ORIGINAL ARTICLE

Cost-effectiveness analysis of the treatment of mild and moderate Alzheimer's disease in Brazil

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Objective: To perform a cost-effectiveness analysis of donepezil and rivastigmine therapy for mild and moderate Alzheimer's disease (AD) from the perspective of the Brazilian Unified Health System.
Method: A hypothetical cohort of 1,000 individuals of both sexes, aged > 65 years, and diagnosed with AD was simulated using a Markov model. The time horizon was 10 years, with 1-year cycles. A deterministic and probabilistic sensitivity analysis was performed.
Results: For mild AD, the study showed an increase in quality-adjusted life years (QALYs) of 0.61 QALY/21,907.38 Brazilian reais (BRL) for patients treated with donepezil and 0.58 QALY/BRL 24,683.33 for patients treated with rivastigmine. In the moderate AD group, QALY increases of 0.05/ BRL 27,414.96 were observed for patients treated with donepezil and 0.06/BRL 34,222.96 for patients treated with rivastigmine.
Conclusions: The findings of this study contradict the standard of care for mild and moderate AD in Brazil, which is based on rivastigmine. A pharmacological treatment option based on current Brazilian clinical practice guidelines for AD suggests that rivastigmine is less cost-effective (0.39 QALY/BRL 32,685.77) than donepezil. Probabilistic analysis indicates that donepezil is the most cost-effective treatment for mild and moderate AD.

Keywords: Alzheimer's disease; economic issues; administration; geriatric psychiatry

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that causes dementia with gradual loss of cognitive function, leading to declines in social and functional activities of daily living. Up to 75% of cases of dementia involve AD.[1]

The World Health Organization (WHO) and Alzheimer's Disease International (ADI) report that the global prevalence of dementia will rise from 35 million in 2012 to 115 million by 2050.[2] In Latin America, the prevalence of dementia in the population over age 65 is 7.1%, increasing with advancing age.[3-5] In Brazil, the incidence of dementia ranges from 13.8 to 34.2 per 1,000 population/ year.[4,6] Despite the scarcity of further data on the prevalence and incidence of AD in Brazil, studies have reported incidence rates between 7.7 new cases/year in São Paulo to 14.8 new cases/year in Rio Grande do Sul.[4,7]

The impacts of AD can be observed at different levels in society. Disease progression and the consequent demential process cause loss not only of cognitive and functional abilities but also of quality of life. In addition to the social impact, there is an economic impact caused by the care needs that result from AD progression.[8] The economic burden of AD is also felt by governments, as the social cost of AD has risen to become one of its most significant chronic effects in recent decades.[9,10]

To date, only two countries in Latin America have specific policies for dementia. Bolivia approved Law No. 4034, Creación de Centros de Apoyo a Enfermos de Alzheimer y otras Demencias (Creation of Support Centers for Patients with Alzheimer and Other Dementias) in 2009, while Peru implemented Law No. 30020 in 2013, which establishes the Plan Nacional para la Enfermedad de Alzheimer y otras Demencias (National Plan for Alzheimer's Disease and other Dementias). Despite pushes by the Pan American Health Organization (PAHO)/ WHO and ADI for the development of plans of action for mental health, the current Brazilian policy for dementia care is largely based on pharmacotherapy and compliance with the Brazilian Ministry of Health's corresponding clinical practice guideline (Protocolo Clínico e Diretrizes Terapêuticas, PCDT).[11]

Medications currently approved for the treatment of AD are still purely symptomatic, and produce only modest effects.[12] Anticholinesterase agents are the mainstay of AD pharmacotherapy, and there is some evidence that they work to slow disease progression.[13] Among these agents, donepezil, galantine, and rivastigmine are listed in the Brazilian PCDT.

