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Cost-utility analysis of memantine in Alzheimer's Disease in Brazil

Custo-utilidade da memantina para Doença de Alzheimer no Brasil

Costo-utilidad de la memantina en la Enfermedad de Alzheimer en Brasil

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Abstract
Accelerated population aging has led to a progressive increase in dementia, particularly Alzheimer's Disease (AD). The study's objective was to perform a cost-utility analysis on the use of memantine in the severe stage of AD in Brazil compared to no specific pharmacological treatment from the perspective of the Brazilian Unified Health System (SUS). A Markov model was designed to simulate the progression of AD through five finite stages of health that considered cognitive function and a time horizon of five years. Progression probabilities were derived from clinical trials and population-based studies. Direct costs included hospitalization, medical consultation, use of additional medications, as well as laboratory tests. The measures for Quality Adjusted Life Year (QALY) were derived from the international literature. Costs and benefits were discounted by 5%. Compared to no specific pharmacological treatment, memantine was associated with gains in QALY and additional costs. The model showed that memantine resulted in a gain of 0.00308 QALY over the simulated 5 years and an increase in costs of R$351.50 per patient in already discounted values, resulting in an incremental cost-effectiveness ratio (ICER) of R$114,123.38 per QALY. The cost and effect of memantine on AD progression were the variables under the most uncertainty. Although memantine represents gains in QALY, its ICER is considered high for the Brazilian context considering its high costs and its small and limited benefit in time.
Keywords: Alzheimer's disease; Cost-utility analysis; Memantine; Unified health system.

Resumo
O envelhecimento populacional acelerado ocasiona um aumento progressivo dos quadros demenciais, sobretudo da Doença de Alzheimer (DA). O objetivo do estudo foi realizar uma análise de custo-utilidade acerca do uso da memantina para a DA no estágio grave em comparação a nenhum tratamento farmacológico específico, na perspectiva do Sistema Único de Saúde (SUS). Um modelo de Markov foi elaborado para simular a progressão da DA através de cinco estágios finitos de saúde que consideraram a função cognitiva e um horizonte temporal de cinco anos. As probabilidades de progressão foram derivadas de ensaios clínicos e estudos de base populacionais. Os custos médicos diretos incluíram hospitalizações, consultas médicas, uso da memantina e de medicamentos adicionais, além de testes laboratoriais. As medidas de anos de vida ajustados pela qualidade (QALY, Quality Adjusted Life Year) foram derivadas da literatura. Custos e benefícios foram descontados em 5%. O uso da memantina, comparada a nenhum tratamento farmacológico específico, esteve associado a ganhos em QALY e a custos adicionais. O modelo mostrou que a memantina resultou em um ganho de 0,00308 QALY ao longo dos 5 anos simulados e um aumento dos custos de R$ 351,50 por paciente em valores já descontados, resultando em uma razão de custo-efetividade incremental (RCEI) de R$ 114.123,38 por QALY. O custo e efeito da memantina na progressão da DA foram as variáveis sob maior incerteza. Apesar da memantina representar ganhos em QALY, sua RCEI é elevada na realidade brasileira, considerando custos elevados e um benefício pequeno e circunscrito no tempo.
Palavras-chave: Doença de Alzheimer; Análise de custo-efetividade; Memantina; Sistema único de saúde.

Resumen
El envejecimiento acelerado de la población ha provocado un aumento progresivo de la demencia, sobre todo de la enfermedad de Alzheimer (EA). El objetivo del estudio fue realizar un análisis de costo-utilidad sobre el uso de memantina en la etapa grave de EA en Brasil en comparación con ningún tratamiento farmacológico específico, en la perspectiva del Sistema Único de Salud (SUS). Se diseñó un modelo de Markov para simular la progresión de la EA a través de cinco etapas finitas de salud que consideraban la función cognitiva y un horizonte temporal de cinco años. Los costes médicos directos incluían las hospitalizaciones, las consultas médicas, el uso de memantina y de medicamentos adicionales, y las pruebas de laboratorio. Las medidas de QALY (Quality Adjusted Life Year) se derivaron de la literatura. Los costes y beneficios se descontaron al 5%. El uso de memantina, en comparación con ningún tratamiento farmacológico específico, se asoció con ganancias QALY y costos adicionales. El modelo mostró que la memantina resultó en una ganancia de 0,00308 QALY en los 5 años simulados y un aumento en los costos de R$ 351,50 por paciente en los valores ya descontados, resultando en una relación costo-efectividad incremental (RCEI) de R$ 114.123,38 por QALY. El coste y el efecto de la memantina sobre la progresión de la EA fueron las variables con mayor incertidumbre. Aunque la memantina represente ganancias en QALY, su RCEI es alto para la realidad brasileña, considerando sus altos costos y su pequeño beneficio, limitado en el tiempo.
Palabras clave: Enfermedad de Alzheimer; Análisis costo-benefício; Memantina; Sistema único de salud.

1. Introduction

Alzheimer's Disease (AD) is a complex, age-related neurodegenerative disorder characterized by progressive loss of cognitive function, changes in behavior and mood, and significant impairment in the performance of daily living activities by those affected (Alzheimer Association, 2017). This is the most common cause of dementia, accounting for about 70% of these cases in Brazil (Boff et al., 2015).

It is estimated that the number of elderly people in Brazil will reach 32 million in 2020 (Veras, & Oliveira, 2018) and that, in 2040, this amount will represent 23.8% of the Brazilian population and a ratio of almost 153 elderly people for every 100 young people (Miranda et al, 2016). Middle and low-income countries are projected to have more alarming increases in the number of dementia cases compared to developed countries (Nitrini et al, 2009), as illiteracy and low educational attainment seem to be associated with greater cognitive decline in the elderly population (Livingston, 2017; Nitrini, 2005). This fact makes the magnitude of the problem even greater in Brazil, given the demographic changes that have occurred in recent decades in the country, with accelerated population aging and a higher prevalence of AD cases than the world's mean prevalence (Alves, 2014).

Precise data on the AD cost in Brazil are not known (Gutierrez et al, 2014). Nonetheless, it is known that AD significantly increases health care costs, thus significantly impacting health systems and families (Castro et al., 2010; Lebrão, 2007).

The specific pharmacological treatment is currently done with anticholinesterase drugs, indicated for the mild and moderate stages of AD, and with memantine, a non-competitive antagonist of the NMDA (N-methyl-D-aspartate) receptors, whose use in Brazil is approved by the National Health Surveillance Agency (ANVISA) for the treatment of moderate to severe AD.

