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A systematic review of economic evaluations of the use of memantine alone or combined with donepezil for moderate to severe Alzheimer's disease

Ione Ayala Gualandi de Oliveira[1]
Rosângela Caetano[1]
Ricardo Ewback Steffen[1]
Aline Navega Biz[1]

Abstract

Objective: To synthesize the available evidence and state of the art of economic evaluations which evaluate the use of memantine, whether alone or combined with donepezil, for moderate to severe Alzheimer's disease (AD), focusing on the analytical decision models built. *Method*: The electronic databases MEDLINE, EMBASE, NHS EED, CEA Registry and LILACS were searched for references. After duplicates were removed, two independent reviewers evaluated the titles and abstracts and subsequently the full texts. The Drummond M. tool was used to evaluate the quality of the studies. *Results:* After the application of the eligibility criteria, twelve complete economic evaluations were included. One evaluation was a clinical trial, two involved simulations and nine used Markov models. The main outcome measure adopted was dominated by cost per quality adjusted life year (QALY). The use of memantine was considered cost-effective and dominant in eight studies; while in a single study, its use was dominated when compared to donepezil for moderate AD. Sensitivity analyzes were systematically performed, with robust results. The quality assessment indicated that the methodological quality of the studies was good. *Conclusion*: Although there is some controversy regarding the benefits derived from the use of memantine, whether combined or not with donepezil, the evidence collected suggests that it is cost-effective in the countries where the studies were performed. However, local economic studies need to be performed, given the significant variability derived from the different parameters adopted in the evaluations.

Keywords: Alzheimer Disease. Memantine. Cost and Cost Analysis. Review.

[1] Universidade do Estado do Rio de Janeiro (UERJ), Instituto de Medicina Social. Rio de Janeiro, RJ, Brasil.

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Correspondence
Ione Ayala Gualandi de Oliveira
ionegualandi@yahoo.com.br

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INTRODUCTION

Alzheimer's Disease (AD) represents a serious public health problem, as it is the main cause of cognitive decline and dementia in adults, especially older adults. Its diagnosis is primarily clinical, based on the application of standardized criteria, and it progresses with damage to memory and other cognitive and behavioral functions[1].

AD affects around 25 million people around the world[2] and projections suggest that this total may reach 100 million by 2050[3]. In addition, a meta-analysis published in 2013 reports that the prevalence of dementias, standardized by age, varies between 5% and 7% in those aged 60 or older, and is higher in less developed countries, most of all in Latin America[4].

It is estimated that, in 2030, the elderly population in Brazil will reach approximately 41.6 million and that by 2060, one in every three Brazilians will be older than 60[5]. Brazilian studies have indicated a prevalence of dementia in the population aged over 65 of 7.1%, with AD responsible for more than 44% of cases[6].

There is currently no cure for AD and the impact of the illness on patients and caregivers leads to political pressure to ensure that all the possible treatments are widely available. In addition, there are limited options in terms of interventions during the course of the disease, which include two main groups of drugs.

Acetylcholinesterase inhibitors represent the first line of treatment of mild to moderate AD. Their use is based on the reduction of the cholinergic deficit, through the inhibition of the enzymes that degrade acetylcholine, increasing its synaptic availability and improving cognitive symptoms[1]. Memantine is a non-competitive NMDA (N-Methyl-D-Aspartate) glutamate receptor antagonist. It is the only drug in its class used in humans and is approved by the Food and Drug Administration, the European Medicines Agency and the National Health Surveillance Agency for the treatment of moderate to severe AD[7,8].

Studies on the efficacy of memantine in severe AD have produced controversial results. The drug's ability to delay symptom worsening and improve the functional capacity of patients with moderate to severe AD was originally demonstrated in two phase III randomized controlled clinical trials (RCCT)[9,10], both with a very short follow-up of 24 weeks.

Other trials, however, have failed to show such favorable results in measures of cognitive function and activities of daily living[11]. Meta-analyzes examining the efficacy of memantine used alone or in combination with anticolinesterase inhibitors have found that improvements in cognitive functions and activities of daily living in patients with moderate to severe AD when present were systematically small in scale[12-14]. The evidence is also conflicting in terms of behavioral and neuropsychiatric symptoms[15]. In contrast, although usually mild to moderate, patients on memantine may experience headaches, dizziness, fatigue, mental confusion, and hallucinations[10]. Some other aspects that undermine the available evidence on the efficacy of memantine are worth mentioning: some RCCTs had small sample sizes, significant follow-up losses, received direct funding, or had authors who declared having received different types of funding from the pharmaceutical industry, and, therefore, potential conflicts of interest could not be excluded[16].