In an analysis of anticholinesterase agent procurement data available through the Outpatient Information System (Sistema de Informações Ambulatoriais, SIA) of the Brazilian Unified Health System, Lima & Coradi[14] reported a 109% increase in expenditures over a 5-year period, from BRL 75.6 million in 2007 to BRL 157.8 million in 2011. From 2008-2013, more than 47 million unit doses of these medicines were purchased, at a total cost exceeding BRL 90 million. Rivastigmine, in its various dosage forms, was the most commonly used drug (46.4% of all purchases). Drugs not indicated in the PCDT accounted for 3% of expenditures, with a negligible percentage of purchases[9] occurring as the result of legal action. The trend for increased donepezil purchasing continued until 2012, at which time a decline occurred. Rivastigmine purchases presented a fluctuating trend in the period of analysis, with significant reductions in the volumes purchased in 2012 and 2013, when Productive Development Partnership (PDP) agreements were implemented.[9] Given this context, to what extent can a cost-effective AD care policy be sought from the standpoint of medications?

The objective of this work is to perform an analysis of the cost-effectiveness of donepezil and rivastigmine, the drugs most commonly prescribed for mild and moderate AD,[15] from the perspective of the Unified Health System.

Method

A Markov chain simulation was used to carry out cost-effectiveness analysis of pharmacological treatment strategies for AD. Therapeutic scenarios for the treatment of AD were modeled according to the corresponding PCDT.[11] The transition stages of the disease according to the Mini Mental State Examination (MMSE)[16] were also included, with death as an absorptive stage (Figure 1).

The Markov simulation model was calculated using TreeAge Pro® software version 2011. A hypothetical cohort of 1,000 individuals diagnosed with AD according to the PCDT criteria[11] was considered. The study population consisted of men and women aged 65 years and older – the age group with the highest incidence of AD, which is consistent with the natural history of the disease.[1,3,4,6,7] The onset of the cycle was established with an initial distribution of subjects without the disease and patients with AD in the mild or moderate stages. Transition probabilities were used recursively over time to simulate the progression of patients through the stages of illness. Disease progression was established through MMSE scores for each stage in the three scenarios studied.

The treatment strategies being compared were pharmacotherapy with (1) donepezil 5 mg/day and 10 mg/day and (2) rivastigmine according to the PCDT dosage scheme (3 mg/day, 6 mg/day, and 9 mg/day). As noted above, the proposed scenarios, as well as dose escalation procedures for both drugs, were based on the PCDT.[11] We assumed a 10-year time horizon, with 1-year cycles, corresponding to the natural history of AD.[17]

Transition probabilities were derived from randomized clinical trials and from international economic assessments.[17-24] Three summative outcomes of AD were included in the simulation model, with probabilities were taken from national and international studies: a) depression and agitation[25-30]; b) hospitalization for femoral fracture[31-33]; and c) pneumonia.[34]

The effectiveness of treatment was measured in quality-adjusted life years (QALYs).[17,18] This measure was calculated based on the transition probability of the mild and moderate stages, in the different scenarios, multiplied by the utility scores of the corresponding states, as described in the international literature.[35-38] The main outcomes used in the model are shown in Table 1.
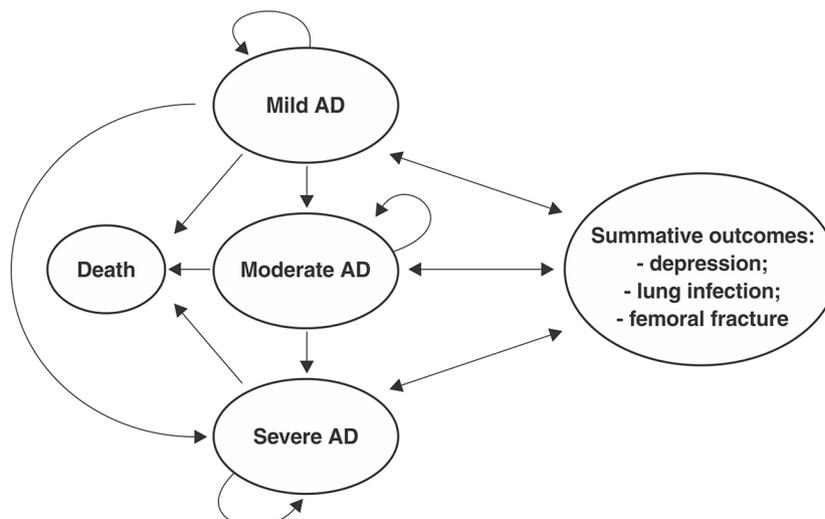

Figure 1 Schematic representation of the disease stages of the simulation model. AD = Alzheimer's disease.