Some studies have shown that memantine is able to improve patients' overall clinical status and functional abilities and reduce cognitive decline in AD patients (Matsunaga et al, 2015; Howard et al, 2012; Reisberg et al, 2003), but the effects are usually small and of limited duration (Blanco-Silvente et al., 2018). However, there are controversies regarding the relationship between risks and benefits with the use of the drug, and some countries that had incorporated memantine into their funding systems have removed the drug from the list in recent years (Prescrire, 2018).

Although several economic studies have demonstrated the cost-effectiveness of memantine compared to no specific pharmacological treatment (Knapp et al., 2016; Thibault et al., 2015; Lachaine et al., 2013), to date there are no economic evaluations conducted in the country focusing on the advanced stage of the disease (Oliveira et al, 2019).

In 2017, memantine was incorporated into the Brazilian Unified Health System (SUS) for the pharmacological

treatment of moderate AD, in association with anticholinesterase drugs, and severe AD, in monotherapy (Brasil, 2017a). The entry of the drug into the SUS was not, however, accompanied by any complete economic evaluation study that would justify the efficiency of its inclusion in terms of the best use of resources, which is recommended by the legal regulations governing the process of incorporation of technologies into the SUS (Brasil, 2011).

This study aimed to perform a cost-utility assessment about the use of memantine compared to no specific pharmacological treatment in severe Alzheimer's Disease from the perspective of SUS as a health care funder.

2. Methodology

The study evaluated outcomes in terms of Quality Adjusted Life Years (QALYs), comparing the addition of pharmacological treatment with memantine monotherapy to no specific pharmacological treatment for patients with severe AD.

Given the absence of population-based epidemiological data or data from the SUS information systems on the prevalence of severe AD in the country or of its distribution by age or education level, we chose a hypothetical cohort of 1,000 patients of both sexes, aged 70 years, with severe AD defined by a Mini Mental State Examination (MMSE) score of 11 or less, the minimum threshold indicated by the Clinical Protocol and Therapeutic Guideline (CPTG) for introducing therapy with this drug in patients with this stage of the disease (Brasil, 2017b).

Memantine was considered at a daily dose of 20mg, in a monotherapy regimen. Supportive care in both strategies included the use of antidepressants, antipsychotics, and anxiolytics to control additional psycho-behavioral symptoms, and hospitalization for treatment of complications associated with AD.

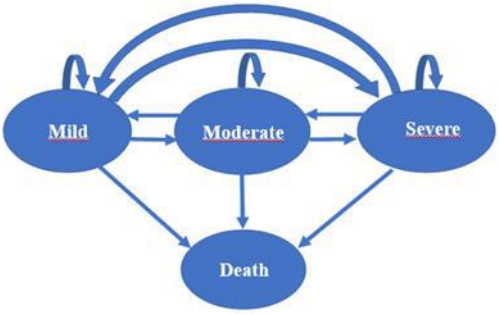
The perspective of the SUS as a health care funder was adopted, as recommended by the Brazilian Ministry of Health's Guidelines for the Preparation of Economic Evaluations (BRASIL, 2014).

2.1 Model structure

A Markov model was designed to simulate the AD progression in treated and untreated patients over the time horizon of analysis through a finite series of health states defined by disease severity.

All patients entered the model already in the severe AD state. In each yearly cycle, patients could be in one of four possible states: regress to mild AD (MMSE>20); regress to moderate (11<MEMSE<20); remain severe (MMSE≤11); or pass away. The state of death (absorptive state) was included in the model, considering the advanced age range of patients affected by the disease, AD being associated with increased mortality (Brookmeyer et al., 2002; Zanetti et al., 2009) and the fact that one of the predictors of a low survival is exactly low MMSE scores (Larson et al., 2004). Figure 1 schematically displays the developed Markov model.

Figure 1. Schematic representation of the developed Markov model.



Source: Authors.

The model was developed based on previously published economic studies (Antonanzas et al., 2006; Jonsson et al., 2005; Jones et al., 2004; François et al., 2004), but using only the cognitive function to define health states, without considering states related to the patients' home situation (institutionalization). This choice was based on three aspects. The first is the fact that the institutionalization of patients with more severe AD in nursing homes is not a common situation in Brazil, where they are usually cared for by their families, nor is this institutionalization paid for by the state, as occurs in other countries (Lachaine et al., 2013: Bond et al., 2012; Rive et al., 2012; Rive et al., 2010). Furthermore, more robust population-based studies that assess the probability of AD progression by jointly associating disease severity and independence in performing activities of daily living are scarce in the national literature, in order to allow the modeling of AD progression according to these combined health states. Finally, the CPTG of the Brazilian Ministry of Health, which regulates the care to be provided to AD patients in SUS, considers only the cognitive function defined by the MMSE for access to pharmacological treatment.

A time horizon of five years was adopted, in agreement with that defined in other economic studies already published (Rive et al., 2012; Rive et al., 2010; Jonsson et al., 2005; François et al., 2004) and to the fact that AD is a chronic, progressive disease, already in an advanced stage and with low life expectancy, as in the case of severe AD (Suthers et al., 2003; Agüero-Torres et al., 2002).

One-year cycles were employed, consistent with the AD progression study used to model disease progression (Spackman et al., 2012) and consistent with the duration of the clinical trial elected to use the effects of memantine on cognitive function (Howard et al., 2012).

The model was developed in the TreeAge Pro HealthCare 2017 software.

2.2 Data source

At the moment the analysis was conducted, there were no cohort studies that reported the AD progression in the Brazilian population, leading to the use of data from the international literature.

The yearly probabilities of progression between AD severity states in natural history were obtained from the Spackman et al study (2012), including the probabilities of death related to each severity grade. This work takes data from the National Alzheimer Coordinating Center (NACC), which contains demographic and clinical information from 32 U.S. AD treatment centers, and analyses of disease progression were based on 9,730 observations of 3,582 patients of both genders (55.2% female), aged over 50 years (average age 77.3 years), with a diagnosis of probable/possible AD, who had two (55.1%) or more follow-up visits, and who lived in a family environment in 88.9% of cases. The Clinical Dementia Rating (CDR) scale was used to determine AD status and the MMSE was used to measure cognitive deficit. Data for patients with severe AD

(defined as CDR 3) corresponded to 435 patients, with an average MMSE of 5.32 ± 5.98 (Spackman et al., 2012).