Due to the transient efficacy of AD treatment drugs, the progression to functional dependence continues even with their use[17]. In addition, they are often difficult to use due to their adverse events, such as hypertension, drowsiness and central nervous system-related disorders, and interactions with other drugs.

Considering the harm-benefit ratio as unfavorable, with low efficacy results and potentially significant adverse events in frequency and severity, the French Ministry of Health decided that as of August 2018 anticholinesterases and memantine would no longer be reimbursed by the national health insurance system. At the end of 2016, the Pharmacoeconomic Transparency Committee, which makes recommendations on public drug reimbursement in France, concluded that these drugs did not bring sufficient clinical benefits and called for their exclusion from the list of publicly provided drugs in France, which only became official following the *Haute Autorité de Santé* report

in May 2018[18,19]. The drug, however, is still present in clinical treatment protocols and is reimbursed in other countries, such as through Medicare in the US, the UK and Australia[20].

In Brazil, anticholinesterases have been available in the Unified Health System (or SUS) since 2002, restricted to patients with mild to moderate forms of the disease[21]. Memantine, however, was only incorporated within the SUS for the treatment of moderate and severe AD in 2017[7]. Even before that, however, it was bought by the Ministry of Health (MoH), with a total purchase of approximately 33,000 10mg tablets between 2010 and 2014, to meet judicial orders[22].

The burden of disease and the costs associated with AD, population aging, and the lack of disease-modifying treatment options raise concerns about the efficient use of resources. While current legislation in Brazil requires comparative cost-effectiveness evidence for the incorporation of a new technology into the SUS[23], economic evaluation studies have not been carried out by the Ministry of Health, with their introduction into the system being justified by clinical data and the drug's incorporation into the payment systems of other countries[7].

Given the uncertainties in literature, the present study aimed to synthesize the evidence available in economic studies regarding the use of memantine, whether alone or combined with donepezil, to treat moderate to severe AD, focusing on the analytical decision models used in these evaluations.

METHOD

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)[24] guidelines and registered with the PROSPERO International Prospective Register of Systematic Reviews under Nº. CRD42017076469, in October 2017.

Study identification and search strategy

The MEDLINE, EMBASE, and LILACS bibliographic databases, as well as the Cochrane Collaboration and specific bases for economic studies – the NHS Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE) and the Cost-Effectiveness Analysis (CEA) Registry - were used to search for studies published up to March 2017.

Search strategies were developed for each database based on specific descriptors, combined with the Boolean operators for AD and the drugs of interest (donepezil and memantine), using specific filters for economic studies. Search strategies specific to each database can be obtained by correspondence with the authors.

There was no restriction on publication period or language in the search. Narrative and systematic reviews of economic studies on the subject were examined for cross-references that might not otherwise have been identified.

References identified in electronic databases were managed using the ENDNOTE® software (version X4) for the elimination of duplicates.

Study selection

The articles were selected in two stages (titles and abstracts and, later, the full text), by two reviewers (IAGO and ANB), with disagreements resolved by consensus or, when necessary, through consultation with a third reviewer (RC).

To be included, studies were required to meet the following eligibility criteria: either primary studies (economic assessments conducted through observational studies and randomized controlled trials) or modeling studies related to the use of memantine, whether alone or in combination with donepezil, in adult patients diagnosed with moderate to severe AD, with disease severity determined by a specified assessment scale. Only complete economic assessments (cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis) with the clear identification of comparators (placebo, no specific treatment, galantamine, rivastigmine or donepezil anticholinesterases or other types of non-pharmacological treatment) and measures of

outcome, such as cost per year of life gained, cost per quality adjusted life year (QALY) and cost per time spent in a non-dependent state, were considered. All studies written in English, Portuguese and Spanish were included.

Letters, editorials, narrative reviews, partial economic assessments, and studies that did not contain explicit information on the methods and criteria defined above were excluded.

Methodological Quality Assessment

The quality assessment of the included economic studies was also performed by two independent reviewers (IAGO and RES), with disagreements resolved as described above.