Table 1 Outcomes of interest incorporated into the Markov model

Probability	Mean (SD)	Source
Natural history of AD		
Death during the mild stage	0.038 (0.024)	Morris et al.[23] and Spackman et al.[18]
Death during the moderate stage	0.134 (0.081)	
Stable-mild stage	0.694 (0.113)	
Moderate-mild stage	0.057 (0.014)	
Severe-mild stage	0.001 (0.001)	
Death during the severe stage	0.317 (0.164)	
Mild-moderate stage	0.240 (0.116)	
Mild-severe stage	0.028 (0.021)	
Stable-moderate stage	0.533 (0.032)	
Moderate-severe stage	0.227 (0.062)	
Severe-moderate stage	0.014 (0.014)	
Stable-severe stage	0.670 (0.178)	
Rivastigmine		
Mild stage	0.724 (0.110)	Fenn & Gray[20] and Hauber et al.[19]
Moderate stage	0.274 (0.231)	
Severe stage	0.070 (0.071)	
Death during the mild stage	0.038 (0.024)	
Death during the moderate stage	0.134 (0.115)	
Death during the severe stage	0.316 (0.241)	
Donepezil		
Stable-mild stage	0.668 (0.092)	Stewart et al.,[24] Neumann et al.,[22]
Mild-moderate stage	0.210 (0.097)	Jonsson et al.,[21] and Ikeda et al.[17]
Mild-severe stage	0.018 (0.022)	
Death during the mild stage	0.038 (0.024)	
Stable-moderate stage	0.560 (0.057)	
Moderate-severe stage	0.261 (0.068)	
Death during the moderate stage	0.134 (0.115)	
Moderate-mild stage	0.089 (0.058)	
Severe-mild stage	0.001 (0.001)	
Severe-moderate stage	0.014 (0.014)	
Stable-severe stage	0.835 (0.208)	
Death during severe stage	0.085 (0.231)	
Utility[4]		
Mild AD with NH	0.695 (0.021)	Ikeda et al.,[17] Hartz et al.,[39] Jonsson et al.,[37] Naglie et al.,[38]
Moderate AD with NH	0.510 (0.042)	Mesterton et al.,[36] and Oremus et al.[35]
Severe AD with NH	0.340 (0.042)	
Mild AD with AChEI	0.774 (0.104)	
Moderate AD with AChEI	0.510 (0.042)	
Severe AD with AChEI	0.457 (0.201)	

AChEI = acetylcholinesterase inhibitors; AD = Alzheimer's disease; NH = natural history; SD = standard deviation.

The direct costs included in the study were those of the diagnostic tests recommended in the Brazilian AD PCDT[11] (complete blood count, electrolytes, blood glucose, urea, creatinine, TSH, computed tomography and magnetic resonance imaging, neuropsychological tests) and pharmacological treatment (donepezil and rivastigmine). Costs were evaluated from the perspective of the Brazilian health system and were accounted for in U.S. dollars and Brazilian reais (BRL). Indirect costs were not considered.

The estimated drug cost was based on the mean unit price and duration of treatment. Prices were obtained from the System of Management of the Table of Procedures and Medications (SIGTAP), for the year 2016,[40] and the Federal Government Purchasing Portal (COMPRASNET), for the years 2015/2016.[41] For diagnostic tests, the reference date for SIGTAP values was December 2016. The frequency and cost of tests were defined for: a) four annual medical appointments; b) hospitalization according to the prevalence of the outcomes of

interest and treatment of the AD summative outcomes, i.e., medical conditions resulting from the disease; c) depression; d) pulmonary infection; and e) femoral fracture, which was included in the simulation because such fractures make treatment of AD more expensive and bring the model closer to reality. These costs are represented in Table 2.