Because most of the meta-analyses found in the literature presented the effect measures of memantine in terms of the difference in standardized means and combined studies with populations with AD of different levels of severity and with cognitive function measured by a diversity of scales, we chose to select primary studies that evaluated memantine in monotherapy for severe AD with outcomes measured by the MMSE.

In most of the trials available in the literature, the follow-up time of patients and the observation of its effects on disease progression are short, usually equal to or less than six months (Tariot et al., 2004; Reisberg et al., 2003). This fact led to the choice of using the Howard and colleagues (2012) study to capture the measure of efficacy of memantine, since it presented the populations with their initial MMSE scores and had a follow-up duration of 52 weeks, directly compatible with the selected yearly probabilities.

Howard's study, acronymed DOMINO (Donepezil and Memantine in Moderate to Severe Alzheimer's Disease), was a multicenter, double-blind, placebo-controlled clinical trial that included patients who met standard criteria for probable/possible moderate to severe AD, residing at home, with an MMSE between 5 and 13. The study was structured with 295 patients randomly assigned to four treatment arms (donepezil+placebo, memantine+placebo, donepezil + memantine, and placebo alone), with data from the group receiving memantine alone versus placebo being used (N=76). The dose of memantine used in the study was 20mg/day, patients had a mean initial age of 76.2±8.9 years and an initial MMSE of 9.2±2.5, with a follow-up time of 52 weeks. Patients who received memantine, when compared to those assigned to the placebo group, had a higher average score of 1.2 points on the MMSE scale at the end of the follow-up time (95% CI 0.6-1.8, $p<0.001$) (Howard et al., 2012).

The effectiveness of memantine with respect to AD progression was applied to the probabilities of the natural history of AD in the first cycle (1 year), consistent with the length of the used clinical trial (Howard et al., 2012) and with different published economic studies that reported that the efficacy of the drug would be limited only to the first 12 months (Gagnon et al., 2007; Antonanzas et al., 2006; Jonsson et al., 2005).

For application of memantine efficacy, a calculation strategy was employed that followed that used by Budd and colleagues (2011), with the relative efficacy of memantine corresponding to a reduction in the progression rate of 18.47%. Starting with the second cycle of the model, the transition probabilities in the memantine arm were assumed to be the same as in the natural history of the disease. Although the effect was considered for only one cycle, it was assumed that memantine would be used for 2 years, incurring costs for that period.

Although some studies point out that there is no statistical difference in treatment discontinuation between the memantine and placebo arms (Matsunaga et al., 2015; Blanco-Silvente et al., 2018), discontinuation of use can occur, motivated by the occurrence of adverse events, lack of adherence, or no improvement perceived with treatment use. Discontinuation of use usually occurs in the first few months of treatment (Findling et al., 2007; Reisbberg et al., 2003) and has impacts on costs and associated efficacy. Therefore, this possibility was included in the model and patients starting memantine could discontinue treatment, it was assumed that treatment would be given for three months and that this short use would have no effect on disease progression.

Based on the literature, the assumption was made that the use of memantine does not interfere with mortality, and therefore the chances of dying in each health state would be the same in the two strategies under comparison, as also adopted in other published economic evaluations (Jones et al., 2004; François et al., 2004; Antonazas et al., 2006; Hartz et al., 2012; Rive et al., 2012).

AD patients are more likely to be hospitalized and to use additional medications for the management of psychiatric and behavioral symptoms throughout their illness, with both varying depending on the severity of the illness (SrikantH et al.,

2005; Selbaek et al., 2013; Bremenkamp et al., 2014; Taipale et al, 2016; Motzek et al., 2018). Studies point out that these odds are lower in patients using memantine (Gilligan et al., 2013). The probabilities of hospitalization and use of accessory medications (antidepressants, antipsychotics, and anxiolytics) by severity status were surveyed from a specific literature search (Laitinen et al., 2011; Laitinen et al., 2015; Taipale et al., 2015). The effects of the use of memantine on these probabilities were included only during the first yearly cycle, consistent with efficacy restricted to the same period, and thereafter the probabilities associated with the natural history of the disease were included.

It was also considered that some patients with AD were hospitalized and died, although in most cases they died at home or in emergency units (UPA, emergency room, etc.), which do not have authorization for hospital admission (AIH) in the public health system. Given the absence of this information in SUS databases, it was assumed that 40% of AD patients who died were admitted to the health system, with variations from 0% to 60% considered in the sensitivity analysis.

In the absence of utility measures related to Alzhmeier's disease in the Brazilian population, a review was carried out for international population-based studies that evaluated preferences according to AD severity states as measured by the MMSE (Ekman et al., 2006; Jonsson et al., 2006; Wlodarczyk et al., 2006; Wlodarczyk et al., 2004; Andersen et al., 2004; Newman et al., 1999). The preferences available in the literature were measured by different scales, and consider values assigned by patients and caregivers. The QALY values by health status used in the model were average to those extreme points found in the review, which were varied in the sensitivity analysis.

The clinical parameters used in the study, with the respective ranges employed in the sensitivity analysis, are displayed in Table 1.

Table 1. Clinical-epidemiological parameters used in the model for Alzheimer's Disease progression.

Parameters	Base case	Range used in the sensitivity analysis	Reference
Probability of Alzheimer's Disease progression in natural history			
Severe to mild	0.00100	(0.00000-0.00300)	Spackman et al., 2012
Severe to moderate	0.02700	(0.01300 -0.04000)	Spackman et al., 2012
Serious to severe	0.49200	(0.44700-0.53600)	Spackman et al., 2012
Severe to death	0.48000	(0.48000-0.52500)	Spackman et al., 2012
Moderate to mild	0.07000	(0.05100-0.08900)	Spackman et al., 2012
Moderate to moderate	0.50100	(0.46600-0.53600)	Spackman et al., 2012
Moderate to severe	0.21400	(0.18600-0.24300)	Spackman et al., 2012
Moderate to death	0.21500	(0.18600-0.24400)	Spackman et al., 2012
Mild to mild	0.77400	(0.75000-0.79800)	Spackman et al., 2012
Mild to moderate	0.15800	(0.13900-0.17600)	Spackman et al., 2012
Mild to severe	0.01300	(0.00900-0.01700)	Spackman et al., 2012
Mild to death	0.05500	(0.04600-0.06400)	Spackman et al., 2012
Probability of Alzheimer's Disease progression with use of memantine			
Severe to mild	0.00118	(0.00105-0.00137)	Spackman et al., 2012; Howard et al., 2012; Budd et al., 2011
Severe to moderate	0.03198	(0.02846-0.03707)	Spackman et al., 2012; Howard et al., 2012; Budd et al., 2011
Serious to severe	0.48684	(0.49049-0.48155)	Spackman et al., 2012; Howard et al., 2012; Budd et al., 2011
Severe to death	0.48000	(0.48000-0.52500)	Spackman et al., 2012; Howard et al., 2012; Budd et al., 2011
Probability of hospitalization according to severity stage in natural history			
Mild	0.07350	(0.04685-0.14500)	Russ et al., 2014; Feng et al., 2013; Rudouph et al., 2010; Frytak et al., 2008; Andrieu et al., 2002; Albert et al., 1999
Moderate	0.14700	(0.09370-0.26900)	
Severe	0.16400	(0.15000-0.38600)	
Probability of hospitalization according to severity stage with the use of memantine 20mg/day			
Mild	0.07350	(0.04685-0.14500)	Gilligan et al., 2013; Russ et al., 2014: Feng et al., 2013; Rudouph et al., 2010; Frytak et al., 2008; Andrieu et al., 2002; Albert et al., 1999
Moderate	0.14700	(0.09370-0.26900)	
Severe	0.14432	(0.13200-0.33968)	
Probability of antidepressant drug use according to severity in natural history			

