, British pound; LY, life years; NOK, Norwegian krona; NR, Not reported; PSA, probabilistic sensitivity analysis; PSS, Personal Social Service; QALY, quality adjusted life years;

Table 3: Details of cost and QALY in the included economic evaluations of pharmaceutical treatments for dementia disorders

First author, year, country	Cost				QALY			
	Direct cost	Source	Indirect cost*	Source	Patient	Source	Caregiver	Source
Getsios, 2010, UK [21]	Donepezil, GP visits, patient care cost in the community care and institutionalized care	Direct cost form National register and national study.	Caregiver productivity loss (£5.20/hour) ($11.89/hour)	Indirect cost from two RCTs performed in northern Europe	EQ-5D (regression equation)	From 272 AD patients from Nordic countries	SF-36 (Regression equation)	From 272 AD patients from Nordic countries
Hartz, 2012, Germany [22]	Donepezil, GP visits	Country specific	Caregiver productivity loss (€5.21/hour) ($8.40/hour)	Indirect cost from two RCTs performed in northern Europe	EQ-5D (regression equation)	From 272 AD patients from Nordic countries	SF-36 (Regression equation)	From 272 AD patients from Nordic countries
Guo, 2010, Germany [23]	Medication, homecare and institutional care depending on disease severity	Country specific	Caregiver productivity loss (€5.50/hour) ($8.44/hour)	A study from Germany	NA	NA	NA	NA
Lachaine, 2011, Canada [24]	Medication, community care, nursing home	A study on 750 AD patients from Canada	Caregiver productivity loss (CAN$ 6.85/hour) ($6.36/hour)	A study on 750 AD patients from Canada	EQ-5D (regression equation)	From 272 AD patients from Nordic countries	Not Included	Not Relevant
Pfeil, 2012, Switzerland [25]	Medication, hospital, nursing home, outpatient nursing, physician, memory clinics	Treatment costs from a French study	Informal care (NM)	A study of 943 AD patients in USA	Health Utility Index	A study of 679 AD patients and caregivers in USA	Not Included	Not Relevant
Touchon, 2014, France [26]	Medication, community care and nursing homes	Country specific data	Informal care, nursing home care (€5123/year)	Not mentioned	Health Utility Index	A study of 679 AD patients and caregivers in USA	Not Included	Not Relevant
Thibault, 2015, USA [27]	Medication, community care, institutionalization	A multinational study of 1,222 patients	Informal care	A study of 679 caregivers of AD patients in USA (depend on AD severity level)	Health Utility Index	A study of 679 caregivers of AD patients in USA (depend on AD severity level)	Health Utility Index	A study of 679 caregivers of AD patients in USA (depend on AD severity level)
Bond, UK, 2012 [28]	Treatment, disease management and care	Literature and country specific	Not clear	Not clear	Averages of the caregiver-proxy EQ-5D, EQ-5D VAS, Qol-AD	Country specific and a retrospective study of 100 AD patients.	Not Included	Not Relevant
Rive, 2010, UK [29]	Medication, accommodation, inpatient care, outpatient care	A study from UK with 224 AD patients (LASER-AD study)	Not Included	Not Relevant	EQ-5D (regression equation)	A study from UK with 224 AD patients (LASER-AD study)	Not Included	Not Relevant