The perspective adopted was that of the SUS. The comparative efficiencies of alternative treatment strategies were measured by the incremental cost-effectiveness ratio. The discount rate was 5% per year for both costs and outcomes, and a sensitivity analysis was performed.[42]

The following assumptions were used in the simulation model: a) the probability of severity transition depended on the severity of the disease at the onset of treatment; b) the probability of death used in the model was set according to the stage of the disease; c) the model did not use the severe stage of AD in its analysis because the SUS does not offer treatment for this condition – i.e.,

Table 2 Cost of the pharmacological treatment of selected outcomes, in Brazilian reais (BRL)

Description	Mean (SD)
Laboratory tests and imaging	248.68 (74.47)
Treatment with donepezil following a therapeutic regimen	154.70 (121.16)
Treatment with rivastigmine following a therapeutic regimen	1,003.45 (114.77)
Outpatient medical follow-up (4 visits per year)	94.02 (8.63)
Treatment of pneumonia	855.79 (153.14)
Treatment of femoral fracture	3,326.00 (1,585.09)
Maintenance treatment with sertraline	185.70 (4.52)
Acute event treatment with sertraline	264.30 (44.93)
Maintenance treatment with citalopram	99.99 (71.94)
Acute event treatment with citalopram	133.20 (92.37)
Maintenance treatment with risperidone	268.20 (27.30)
Acute event treatment with risperidone	215.10 (31.35)
Maintenance treatment with olanzapine	247.50 (67.84)
Acute event treatment with olanzapine	900.03 (182.66)
Fracture investigation	254.11 (123.96)

SD = standard deviation.

Table 3 Cost analysis of the selected Alzheimer's disease treatment scenarios

Comparison strategy	Annual cost (BRL)	Effectiveness	Incremental cost (BRL)	Incremental effectiveness	ICER
Natural history	28,080.13	3.52	0	0	0
Donepezil	30,556.45	4.26	2,476.32	0.741	3,342.13
Rivastigmine	32,685.77	3.87	-	-	(Dominated)

BRL = Brazilian reais; ICER = incremental cost-effectiveness ratio.

patients leave the model as they progress from moderate to severe AD; d) drug treatment does not alter disease mortality, but rather its progression to more severe stages; e) the 12-mg dose of rivastigmine was excluded in the model because of its restricted use in the public sector; and f) the cost of institutionalization was not included in the model due to the scarcity of cost information in the SUS databases.

Results

The average cost of AD diagnosis was BRL 248.68/ patient (standard deviation [SD] = BRL 74.47). According to SIGTAP, the annual cost of follow-up for a patient with AD was BRL 94.02 (SD = BRL 8.63). The mean costs of outpatient follow-up (BRL 27.05/person), emergency-department hospitalization (BRL 189.043/ day) and other types of special care for patients with this condition were similar in both scenarios. The annual cost of pharmacological treatment with donepezil and riva-stigmine was estimated at BRL 154.70 and BRL 1,003.45, respectively.

Using a Markov model, we were able to simulate scenarios of treatment with donepezil and rivastigmine versus a baseline of untreated AD. This simulation yielded the costs of pharmacological treatment and the overall cost of AD care, including the cost of the summative outcomes of the mild and moderate stages. Moderate AD was the most costly phase of the disease, especially with rivastigmine treatment. Compared with other drug interventions, the use of rivastigmine is less supported than treatment with donepezil, which has the best cost-effectiveness ratio (Table 3).

Sensitivity analysis

The sensitivity analysis aimed to test the robustness and results of the variations between the parameters used in the model. Brazil does not have a formal threshold of acceptability for the incorporation of health technologies. In this scenario, i.e., health systems that do not have a formal threshold, a value of three times the per capita gross domestic product (GDP) is recommended.[43] For the year 2016, the value adopted was BRL 91,221/QALY; using this threshold, the likelihood of donepezil not being cost-effective was 2.8% when compared to rivastigmine (Figure 2).