The tool developed by Drummond M.[25] was used. It presents 35 evaluation items, distributed in three sections: aspects of study design; sources and quality of the collected data; data analysis and interpretation of results. Six additional items were introduced: data related to the presence of subgroup analysis, study limitations, potential for generalization of results, declarations of conflict of interest and study funding.

Each item was judged as *yes, no, not clear,* or *not-applicable*.

Data extraction

The relevant data were independently extracted by two reviewers and recorded in a standardized electronic form built on EPIDATA software, with disagreements resolved by a third reviewer.

Data were extracted related to (i) study identification; (ii) general characteristics of economic assessments (type and design of study; country; characteristics of population studied; type of intervention and comparator; measure of effectiveness adopted and data source; types and details of included costs; currency and year of reference; Alzheimer's disease progression model; outcomes; presence of cost-effectiveness threshold) (iii) general characteristics of the analytical decision models used (perspective, time horizon, main health outcomes, analytical approach, discount rate application, sensitivity analysis), as well as (iv) main model conclusions and limitations.

The collected data were analyzed descriptively using Microsoft Excel 2010. For the nominal data, numbers and percentages are provided, while median and ranges are used for the ordinal data. No summary measures related to the incremental cost-effectiveness measures, which are not usually recommended in systematic reviews of economic analyzes, were calculated, given the methodological, population and interventions predictable differences between studies, which may generate significant heterogeneity of results[26].

The characteristics and results of the included studies were summarized using tables, complemented by a narrative summary that sought to compare and evaluate the methods used and the main results between the studies.

RESULTS

A total of 1,171 references were identified in the bibliographic databases searched. After eliminating 167 duplicate records, 1,004 abstracts were examined and 63 full-text articles were evaluated. Of these, 12 economic assessments met the eligibility criteria[27-38] and were included in the review (Figure 1).

There was considerable variation in the countries where the evaluations were conducted, with five studies carried out in the United Kingdom. More than half of the studies were published from 2010 onwards. Data on the age of the simulated populations varied considerably, but 83.3% considered the study population to be 60 years or older (Table 1).

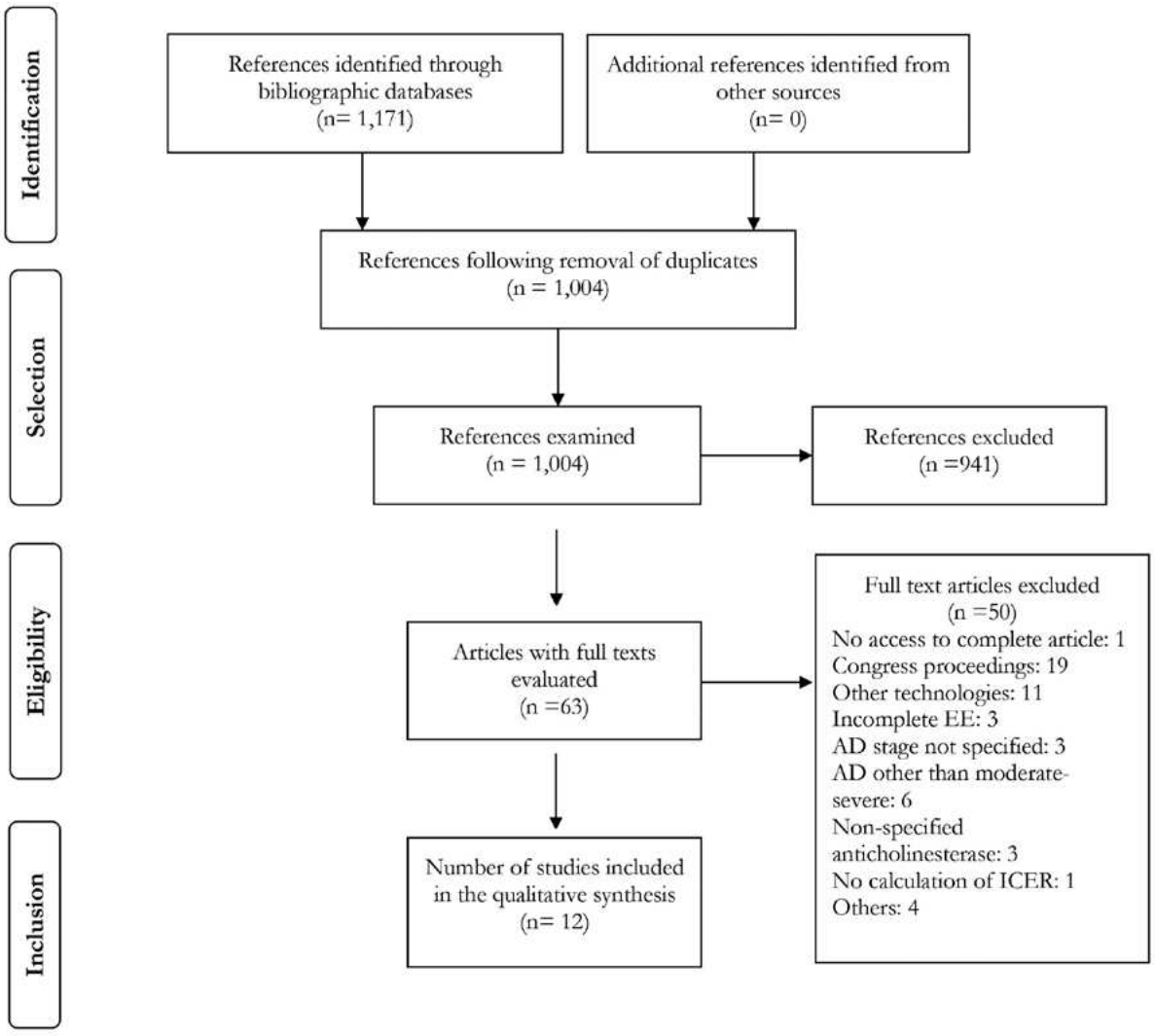
Cost-utility studies that measured outcomes in terms of cost per QALY gained were the predominant type of economic assessment (75%), and there were only two studies[35,38], both cost-effectiveness studies, in which results were expressed only in terms of cost per year of life with independence gained. Eleven studies included populations with moderate-severe