Rive, 2012, Norway [30]	Medication, accommodation, inpatient care, outpatient care	Country specific studies but not specific to AD patients	Informal care by loss of production (NOK 315/hour) and leisure time (NOK 49/hour) ($55.34/hour, $8.61/hour)	Norwegian value of time study (travel time) and OECD statistics	EQ-5D	A study on 272 patients with AD from Nordic	Not Included	Not Relevant
Hoogveldt, 2011, The Netherlands [31]	Medication, disease management and care by dependency and location of care	Country specific	Family and informal care (€7.94/hour) ($12.77/hour)	Not mentioned	EQ-5D	A study from UK with 224 AD patients (LASER-AD study)	Not Included	Not Relevant
Nagy, 2010, UK [32]	Medication, monitoring, institutionalization, community care	Country specific study	Informal care (£5.52/hour, UK minimum wage) ($11.01)	From a review study of Alzheimer's treatment	Health Utility Index version 3 (regression equation)	Country specific study	Not Included	Not Relevant
Skoldunger, 2013, Sweden [33]	Medication, home care, short- and long-term institutional care	Medication costs are hypothetical, other costs are country specific study	Informal care (SEK 91/hour) ($14.56/hour)	Country specific study	Time-trade off	A Swedish study based on mild cognitive impairment and dementia patients	Not Included	Not Relevant
Banerjee, 2013, UK [34]	Medication, healthcare and social care	Study specific	Informal care (productivity loss of work and leisure time)	Study specific	EQ-5D	Study specific	Not Included	Not Relevant

*Costs in parentheses are converted to 2015 USD using consumer price index and purchasing power parity. **Abbreviations:** AD, Alzheimer Disease; AMCI, Amnestic Mild Cognitive Impairment; MCI, Mild Cognitive Impairment;No EQ-5D, EuroQol Five Dimensions; GP, General Physician; HUI, Health Utility Index; NOK, Norwegian Krona; OECD, Organization for Economic Co-operation and Development; Qol-AD, Quality of Life-Alzheimer Disease; RCT, Randomized Controlled Trial; SF-36, 36-Item Short Form Health Survey; VAS, Visual Analog Scale; 15D, 15 dimensions.

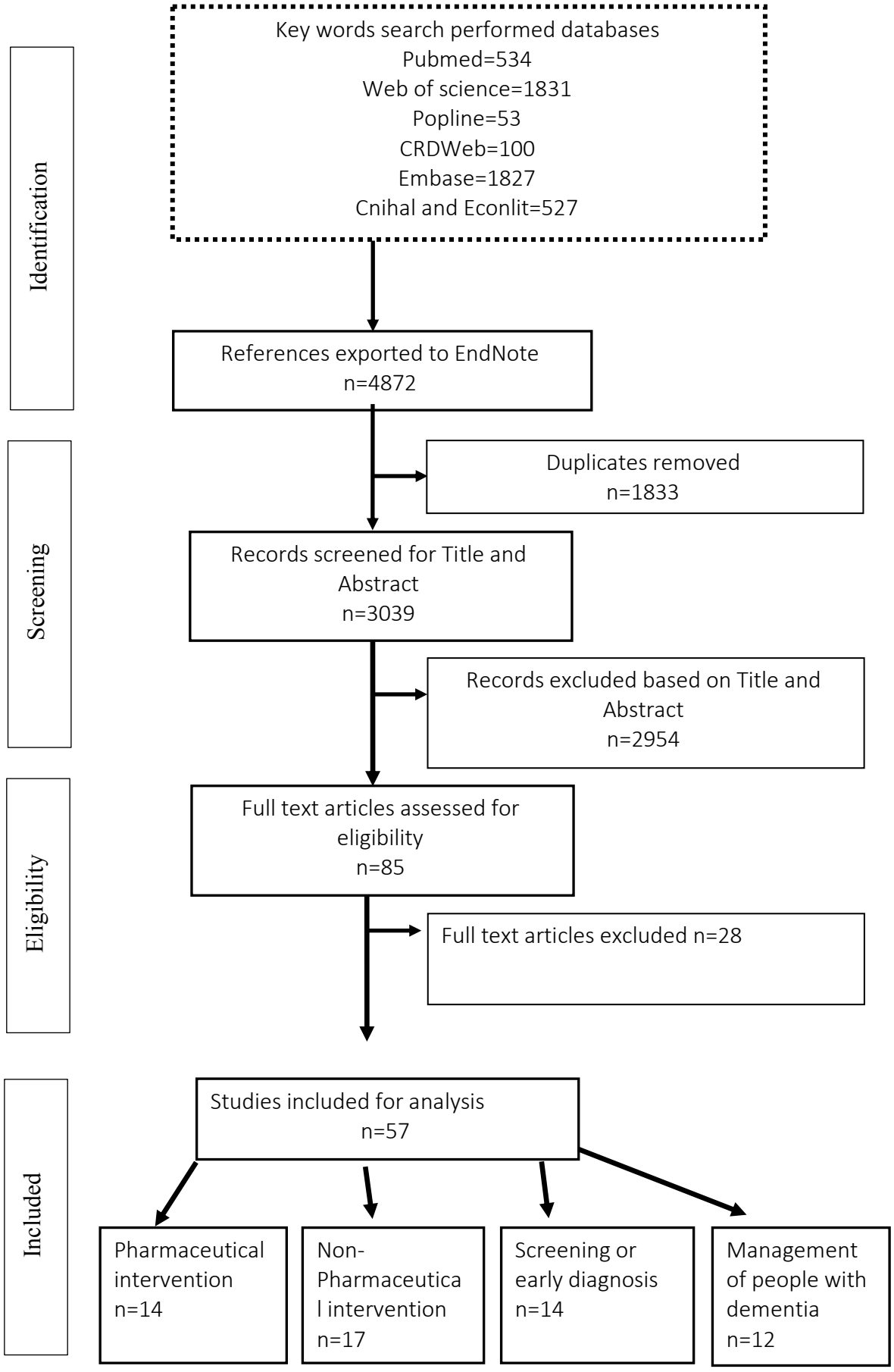
Table 4: Reported and evaluated cost-effectiveness of the selected studies