Discussion

In our analysis of overall AD treatment scores, there was a difference between letting the disease run its course (natural history) and administering anticholinesterase therapy, as well as between different stages of AD. The cost of donepezil and rivastigmine treatment was lower than that of no treatment. A similar finding was reported by Ikeda et al.[17] Despite the similarity of the results, it is not possible to explain the difference in cost between pharmacological treatment and no treatment because the authors did not adequately discriminate among the costs of the resources used to calculate treatment. Differences between costs were also observed in a study by Hartz[39] which evaluated donepezil and memantine at the more advanced stages of AD.

Regarding the effectiveness of the technologies for mild AD, the study reported a QALY increase of 0.61/BRL 21,907.38 for patients treated with donepezil and a QALY
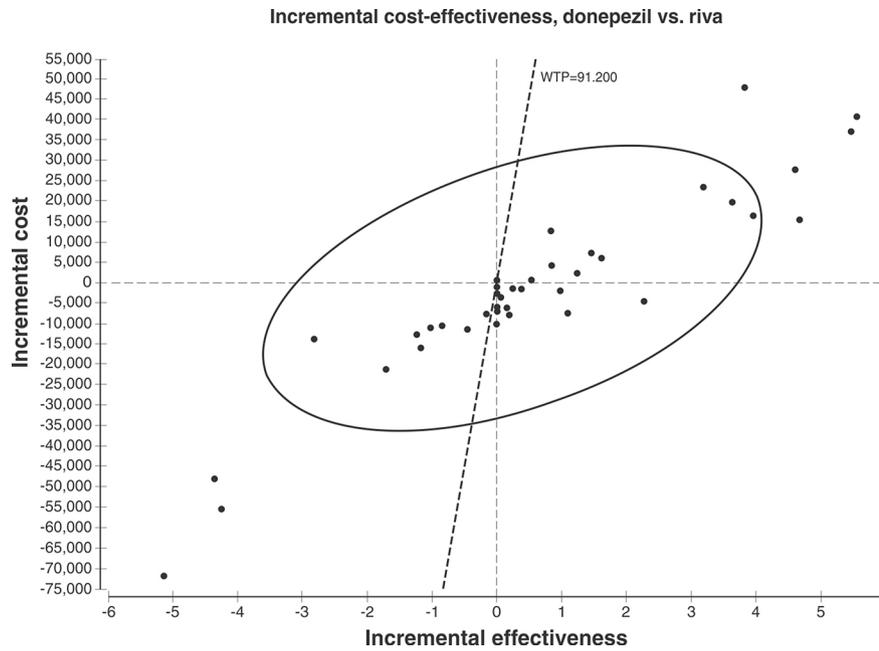
Incremental cost-effectiveness, donepezil vs. riva

Figure 2 Monte Carlo cost-effectiveness analysis of donepezil vs.rivastigmine. WTP = willingness to pay.

increase of 0.58/BRL 24,683.33 for patients treated with rivastigmine in the mild stage; in the moderate stage, the increases observed were 0.05 QALY/BRL 27,414.96 for patients treated with donepezil and 0.06 QALY/BRL 34,222.96 for patients treated with rivastigmine. The results of the present study are thus consistent with the international literature, where QALY gains in AD have been shown to be more significant in the mild phase of the disease than at the moderate stage.[17,19,22]

Ikeda et al.[17] conducted an economic evaluation of the use of donepezil (3 mg/day) in the treatment of mild and moderate AD in Japan. Efficacy data were obtained from Japanese studies published in 1995 and 2000, and the unit costs of drugs were based on year-2000 prices. A Markov model was simulated to characterize the progression of patients between the stages of AD. At the mild stage, a QALY increase of 0.58/BRL 82,944.00 was observed, whereas at the moderate phase, the QALY increase was 0.31/BRL 148,716.00, indicating donepezil is a cost-effective treatment for AD when compared to natural history of disease. Neumann et al.[22] conducted a cost-effectiveness analysis of the economic impact of donepezil treatment of mild and moderate AD in the United States. The cost of donepezil was partially offset by the reduction in care costs related to improved cognitive function and delayed onset of the costlier stages of the disease. The cost-effectiveness of donepezil treatment was $32,000.00 per QALY at the mild stage and $140,000.00 per QALY at the moderate stage of AD.