Mild	0.18500	(0.20000-0.31410)	
Moderate	0.20000	(0.18900-0.37000)	Spackman, 2012; Rhee, 2011, Laitinen, 2015; Taipale, 2014; Mendez, 1990
Severe	0.34100	(0.07400-0.37100)	
Probability of antipsychotic drug use according to severity in natural history			
Mild	0.03620	(0.03000-0.12000)	
Moderate	0.13680	(0.09000-0.21400)	Martinez, 2013; Spackman, 2012; Taipale, 2014; Rhee, 2011, Tifratene, 2017
Severe	0.26200	(0.19100-0.34600)	
Probability of anxiolytic use according to severity in natural history			
Mild	0.03865	(0.00300-0.05500)	
Moderate	0.07730	(0.00600-0.11000)	Martinez, 2013; Spackman, 2012; Taipale, 2014, Mendez, 1990
Severe	0.13200	(0.09200-0.30000)	
Probability of antidepressant drug use according to severity with memantine 20 mg/day			
Mild	0.18500	(0.20000-0.31410)	
Moderate	0.20000	(0.18900-0.37000)	Rhee, 2011, Laitinen, 2015; Taipale, 2014; Mendez, 1990
Severe	0.30100	(0.06700-0.32700)	
Probability of antipsychotic drug use according to severity with memantine 20mg/day			
Mild	0.03620	(0.03000-0.12000)	
Moderate	0.13680	(0.09000-0.21400)	Martinez, 2013; Spackman, 2012; Taipale, 2014; Rhee, 2011, Tifratene, 2017
Severe	0.19100	(0.14000-0.25300)	
Probability of anxiolytic use according to severity with memantine 20 mg/day			
Mild	0.03865	(0.00300-0.05500)	
Moderate	0.07730	(0.00600-0.11000)	Martinez, 2013; Spackman, 2012; Taipale, 2014, Mendez, 1990
Severe	0.13000	(0.09100-0.29700)	
Utilities			
Mild	0.63600	(0.52000-0.68000)	Ekman et al., 2006; Jonsson et al., 2006; Wlodarczyk et al., 2006; Andersen et al., 2004; Newman et al., 1999
Moderate	0.47500	(0.30000-0.61000)	Ekman et al., 2006; Jonsson et al., 2006; Wlodarczyk et al., 2006; Andersen et al., 2004; Newman et al.,1999
Severe	0.38000	(0.12000-0.52000)	Ekman et al., 2006; Jonsson et al., 2006; Wlodarczyk et al., 2006; Andersen et al., 2004; Newman et al., 1999

Source: Authors (2019).

2.3 Costs

The study adopted the perspective of the SUS as the health care funder. Therefore, only the direct medical costs of AD care were included, based on the amounts paid by SUS to providers, without including the indirect medical costs and the costs of informal care.

The costs of care in the different health states were estimated based on the items considered relevant in previously published studies and on the clinical management recommended by the current CPGT (Brasil, 2017b).

According to the CPGT, patients need to have their diagnosis of AD properly established prior to therapy. To do so, a series of imaging and laboratory tests, as well as a specialist consultation, are performed to diagnose and exclude of others cause of dementia. We included for both treated and untreated patients the costs related to the following items involved with the diagnosis: complete blood count, biochemical evaluation from the dosage of serum sodium, potassium, calcium, glucose, creatinine and liver transferases (ALT/TGP and AST/TGO), evaluation of thyroid dysfunction with TSH dosage, serology for Lues (VDRL) and HIV, and serum dosages of vitamin B12 and folic acid. The costs of a computed tomography (CT) of the brain was also included as part of imaging tests, given the lower availability and difficulties of access to magnetic resonance imaging in SUS by patients and its considerably higher costs. Once the diagnosis is established, the CPGT recommends that patients with severe AD have quarterly consultations with a specialist (neurologist) for evaluation and follow-up.

Unit cost were obtained from the Management System of the Table of Procedures, Medications and OPM of the SUS (SIGTAP), which provides information about the payment values per procedure in the public system.

The cost of memantine was estimated considering a daily treatment dose of 20 mg, i.e. 2 tablets of 10 mg. At the time of the analyses (07/2019), there was no list value established in SIGTAP for this drug, and it was still under discussion which government entity would be responsible for funding the drug (Brasil, 2018). The unit cost of memantine was calculated using the weighted average unit price per pharmaco-technical unit of memantine (10mg tablet) from the acquisitions made from January to April 2019 registered in the Integrated System for General Services Administration (SIASG). This system mandatorily registers all government purchases made by agencies linked to the federal administration. In this period, nine purchases of memantine 10mg from federal agencies registered in the SIASG were recorded, totaling 186,350 units, seven of which were made by electronic trading.

Patients who started treatment and then discontinued it had attributed the costs of three months of memantine therapy, whilst for those who continued use, the cost corresponding to 24 months of treatment was included.

Costs related to the additional treatment of mood and behavioral disorders common in AD were included and comprised the use of antidepressants (sertraline 50 mg/day), antipsychotics (risperidone 2 mg/day), and anxiolytics (lorazepam 2 mg/day). The choice of these specific drugs within their therapeutic classes was due to those being the most frequently used in the elderly and considered the safest, using the recommended daily doses for the elderly (Lima, 2007; Forlenza et al., 2008). Costs for risperidone, which is part of the Specialized Pharmaceutical Care Component, were available in SIGTAP. For the other two drugs, the unit costs per pharmaco-technical unit were obtained from the Price Panel on the federal government's government procurement portal for the period January to April 2019, using the mean price when more than one purchase was available.