First author, year, country	Effectiveness measures	Reported	Evaluation	Remarks
Getsios, 2010, UK [21]	QALY (EQ-5D)	Dominant	95% CIs were not presented for either costs or QALYs. CEAC showed 85% probability to be cost-effective at £30,000 WTP from societal perspective for moderate severe patients	Weakly cost-effective
Hartz, 2012, Germany [22]	QALY (EQ-5D)	Dominant	95% CIs were not presented for either costs or QALYs. CE plane showed 99% probability donepezil is dominate for mild to moderate AD patients and 70% probability for moderate to severe patients	Cost-effective for mild to moderate AD patients and not cost-effective for moderate to severe AD patients
Guo, 2010, Germany [23]	Time spent in institutional care	Cost saving	95% CIs were not presented for either costs or effect.	Unknown due to lack of information and no agreed cost-effective threshold value
Lachaine, 2011, Canada [24]	QALY (EQ-5D)	Dominant	95% CIs were not presented for either costs or QALYs.	Unknown due to lack of information
Pfeil, 2012, Switzerland [25]	QALY (Health Utility Index)	Dominant	95% CIs were not presented for either costs or QALYs.	Unknown due to lack of information
Touchon, 2014, France [26]	QALY (Health Utility Index)	Dominant	95% CIs were not presented for either costs or QALYs. CEAC showed 99% probability to be cost-effective at £30,000 WTP from both healthcare and societal perspective	Cost-effective
Thibault, 2015, USA [27]	QALY (Health Utility Index)	Dominant	95% CIs were not presented for either costs or QALYs. CE plane showed that 97% probability the intervention was dominant	Cost-effective
Bond, UK, 2012 [28]	QALY (Averages of the caregiver-proxy EQ-5D, EQ-5D VAS, Qol-AD)	Not cost-effective (assuming the effects of drugs on survival)	95% CIs were not presented for either costs or QALYs. CEAC showed 28% probability to be cost-effective at £30,000 WTP for donepezil	Not cost-effective