Hauber et al.[19] estimated the potential cost savings per patient using rivastigmine for the treatment of AD in Canada. Their research suggested that this drug may delay onset of the most severe stage of AD for up to 188 days in patients with mild AD after 2 years of treatment. For patients with mild-to-moderate and moderate AD, the estimated delays were 106 and 44 days, respectively.

The mean cost saved per patient was $0.45 per day at 6 months and $6.44 per patient after 2 years for mild AD. Although these results are promising, there is uncertainty about the cost-effectiveness of rivastigmine because data on the natural history of disease were not available in the study, making interpretation difficult. In a systematic review, Loveman et al.[44] evaluated cost-effectiveness studies of pharmacological treatments for AD. Four economic evaluations of rivastigmine, all sponsored by pharmaceutical industries, were analyzed. According to the review, reducing treatment costs does not offset the treatment cost with rivastigmine enough for it to be considered cost-effective at levels acceptable to the UK National Health Service ($<£50,000$ per QALY).

The present study has several limitations that merit discussion. Some are inherent to the modeling process, which might oversimplify the process of disease progression because of its divergence from real-world circumstances. In addition, international data were used, given the scarcity of information about AD in the Brazilian context. Different data sources were used to obtain probabilities for AD stage transitions.[17-23] The differences between these probabilities may be related to the timing of publication of the original studies; other values might have modified the results of our simulation. The cost of institutionalization was not included in the model due to the scarcity of such information. Finally, the social costs involved in the treatment of AD, which, according to the literature, account for a large part of disease-related costs,[45] were not considered, despite their potential impact on the cost-effectiveness analysis.

Finally, it is worth noting that economic health assessments are not intended to exhaust all existing technological alternatives. The analysis performed herein, for example, included the alternatives most prevalent in the SUS. Thus, we did not consider use of the anticholinesterase

agent galantamine, which is also approved and dispensed in the SUS for mild to moderate AD, nor of the 12-mg dose of rivastigmine, due to its restricted use in the public sector.

In conclusion, this is one of the first cost-effectiveness studies of AD treatment in the mild and moderate stages and, to our knowledge, is the first to use a Markov model. No Brazilian studies had ever estimated the costs of diagnosis, follow-up, and treatment of AD.

The purpose of pharmacological treatment is to treat symptoms and slow the progression of AD, thereby reducing its burden on society and postponing the care-related expenditures that accompany the more advanced stages of the disease. From this perspective, our findings suggest that donepezil is the most cost-effective option for the SUS. In this sense, current practice in Brazil represents a worst-case scenario. The most common pharmacological treatment option, based on treatment with rivastigmine, has a lower effectiveness (0.39 QALYs/ BRL 32,685.77) than donepezil.

Probabilistic analysis indicates that donepezil is the most cost-effective treatment for mild and moderate AD. The results of this study can help inform political decisions to establish the best treatment strategy for AD in its initial and moderate stages, as well as suggest pathways to a comprehensive policy for dementia care in Brazil.

Acknowledgements

Disclosure

VM has received grants from Novartis, Wyeth, EMS, Janssen-Cilag, Apsen Farmacêutica, Aché, Lundbeck, Lilly, moksha8, and Servier. JL has received grants from Novartis, Wyeth, EMS, Janssen-Cilag, Apsen Farmacêutica, Aché, Lundbeck, Lilly, moksha8, and Servier. The other authors report no conflicts of interest.

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