The cost of hospitalization was included in the model because AD patients commonly hospitalize for a variety of complications such as pneumonia, fractures, and more serious gastrointestinal disorders. As there is no information in the national literature or in the healthcare system databases about the prevalence of these specific complications that lead to hospitalization in AD patients, we opted for a search in DATASUS for the costs of “hospitalization for AD”, carried outusing a filter for the population aged 70 years (both sexes), and estimating the mean costs from the values of the Hospital Admission

Authorizations – HAAs (corresponding to the Total Amount paid divided by the amount of approved HAAs) for patients who had International Disease Code (ICD) of AD (ICD F001, F002, G300, G301, G308) at the time of hospitalization and considering the 4-year period (2015-2018).

Finally, the cost of death was also included, based on the premise that some patients hospitalize and die during hospitalization. Given the informational gaps present in the DATASUS data, it was assumed that the costs would be lower than the hospitalization for AD complications, using the lowest mean value of hospitalization present in the above search.

The data sources used for costs were the SIGTAP (Management System of the Table of Procedures, Medications and OPM of the SUS), the SIASG (Integrated System for General Services Administration) and the DATASUS. All costs were expressed in Brazilian Reais (R$), using values from April 2019, which are shown in Table 2.

Costs and benefits were discounted at 5%, as recommended by the national methodological guideline for the economic evaluation of health technologies (BRASIL, 2014).

Table 2. Cost parameters used in the cost-effectiveness model (values in R$ as in April 2019).

Variable	Supply Unit	Base Value (R$)	Monthly Cost (R$)	Yearly Cost (R$)	Reference
Specific pharmaceutical treatment					
Memantine 10mg	tablet	0.57	34.20	410.40	SIASG
Imaging exams					
CT brain	exam	97.44	NA	97.44	SIGTAP/DATASUS
Magnetic resonance imaging of the brain	exam	268.75	NA	268.75	SIGTAP/DATASUS
Laboratory tests					
Creatinine	test	1.85	NA	1.85	SIGTAP/DATASUS
Serum sodium	test	1.85	NA	1.85	SIGTAP/DATASUS
Serum potassium	test	1.85	NA	1.85	SIGTAP/DATASUS
TSH	test	8.96	NA	8.96	SIGTAP/DATASUS
Glucose	test	1.85	NA	1.85	SIGTAP/DATASUS
Blood count	test	4.11	NA	4.11	SIGTAP/DATASUS
VDRL	test	2.83	NA	2.83	SIGTAP/DATASUS
Vitamin B12	test	15.24	NA	15.24	SIGTAP/DATASUS
Folic acid	test	15.65	NA	15.65	SIGTAP/DATASUS
ALT	test	2.01	NA	2.01	SIGTAP/DATASUS
AST	test	2.01	NA	2.01	SIGTAP/DATASUS
Clinical monitoring					
Medical consultation with a specialist	consultation	10.00	NA	40.00	SIGTAP/DATASUS
Accompanying pharmacological therapy					
Sertraline 50mg	tablet	0.32	9.60	115.20	Price Panel
Risperidone 2mg	tablet	0.11	3.30	39.60	SIGTAP/DATASUS
Lorazepam 2mg	tablet	0.28	8.40	100.80	Price Panel
Hospitalization					
Hospitalization for AD	event	1156.18	NA	1156.18	DATASUS
Death	event	867.14	NA	867.17	DATASUS

Caption: ALT: Alanine Amino Transferase; AST: Aspartate Amino-Transferase; AD: Alzheimer's Disease; DATASUS: SUS Department of Informatics; SIASG: Integrated System for General Services Administration; SIGTAP: Management System of the Table of Procedures, Medications and OPM of the SUS; CT: Computed Tomography; TSH: Thyroid-Stimulating Hormone; VDRL: Venereal Disease Research Laboratory. Source: Authors (2019).

2.4 Analysis

In the Markov model, mid-cycle correction was applied to both strategies under comparison, meeting the

recommendation of the Brazilian guidelines for economic evaluation (BRASIL, 2014) and aiming to minimize the effects of transitions occurring only at the end of the cycle, which does not correspond to most clinical situations (Siebert et al., 2012).

Costs and QALYs per cycle were calculated for the memantine arm and the no specific treatment arm, both undiscounted and discounted.

The comparative efficiency of the strategies was measured by the incremental cost-effectiveness ratio (ICER), with the most cost-effective strategy being the one with the lowest ICER per QALY gained.

Deterministic sensitivity analysis was conducted to assess the robustness of the model and its input data, considering changes for all variables in the model, including the effect of memantine on the probability of AD progression, the AD costs, and the discount rate. A Tornado graph was generated to facilitate visualization of the impacts of changes on the ICER.

Additionally, an extreme scenario analysis was performed, considering the effects of memantine on AD progression and its costs. In the most favorable scenario, the efficacy of memantine was considered to be 100% higher than the reference case - taking as a basis the lowest values of the MMSE score in the study by Howard and collaborators (2012) to calculate the treatment effect - and for the cost of treatment, the lowest values per pharmacotechnical unit of the purchases obtained in the SIASG for the same period were considered. In contrast, for the worst-case scenario analysis, the efficacy considered was 30% of that obtained in the reference case - taking as a basis the higher MMSE scores at baseline in the study by Howard and collaborators (2012) to calculate the effect of memantine - and for costs, the highest acquisition values per pharmacotechnical unit of memantine observed in SIASG for the period considered in the analysis.

3. Results

In the base case, the treatment of 1,000 patients in the hypothetical cohort with memantine 20 mg/day led to total costs of R$1,230,920.00 (discounted), representing an additional cost of R$351.50 per patient compared with no specific treatment. The total gain in effectiveness was 106.93 QALYs in discounted values, corresponding to 3.08 incremental QALYs. The use of memantine generated an ICER of R$114,123.38 per QALY gained (Table 3).