Rive, 2010, UK [29]	QALY (EQ-5D)	Cost-effective	No significant differences in costs but significant differences in QALY gains were observed. CEAC showed 99% probability to be cost-effective at £30,000 WTP	Cost-effective
Rive, 2012, Norway [30]	QALY (EQ-5D)	Dominant	95% CIs were not presented for either costs or QALYs. CE plane showed that 99% probability the intervention was dominant.	Cost-effective
Hoogveldt, 2011, The Netherlands [31]	QALY (EQ-5D)	Dominant	No significant differences in costs but significant differences in QALY gains were observed.	Cost-effective
Nagy, 2010, UK [32]	QALY (Health Utility Index)	Cost-effective	95% CIs were not presented for either costs or QALYs. CEAC showed around 90% probability to be cost-effective at £30,000 WTP for all the interventions.	Cost-effective
Skoldunger, 2013, Sweden [33]	Time-trade off	Cost-effective	95% CIs were not presented for either costs or QALYs. CEAC showed around 80% probability to be cost-effective at £30,000 WTP	Weakly cost-effective
Banerjee, 2013, UK [34]	EQ-5D	Dominant	No significant differences in cost and QALY gains were observed. CEAC showed around 90% probability to be cost-effective at £30,000 WTP.	Cost-effective

Abbreviations: CEAC, Cost-effectiveness acceptability curve; DEMQOL, Quality of life dementia; EQ-5D, Euroqol five dimensions; QALY, Quality Adjusted Life Years; Qol-AD, Quality of life-Alzheimer disease; VAS, Visual Analogue Scale; WTP, Willingness-to-pay

Figure 1: A flow chart for selection of articles



Annex 1: Detailed search history in databases with keywords

Pubmed

("economic evaluation"[All Fields] OR "cost-benefit analysis"[MeSH Terms] OR "cost-effectiveness"[All Fields] OR "cost-benefit analysis"[MeSH Terms] OR "cost-benefit analysis"[MeSH Terms] OR "cost benefit"[All Fields] OR "cost utility"[All Fields] OR "cost-utility"[All Fields]) AND ((("dementia"[MeSH Terms] OR "dementia"[All Fields]) OR "dementia"[MeSH Terms]) OR "mild cognitive impairment"[All Fields]) AND (("2000/01/01"[PDAT] : "2015/12/31"[PDAT]) AND English[lang])

= 534

CRDWeb

((dementia)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED FROM 2000 TO 2016

=100

EMBASE

1. 'dementia'/exp OR dementia

2. 'cost effectiveness' OR 'cost utility' OR 'cost benefit analysis' OR 'economic evaluation'
3. 'mild cognitive impairment':ab
4. #1 OR #3
5. 'cost consequence analysis'
6. #2 OR #5
7. #4 AND #6
8. #7 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py)

=1827

Web of science

1. **TOPIC:** Dementia
2. **TOPIC:** Mild cognitive impairment
3. **TOPIC:** Alzheimer
4. **TOPIC:** Vascular dementia
5. **TOPIC:** Parkinson's disease
6. 1 OR 2 OR 3 OR 4 OR 5
7. **TOPIC:** (cost effectiveness) OR **TOPIC:** (cost-effectiveness analysis) OR **TOPIC:** (cost-effectiveness) OR **TOPIC:** (cost utility analysis) OR **TOPIC:** (cost-utility analysis) OR **TOPIC:** (cost benefit) OR **TOPIC:** (cost-benefit) OR **TOPIC:** (economic evaluation)

8. 6 AND 7 (Refined by: Publication Years (2000 to 2015))
9. 8 (Refined by: Language (English)

= 1831

1. Dementia
2. AB dementia
3. AB dementia OR mild cognitive impairment
4. Cost effectiveness
5. Cost benefit analysis
6. Cost utility analysis
7. Cost-utility analysis in healthcare
8. Economic evaluation
9. Cost consequences analysis in health economics
10. 4 OR 5 OR 6 OR7 OR 8 OR 9
11. 10 AND 3
12. 11 (limiters- 20000101-20151231)

= 527

Popline

1. ((((Title:dementia) OR (Title:alzheimer)))) AND ((Language:English) AND (Publication Year:[2000 TO 2015]) AND (Peer Reviewed:1) AND (Journal Article:1))

2. ((((Title:cost effectiveness analysis) OR (Title:cost utility analysis) OR (Title:economic evaluation) OR (Title:cost benefit analysis)))) AND ((Language:English) AND (Publication Year:[2000 TO 2015]) AND (Peer Reviewed:1) AND (Journal Article:1))

3. 1 OR 2

= 53