AD in their analysis. Six studies used more than one analytical perspective to assess costs and benefits; the perspective of society, in which all costs were computed, including those incurred by caregivers or due to loss of productivity of patients and their families, was adopted in seven studies (58.3%) while the health system perspective, in which only the costs incurred by the health care funder are considered, was used in seven (58.3%) studies, and social security costs were considered in three.

The main source of information on drug efficacy measures used to feed the models was previously published controlled clinical trials (75%).

As can be seen in Table 2, which summarizes the main characteristics of the models used in economic evaluations, a single study was conducted through a clinical trial (piggyback evaluation) and did not use modeling in its construction[27], while nine economic evaluations (75%) used Markov's approach as their analytical model.

The main measure of cost-effectiveness outcome was the quality-adjusted life year (QALY). Intermediate outcomes, such as cost per year or period of independence and cost per year without patient institutionalization, were used in three studies[33,35,38] (Chart 2).



EE: Economic evaluations; AD: Alzheimer's Disease; ICER: Incremental cost-effectiveness ratio.

Figure 1. Flowchart of the search and selection process of studies included in the systematic review.

Chart 1. General characteristics of economic assessment studies included in the systematic review.

Author, year Country / Currency (year*)	Type of Economic Evaluation and Target Population	Perspective of Analysis	Intervention Examined Versus Comparator Used in Economic Evaluation /Effectiveness data source type	Costs included in economic assessment studies
Knapp et al., 2016[27] UK / € (2013/14)	ACU Moderate/ severe AD	Health System Society	MEMAN *vs* PL MEMAN + DON *vs* DON/RCCT	Direct: Drugs, Consultations, Hospitalization, Caregiver / Indirect ‡
Hyde et al., 2013[28] UK / £ (2009)	ACU Moderate/ severe AD	Health System	MEMAN *vs* absence of treatment*** (Systematic Review)	Direct: Drugs, appointments, hospitalization, other health professionals
Rive et al., 2012[29] Norway / € (2009)	ACU Moderate/ severe AD	Society Health System	MEMAN *vs* Ach** (Metanalysis)	Direct: Drugs, appointments, tests, hospitalization, caregiver, other health professionals / Indirect ‡
Hartz et al., 2012[30] Germany /€ (2011)	ACU Moderate AD	Society Social Security	MEMAN *vs* DON (RCCT)	Direct: Drugs, appointments, exams, hospitalization, caregiver, other health professionals, / Indirect: ‡
Bond et al., 2012[31] UK /£ (2009)	ACU Moderate/ severe AD	Health System	MEMAN *vs* absence of treatment*** (Systematic review)	Direct: Drugs, consultations, hospitalization, caregiver, other health professionals, institutionalization costs, other support measures
Rive et al., 2010[32] UK / £ (2008/2009)	ACU Moderate/ severe AD	Health System Social Security	MEMAN *vs* Ach** RCCT	Direct: Drugs, hospitalization, other health professionals
Gagnon et al., 2007[33] Canada / CAD$ (2005)	ACU Moderate/ severe AD	Society	MEMAN *vs* absence of tto*** RCCT	Direct: Drugs, consultations, hospitalization, outpatient care, other health professionals, institutionalization costs, caregiver / Indirect ‡:
Weyker et al., 2007[34] USA / US$ (2005)	ACU Moderate/ severe AD	Society	MEMAN + DON *vs* DON RCCT	Direct: Drugs, consultations, hospitalization, institutionalization costs, outpatient appointments / Indirect ‡
Antonanzas et al., 2006[35] Spain / € (2005)	ACE Moderate/ severe AD	Society	MEMAN *vs* absence of treatment*** RCCT	Direct: Medicines, Consultations, Hospitalization / Indirect ‡
Jonsson et al., 2005[36] Sweden / SEK (2004)	ACU Moderate/ severe AD	Health system	MEMAN *vs* PL RCCT	Direct: Drugs, consultations, hospitalization, health professionals.
François et al., 2004[37] Finland / € (2001)	ACE Moderate/ severe AD	Society	MEMAN *vs* PL RCCT	Direct: Drugs, consultations, hospitalization, caregiver, institutionalization costs, other health professionals / Indirect ‡
Jones et al., 2004[38] UK / £ (2003)	ACU Moderate/ severe AD	Health system Social security	MEMAN *vs* PL RCCT	Direct: Drugs, consultations, hospitalization, outpatient care, other health professionals, institutionalization costs

Ach: Cholinesterase inhibtor, ACE: cost-effectiveness, ACU: cost-utility, AD: Alzheimer's Disease; DON: donepezil, RCCT: Randomized Clinical Controlled Trial; USA: United States; MEMAN: memantine, PL: placebo; *Year in which costs were reported, **Author does not discriminate cholinesterase chibinito; *** absence of specific pharmacological treatment; ‡ — Indirect costs involving costs of informal workers

Chart 2. General characteristics of the analytical decision model structures of the studies included in the systematic review.

Study / Year	Time horizon	Main Outcome / Measures	Analytical Approach: Model, States/Cycle Length	Discount rate (%) Costs / Benefits
Hyde et al., 2013[28]	20 years	Cost/QALY	Markov 3 states (pre-institutionalized, institutionalized and dead)/ 12 months	No Information
Rive et al., 2012[29]	5 years	Cost/QALY	Markov 3 states (pre-institutionalized, institutionalized and dead)/ 1 month	3 / 3
Hartz et al., 2012[30]	10 years	Cost/QALY	Discrete-event simulation	3 / 3
Bond et al., 2012[31]	20 years	Cost/QALY	Markov 3 states (pre-institutionalized, institutionalized and dead)/ 12 months	3.5 / 1.5
Rive et al., 2010[32]	5 years	Cost/QALY	Markov 3 states (pre-institutionalized, institutionalized and dead)/ 1 month	3.5 / 3.5
Gagnon et al., 2007[33]	2 years	Cost/QALY Cost/year of independence	Markov 5 states (combination of severity and independence and dead stages) / 6 months	5 / 5
Weyker et al., 2007[34]	6 months / 1 year / 1.5 years / 2 years / Lifetime	Cost/QALY	Discrete-event simulation	3 / 3
Antonanzas et al., 2006[35]	2 years	Cost/year of independence	Markov 6 states (combination of severity and independence and dead stage) / 6 months	6 / 6
Jonsson, 2005[36]	5 years	Cost/QALY	Markov 13 states (combination of three variables: severity, independence, institutionalization status, and dead) / 6 months	3 / 3
François et al., 2004[37]	5 years	Cost/year of independence gained Cost/year without institutionalization	Markov 13 states (combination of severity, independence, institutionalization status, and dead) / 6 months	5 / 5
Jones et al., 2004[38]	2 years	Cost/QALY	Markov 13 states (combination of three variables: severity, independence, institutionalization status, and dead) / 6 months	3.5 / 3.5

QALY: Quality-adjusted life-year;

Eight studies (66.6%) employed in its analysis a time horizon of five years or more, two had a time horizon of 20 years[28,31] and one used lifetime[34].