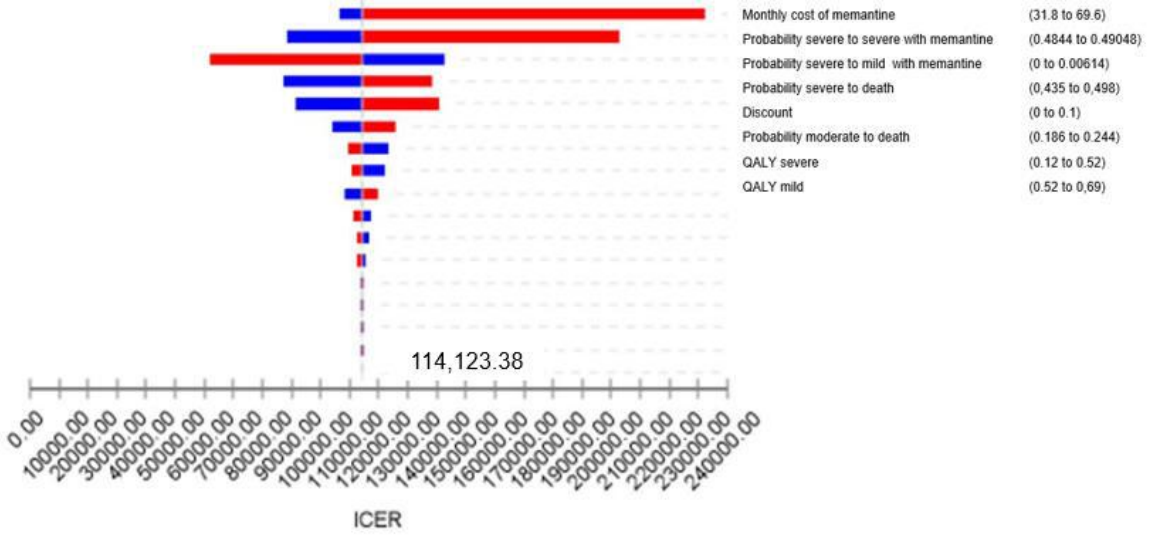
Table 3. Total costs, incremental costs, QALYs, incremental QALYs and ICER (values in 2019 R$, discounted at 5%) of the memantine strategy compared to no specific treatment for severe AD in the reference case, considering a hypothetical cohort of 1,000 patients.

Strategies	QALY	Costs (R$)	Incremental QALYs	Incremental costs (R$)	ICER (R$/year of quality adjusted lifetime earnings)
No specific treatment	103.85	879,420.00	—		—
Memantine 20mg	106.93	1,230,920.00	3.08	351,500.00	114,123.38

Caption: QALY - Quality Adjusted Life Years, ICER - Incremental Cost-Effectiveness Ratio. Source: Authors (2019).

The deterministic sensitivity analysis, with results expressed in the Tornado Diagram, presents the main parameters with impacts on the ICER and is illustrated in Figure 2. The larger horizontal bars represent the variables with the greatest individual impact on the ICER.

Figure 2. Tornado diagram showing the deterministic sensitivity analysis on the cost-effectiveness ratio with the use of memantine for severe AD versus the conventional strategy (no specific treatment).

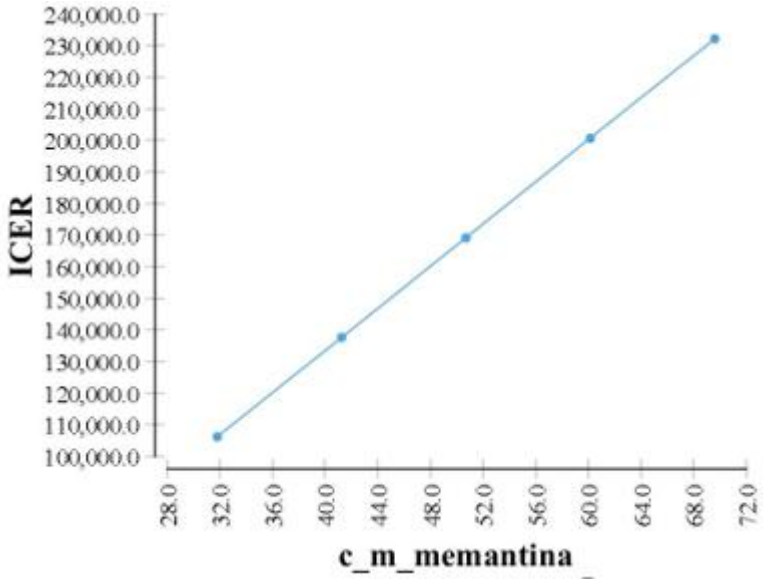


Source: Authors (2019).

The monthly cost of memantine was the parameter with the greatest impact on the ICER in relation to conventional treatment (without specific treatment for severe AD). Its increase to the upper limit of the range (R$ 69.60) determines a significant change in the results, making memantine a strategy with an ICER of R$ 232,116.27 per QALY gained, which means twice the value obtained in the reference case.

In contrast, by reducing the cost of memantine to its lower limit (R$31.80), the ICER decreases to R$106,211.78 per QALY gained, which is still considerably high, even though lower than the value in the base case. Figure 3 indicates the changes in the ICER as a function of changes in the monthly costs of memantine treatment.

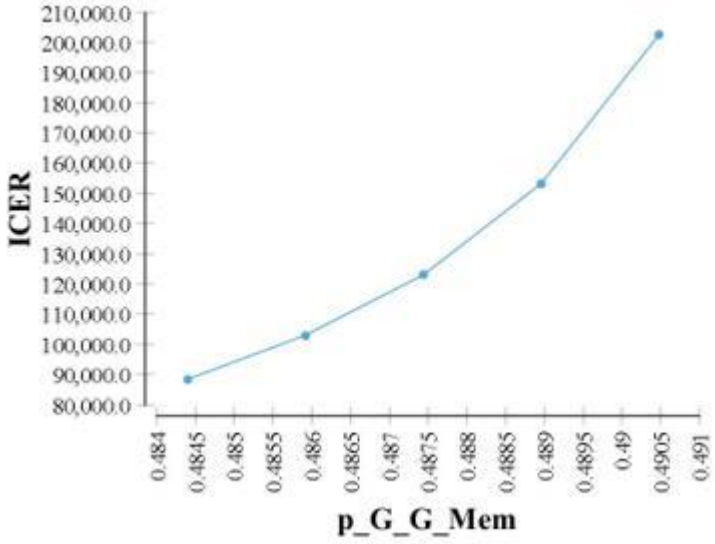
Figure 3. Univariate sensitivity analysis showing the variation of the ICER as a function of the monthly cost of memantine



Source: Authors (2019).