The number of Markov states and the duration of cycles varied between publications. Four studies (33.3%) considered only three health states (pre-institutionalized, institutionalized and dead)[28,29,31,32].

The main study designs used to investigate the progression of AD and the likelihood of change in health status were clinical trials and observational studies from population-based registries.

The scales used for the clinical evaluation of AD and the domains considered differed greatly between studies. The cognitive approach and measures related to activities of daily living, in addition to behavior, were the main competences included.

Regarding the main findings of the economic assessments included, the results of the use of memantine was considered cost-effective and dominant, i.e., less costly and more effective than its comparator, in nine studies (75%), as shown in Chart 3. In one study only[28], memantine was not cost-effective when compared to donepezil in the moderate AD population, defined by the MMSE scores of ≥10 and <25 (Table 3).

A sensitivity analysis to examine the uncertainty regarding the parameters and structure of the models was included in all studies, with deterministic analyses being the most used (66.6%); while extreme scenario analyses were included in two studies[33,36].

The methodological quality of the included studies was considered good (Figure 2). The worst quality items were the justifications for choosing the discount rate adopted, details of the statistical methods and the disaggregated presentation of results. All the manuscripts presented arguments regarding the limitations of their study. In addition, 80% declared a conflict of interest and funding in their publications. Most manuscripts were funded by industry (75%).

Chart 3. Main results of economic assessments and uncertainty analyzes

Author	Main results	Sensitivity Analysis
Knapp et al., 2016[27]	ICER*/ HS: MEMAN *vs* dominant PL / MEMAN +DON *vs* DON cost-effective; Soc. MEMAN+DON vs DON non-cost-effective	Acceptability C.: Chance 95% MEMAN cost-effective *vs* PL with threshold of £30,000 and of 55% of MEMAN + DON *vs* DON cost-effective with same threshold
Hyde et al., 2013[28]	ICER £32,100/QALY / MEMAN cost-effective *vs* no specified treatment	Acceptability C.: Chance of 38% MEMAN cost-effective *vs* no treatment with threshold of €30.000
Rive et al., 2012[29]	Negative ICER ** / MEMAN dominant *vs* Ach***	Deterministic: MEMAN dominant *vs* Ach*** Probabilistic: Chance >98% of MEMAN being cost-effective
Hartz et al., 2012[30]	MEMAN non-cost-effective and dominated by DON Δ costs DON: -€2,225 / ΔQALY: 0.017	Deterministic: DON dominant *vs* MEMAN in all simulations Probabilistic: Chance >70% of DON dominating MEMAN Acceptability C.: Chance >90% of DON cost-effective with threshold of €10,000
Bond et al., 2012[31]	ICER*£32,100/QALY / MEMAN cost-effective *vs* no specified treatment	Deterministic: MEMAN cost-effective; MEMAN effectiveness alters ICER Acceptability C.: Chance 38% MEMAN cost-effective with threshold of £30,000
Rive et al., 2010[32]	ICER negative** / MEMAN cost-effective vs Ach*** Δ costs: -£1,711/ Δ QALY: 0.031	Deterministic: MEMAN dominant *vs* Ach*** Probabilistic: Chance >99% MEMAN being cost-effective Acceptability C.: Chance >98% MEMAN cost-effective with threshold of €20,000
Gagnon et al., 2007[33]	ICER negative** / MEMAN cost-effective *vs* no treatment Δ costs: -CAD$1,276 / Δ QALY: 0.031 / Δ years without complete dependence: 0.09	Deterministic: MEMAN dominant *vs* no treatment Probabilistic: MEMAN cost-neutral in 83.3% Acceptability C.: Chance 89.5% MEMAN cost-effective with threshold of €20,000
Weyker et al., 2007[34]	ICER*: TH of 6m: 3.475 / TH of 12m: 382 / TH de 18m: -5.102 / TH entire life: -US$8,880 / MEMAN + DON is cost-effective *vs* DON	Deterministic: MEMAN cost-effective and dominant *vs* DON
Antonanzas et al., 2006[35]	ICER negative** / MEMAN cost-effective *vs* no treatment Δ costs: -€667 / Δ years independence gained: 0.202	Acceptability C.: Chance >98% MEMAN cost-effective vs PL with threshold of €30,000
Jonsson, 2005[36]	ICER negative** /MEMAN cost-effective *vs* PL Δ costs: -SEK100,528 / Δ QALY: 0,148	Deterministic: MEMAN dominant *vs* PL Extreme scenario analysis: MEMAN dominant
François et al., 2004[37]	ICER negative** / MEMAN cost-effective *vs* PL Δ costs: -€1,687 / Δ years of independence: 0.34	Probabilistic: Chance >93% MEMAN *vs* PL cost-effective and dominant Acceptability C.: Chance >99% MEMAN cost-effective with threshold of €30,000
Jones et al., 2004[38]	ICER negative** / MEMAN cost-effective *vs* PL Δ costs: -£1,963 / Δ QALY: 0.04	Deterministic univariate: MEMAN cost-effective *vs* PL in all scenarios

Acceptability C.: Acceptability Curve; DON: Donepezil; MEMAN: Memantine; PL: Placebo; TH: Time Horizon; QALY: Quality-adjusted life-year; ICER: Incremental cost-effectiveness ratio; HS: Healthcare System; Soc: Society; Δ: Difference; vs: versus; *ICER: Incremental cost-effectiveness ratio; Negative ICER **: use of intervention represents resource savings compared with comparator; Ach***: Non-specified inhibitors

EE: Economic Evaluations; CI: Confidence Intervals

Figure 2. Assessment of methodological quality of economic evaluation studies included.

DISCUSSION

The increase in health-related costs in a scenario of limited resources, as well as the growing prevalence of Alzheimer's disease associated with population aging, mean it is imperative to examine the relationship between costs and clinical benefits the drugs used in their treatment, especially when evidence of the efficacy of therapy isn't strong and the benefits are considered insufficient.

A systematic review of the risk-benefit of inhibitors and memantine use in AD states that its benefits are marginal and short-termed, indicating that it should be used cautiously in the elderly population, where side effects may be more significant, especially with inhibitors of the drugs[17]. Some health systems do not include or have withdrawn memantine funding for the treatment of moderate to severe stages of disease[18,19]. Others restrict this funding to fixed time periods (eg, one year), during which users

are periodically reassessed, with the suspension of coverage if there is evidence of disease progression supported by the application of certain scales such as the Mini-Mental State Exam (MMSE) and the Clinical Dementia Rating (CDR)[39].

Considering the incremental cost-effectiveness ratios and cost-effectiveness thresholds defined in each country, the results showed that the use of memantine for moderate to severe AD was considered cost-effective in most studies, being the dominant therapeutic strategy in eleven articles, that is, less costly and with better health outcomes. Sensitivity analyzes concerning the variation of a large number of parameters reinforce the fact that these results were robust, that is, they remained favorable to memantine.

It should be noted, however, that all studies were conducted in developed countries and mostly applied the societal perspective, computing costs that included caregiver time, costs incurred by families and productivity losses associated disease, wheter by patients or family members.

The incremental cost-effectiveness ratios resulting from the analyzes varied widely. This variability possibly resulted from aspects related to study design, the perspective adopted and the assumptions considered, resulting in limitations related to the comparability between studies.

The results are consistent with some reviews already available on the subject. In 2018, a systematic review published by Ebrahem and Oremus[16] on economic assessments related to the treatment of AD identified 14 studies related to the use of memantine alone or combined with anticholinesterases, with 93.7% of the studies also finding that memantine was cost-effective.

A single study included in the present review concluded that the strategy of using memantine alone was dominated by donepezil for moderate AD, or in other words, the inhibitors had comparatively lower costs and better health outcomes[30]. Sensitivity analyzes reinforced the robustness of these results, being favorable to donepezil based on variations in the parameters, with the acceptability curve showing a greater than 90% chance of inhibitor being cost-effective at a threshold as low as €10,000.00 (2011 figures).

The study by Hartz et al.[30], conducted in Germany with a ten-year time horizon, used discrete-event simulation to capture, from the societal perspective, the costs and effects of treatment with respect to activities of daily living, improvements in function measured by MMSE and in the neuropsychiatric inventory. Unlike the other evaluations, the target population considered had moderate AD, the clinical stage of the disease in which the effects of memantine in isolation remain controversial[40].