Additionally, the effect of memantine on disease progression (probability of patients with severe AD remaining severe with memantine use), was the second variable with the greatest impact on the ICER. When the effect of memantine on AD progression is minimized, that is, when the probability of patients with severe AD remaining severe while taking memantine 20 mg/day is increased, the ICER rises to $202,579.57 per QALY gained. The Figure 4 illustrates the impact of this variable on the ICER.

Figure 4. Univariate sensitivity analysis presenting the change in the ICER as a function of the probability that patients with severe AD remain severe with the use of memantine.



Source: Authors (2019).

The effect of memantine observed in the probability of progression from severe to mild disease with memantine also has important consequences for the ICER. When this probability reaches the lower limit of the range (p=0.00), that is, when there is no longer the possibility of this regression, the ICER rises to R$ 142,448.31.

The other parameters with an impact on incremental costs and QALYs are presented in Table 3. It is noteworthy that, except for the increased utility attributed to severe AD, the other utility measures had no significant impact on the ICER.

Table 3. Univariate Deterministic Sensitivity Analysis – Impact of key parameters on effectiveness, incremental costs, and incremental cost-effectiveness ratio

Strategy	Incremental Cost (in R$)	Incremental Effectiveness (QALY)	ICER (in R$/QALY)
Reference case			
No treatment	—	—	—
Memantine	351.5	0.00308	**114,123.38**
Monthly cost of memantine (increased from 31.80 to 69.60)			
No treatment	—	—	—
Memantine	714.92	0.00308	**232,116.77**
Probability of severe staying severe with memantine (increased from 0.4844 to 0.49048)			
No treatment	—	—	—
Memantine	351.50	0.00173	**202,579.57**
Probability that the patient with severe AD will die in natural history (decreased from 0.480 to 0.435)			
No treatment	—	—	—
Memantine	383.15	0.00439	**87,374.14**
Discount (increased discount from 5% to 10%)			
No treatment	—	—	—
Memantine	343.76	0.00244	**140,938.10**
Probability of moderate AD patient dying in natural history (increased from 0.215 to 0.244)			
No treatment	—	—	—
Memantine	351.46	0.00279	**125,915.86**
Severe utility of AD (increased from 0.38 to 0.52)			
No treatment	—	—	—
Memantine	351.50	0.0032	**125,915.86**

Caption: AD: Alzheimer's Disease; ICER: Incremental Cost-Effectiveness Ratio. Source: Authors (2019).

The analysis of table 3 reaffirms that the main variables associated with uncertainty in the value of are represented by the price of memantine and its effectiveness.

4. Discussion

The cost-effectiveness of treatments for Alzheimer's Disease is an important but often controversial topic (Geldmacher, 2008). This is a chronic condition, related to a disabling and progressive disease, which is often associated with significant costs. Wilmo and colleagues (2017) estimated that the costs of the condition in 2015 amounted to more than US$818 billion worldwide. The economic impacts of AD affect not only healthcare systems, but also individuals and families, in terms of direct medical costs, direct non-medical costs, and lost productivity. In the cost-of-illness study by Wilmo and collaborators (2017), informal care costs had the greatest impact on the total costs of AD. These costs tended to increase with more advanced stages of the disease (Wang et al., 2008).

From the SUS perspective adopted in this study, the evaluation of the use of memantine in patients with severe AD compared to no specific pharmacological treatment showed that memantine is associated with an increase in care costs and also a gain in QALYs. However, the ICER is in the excess of R$110,000 per QALY gained in the reference case, which is high

for the SUS context. This is mainly due to the fact that the drug does not alter the natural evolution of the disease or mortality, with very small effects on its progression, and also limited in time.

In this regard, it should be noted that the literature is not unanimous in stating about gains with the use of memantine. A recent meta-analysis comparing memantine to placebo, involving 18 studies and 5,004 patients, pointed out that with regard to efficacy, the drug showed a small improvement in cognitive function (16 studies, with 4,336 patients, standardized mean difference (SMD) of 0.15 with 95% CI 0.08-0.22), in global symptomatology (10 comparisons, 4. 169 patients, SMD of 0.16, 95% CI 0.08-0.24) and in neuropsychiatric symptoms (14 comparisons, 5011 patients, SMD of 0.16, with 95% CI 0.09-0.24), with no differences found in functional capacity (10 comparisons between memantine and placebo;4,067 patients; SMD = 0.07, 95% CI - 0.02, 0.15) (Blanco-Silvente et al., 2018).

In this analysis, the results suggest that the costs of memantine treatment have a significant impact on the ICER and being a source of significant uncertainty in the model. It is important to highlight that, despite being incorporated into SUS in November 2017 and already appearing in the most recent CPTG available for the disease (Brasil, 2017b), by the time this study was conducted and almost 18 months after its approval, memantine did not have a code in the SUS procedures payment table. This hindered programming and purchasing activities, stalled negotiations that could determine better pricing conditions, and, in concrete terms, ended up preventing access to the medication for those who need it.

Memantine was only included as a procedure belonging to the Specialized Component of Pharmaceutical Assistance (SCPA) and received a code in SIGTAP after Ordinance Nº 960, dated August 13, 2019 (BRASIL, 2019). In RENAME 2022 (Brasil, 2022), the drug is listed as part of group 1A, i.e., of funding and centralized purchase by the Brazilian Ministry of Health, which subsequently passes it on to subnational entities for dispensation. As a result of this delay, the record of memantine dispensation is only present in DATASUS as of October 2019.

Given the absence of a list price for memantine at the time the study was developed, efforts were made to obtain a price to be used in the modeling that was minimally reasonable. This corresponded to the weighted average unit price resulting from nine regular procurement processes, of over 185,000 units, carried out by federal agencies in the first four months of 2019, and corresponded to a value (R$ 0.58) that is well below the mean and median of the maximum selling prices to the government with ICMS of 0% available in the table of the ANVISA Medicines Chamber of April 2019, estimated at R$ 2.27 and R$ 1.80, respectively. Furthermore, the reduction of the monthly cost of memantine to the lower end of the range (R$31.80, corresponding to a unit value per tablet of R$0.53) still represents a very high incremental cost-effectiveness value of around R$106,211.78.

Brazil has no established threshold for cost-effectiveness yet, and this absence has been the subject of intense discussions in recent years (Soarez & Novaes, 2017; Santos et al, 2017; Saad et al., 2017). Thresholds can serve as a parameter to define the value from which a new technology should be incorporated into the health system, corresponding to the ratio between monetary costs (expressed in local currency) and a measure of health gain (e.g., QALY) in the denominator, which allows its comparison to the value of the ICER estimated in the economic evaluation (Soarez & Novaes, 2017).