The included studies that examined memantine in combination with donepezil also indicated divergent cost-effectiveness results between studies, depending on the reference population[27,34]. The study by Knapp et al.[27], an economic evaluation performed in parallel with a controlled clinical trial published in 2016, showed that the memantine-donepezil combination was not cost-effective compared to donepezil alone for moderate disease[23]. The study by Weyker et al.[34], meanwhile, conducted in the US using discrete-event simulation, showed that this association was cost-effective for moderate and severe AD, considering time horizons greater than six months. In addition to examining diverse patient populations, the study designs were also distinct, which may have contributed to the difference in outcomes observed.

Markov's approach was the main type of modeling employed in the economic assessments examined (75%). The use of Markov chains is frequently recommended for modelling chronic diseases, where individuals move between different stages of the disease over time, reflecting their natural history[41].

The simulated time horizons in the studies ranged from two years to lifetime, with most having horizons of five years or more. Considering that AD has a median survival period of 8.3 years in patients diagnosed aged 65 and over[42], the chosen horizons mostly contemplate the life expectancy of these patients and can adequately capture the most relevant costs and benefits expected from the treatments used.

The cognitive domain is a relevant outcome in the natural course of the Alzheimer's disease progression

process and should be adopted in the modeling of this disease. However, modeling should also adopt domains other than the cognitive in order to consider the complexity of this disorder.

Literature suggests that modeling including aspects related to function, level of patient's dependence on a caregiver and quality of life may more accurately reflect the progression of AD[43]. Clinical trials, commonly used as a data source in the economic evaluations found, are often insufficient and too short to evaluate such results, for which economic health models that combine trial data with real-world evidence are particularly useful[44].

The vast majority of the evaluations present in this review used, as an outcome of the cost-effectiveness of the intervention, quality-adjusted life years, whether alone or combined with other dimensions. QALY is a multidimensional concept whose use is particularly important in chronic conditions, and especially when the results of the intervention affect survival less and the domains of relationships and living more (cognition, mood, behavior, functionality and the ability to live longer without requiring special care or institutionalization), as observed in AD[45]. However, some studies suggest that QALY may not be fully accurate for the evaluation of individuals living with AD, as it is often caregivers, and non-patients, who provide proxy measures[46].

There is a relative scarcity of data related to the use of drugs such as memantine and donepezil and their effects on delaying institutionalization[47]. In addition, the reasons leading to the institutionalization of AD patients are multifactorial and complex, involving patient and caregiver characteristics, and the social and cultural environment. These types of outcomes are not usually evaluated in clinical trials, have significant impacts on health costs, and may underestimate overall cost measures, particularly the indirect costs of AD patient care[48].

Finally, it should be mentioned that most evaluations assumed that the drugs did not have an effect on mortality, which was supported by the fact that symptomatic therapies generally had no effect on the underlying disease process, and the lack of evidence of such an effect from relatively short-term clinical trials.

Most of the evaluations used randomized controlled trials as a source of data on the effectiveness of treatment. This can set a good internal validity in the model construction, but has a low external validity, since most trials have a short duration and cannot add long-term treatment effects. In addition, the use of parameters from a clinical trial conducted in one country in evaluations performed in another may pose a problem in generalizing modeling results, which is further accentuated when measures are applied as utilities to generate QALY.

Few economic models used in the simulations contemplated the scope of the natural history of AD. There is great variability in the assumptions made in these studies, in their effectiveness and cost data sources, their utility measure calculations and the transparency of their models. Therefore, caution is advised regarding the conclusions of the present review.

Finally, the number of economic evaluations funded by the pharmaceutical industry in which their drugs dominated their comparators was high, increasing the risk of possible publication bias.

CONCLUSIONS

Most of the economic assessments included in this review indicate that the use of memantine alone or combined with donepezil for moderate to severe Alzheimer's disease is predominantly cost-effective in countries where the studies were conducted. Although most uncertainty analyzes confirm the robustness of the results presented, caution is required when transferring cost-effectiveness findings from one country to another, either because of the difficulty of extrapolating data costs due to different payment structures and systems and national incentives, or because considering a cost-effective strategy is closely related to the cost-effectiveness thresholds implicitly or explicitly adopted in each country. The fact that most evaluations are funded by industry highlights that studies may contain significant biases and,

for that reason, caution should be exercised in the process of interpreting these results.

Therefore, local-based analyzes should be performed in Brazil, paying close attention to the issues and limitations raised from the economic evaluations already performed, so that the cost-effectiveness of memantine, whether combined or not with donepezil, for severe Alzheimer's Disease is more accurately assessed.

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