For many years, the World Health Organization (WHO) suggested that technologies with a threshold between 1 and 3 GDP per capita per Disability-Adjusted Life Years (DALY) averted would be considered cost-effective. Many countries use QALYs instead of DALYs as denominators, although the original document did not recommend their use for other outcomes (Soarez & Novaes, 2017). However, more recently, the recommendation to use one to three GDP as a decision rule has been considered inappropriate, as it does not take into account country specificities and uncertainties surrounding model-generated ICER values, often conducted under various assumptions and often using non-nationally based parameters (Bertram et al., 2016; Robison et al., 2017). Only by way of comparison, if the Brazilian threshold was based on this information, the threshold

would be R$ 97,805.52 in 2018 values. In this situation, the intervention memantine 20 mg/day would not be considered cost-effective, based on the results obtained in the reference case of more than R$114,000.

It is also worth clarifying that on March 22nd, 2022, Law No. 14.313 was published, which, among other changes in Law 8080/1990, establishes a new wording for Article 19-Q and explains in § 3 that the methodologies used in the economic evaluation will later be set forth in regulations and disclosed, "including in relation to the cost-effectiveness indicators and parameters used in combination with other criteria". This regulation and parameter setting, however, has not yet been published as of the writing of this manuscript.

The extreme scenario analysis suggested that the effectiveness of memantine on AD progression and its costs significantly impact the ICER. The worst-case scenario analysis showed that the ICER can increase by more than three times (R$ 429,025.89 per QALY gained) if compared to the reference case, when the effect of the drug is reduced by 70% and its cost is increased by 100% and, in this case, memantine would remain as a non-cost-effective technology in the Brazilian context. However, in the best-case scenario analysis, where the efficacy of memantine is increased by 100% and the costs reduced by 7%, the ICER is reduced to R$63,700.58 per QALY gained, representing a decrease of about 45% compared to the reference case.

The incorporation of the drug to SUS and its inclusion in component 1A of the SCPA, of centralized purchase, may, in this sense, allow the Brazilian Ministry of Health to purchase it in large scale and use the government's bargaining power, enabling a drop in the sale price, even if it does not change the results in terms of the small gain in health outcomes.

The results of this study are difficult to compare with economic evaluations conducted abroad, even those that, as in this paper, compared memantine alone to no specific treatment. Differences in health system and cost structures between countries often limit a priori the possibility of such comparisons. In addition, the main costs associated with the disease, and therefore likely to be impacted by the eventual benefits of the use of memantine, are the global social costs associated with the AD severity and where the patient resides (Castro et al., 2010). The perspective frequently used in economic evaluations published in the literature for this indication is that of society (Knapp et al., 2016; Thibault et al., 2015; Hyde et al., 2013; Bond et al., 2012; Lachaine et al., 2011), which aggregates all the costs of care, including those associated with the institutionalization of patients, informal costs of caregivers and productivity losses of patients and, above all, of their families and caregivers. These other costs were not contemplated in this study, given the difficulties of performing reliable estimates in this regard for the country. Moreover, another relevant aspect in these economic evaluations is the inclusion of the dependency status of these patients, particularly relevant in severe AD, being frequent the presence of health statuses related to the degree of dependence of the patients in performing daily activities (dependent or independent) and their institutionalization, in more advanced cases (Bond et al., 2012; Rive et al., 2012; Antonanzas et al., 2006; Jonsson et al., 2005; Jones et al., 2004; François et al., 2004;). In Brazil, the institutionalization of patients funded by the health system is not usual, and the elderly are mainly cared for by their own families (Veras et al., 2007), with its costs not being included among the direct medical costs covered by the perspective of SUS as a funder of care.

Since indirect costs are high as AD worsens and the burden on the caregiver significantly interferes physically and psychologically with their quality of life, if memantine could improve domains other than cognitive function alone, this drug could generate more QALY gains and minimize indirect costs. However, the analysis performed here does not allow us to make such a claim, given the perspective chosen.

One of the limitations of the study lies in the great scarcity of national data on the reference population. In the absence of data on the distribution of the population with AD in Brazil, as well as population-based studies that would evaluate the AD progression in the country, all clinical and epidemiological data adopted are of international origin (Spackman et al., 2012;

Lopez-Batista et al., 2006). In addition, the utility measures used to feed the model also came from international literature and may not be entirely adequate for the national reality (Ekman et al., 2006; Jonsson et al., 2006; Wlodarczyk et al., 2006; Andersen et al., 2004; Newman et al., 1999), even more so because QALY is a multidimensional concept and where the cultural and social contexts are very relevant. Its use was necessary given the informational gap situation already mentioned.

The values used to estimate the costs of memantine represent the best and most up-to-date information available in the SIASG at the time of execution of the study, but do not necessarily represent the values paid by the health system when regular purchases programmed by the Brazilian Ministry of Health take place. The use of this source of information, however, was necessary because of the unavailability at the time of the study of values for the drug in the SUS payment tables.

The model did not include the costs of treating adverse drug-related events (memantine and additional drugs associated with the treatment of neuropsychiatric disorders). In the case of memantine, these events are known to be small, while the drug is considered to have a good safety profile (Matsunaga et al., 2018; Jiang et al., 2015). As for the others drugs, there were difficulties in estimating the frequency of these events from the literature, and since their use applies to both strategies underevaluation, with a small reduction in use and limited only to year 1, it was assumed that any impacts would be small.

Finally, the evaluation conducted when the drug was incorporated into SUS in late 2017 did not include any cost-effectiveness study, contrary to the legal regulations that guide the process of evaluation and incorporation of technologies into the Brazilian public health system. Despite the limitations mentioned above, data such as that obtained in this study could be another important element to be added to the discussions held at the time.

5. Final Considerations

The results of this economic evaluation indicate that memantine for severe AD when compared to no specific treatment, from the perspective of the SUS as the funder of care, has a considerably high ICER, arising mainly from the relatively small additional gains in QALY. This means that only if the benefits of memantine were significantly greater and the costs of monthly treatment greatly reduced, the ICER would fall below R$ 100,000.00 per QALY gained. It is believed that the information obtained in this study, considering the limitations presented, could have been a contributing element in the decision process regarding the incorporation of memantine in the SUS.

Considering the accelerated aging of the Brazilian population and the impact of AD on health costs, more studies should be developed in order to help the most adequate allocation of health resources. Studies that capture QALY measures in this population at the local level, as well as the adaptation of economic models that consider other parameters, can enrich the discussion and help in the decision-making process.

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