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REGULATORY APPROVALS AND HEALTH TECHNOLOGY ASSESSMENT RECOMMENDATIONS FOR ALZHEIMER'S DISEASE MEDICATIONS: AN INTERNATIONAL COMPARATIVE ANALYSIS

APROVAÇÕES REGULATÓRIAS E RECOMENDAÇÕES DE AVALIAÇÃO DE TECNOLOGIAS EM SAÚDE EM MEDICAMENTOS PARA DOENÇA DE ALZHEIMER: UMA ANÁLISE COMPARATIVA INTERNACIONAL

APROBACIONES REGULATORIAS Y RECOMENDACIONES DE EVALUACIÓN DE TECNOLOGÍAS SANITARIAS PARA MEDICAMENTOS DESTINADOS A LA ENFERMEDAD DE ALZHEIMER: UN ANÁLISIS COMPARATIVO INTERNACIONAL

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ABSTRACT
Alzheimer's disease requires increasing regulatory and Health Technology Assessment (HTA) attention. This study analyzed regulatory approvals and HTA decisions concerning symptomatic and disease-modifying medications indicated for the disease. A documentary review was conducted considering decisions issued by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and Brazilian Health Regulatory Agency (ANVISA), as well as assessments issued by the National Institute for Health and Care Excellence (NICE) and the National Commission for the Incorporation of Technologies into the Unified Health System (CONITEC). Seven medications were identified, comprising four symptomatic and three disease-modifying therapies. All symptomatic medications were approved by the regulatory agencies. Among disease-modifying therapies, only donanemab received convergent approval from all three agencies, whereas aducanumab and lecanemab were not approved by EMA and ANVISA. Aducanumab was rejected due to the severity of adverse events and clinical uncertainty. In the HTA analysis, four of the seven technologies (57%) received simultaneous positive recommendations from NICE and CONITEC. None of the disease-modifying therapies had been assessed by CONITEC, whereas NICE had discontinued the assessment of aducanumab and was still evaluating lecanemab and donanemab. Differences were identified between regulatory decisions and HTA assessments regarding disease-modifying therapies.

KEYWORDS: Alzheimer Disease. Health Technology Assessment. Drug Evaluation.

RESUMO
A Doença de Alzheimer demanda crescente atenção regulatória e de Avaliação de Tecnologias em Saúde (ATS). Este estudo analisou as aprovações regulatórias e decisões de ATS referentes aos medicamentos sintomáticos e modificadores indicados para a doença. Foi realizada revisão documental considerando as decisões das agências Food and Drug Administration (FDA), European Medicines Agency (EMA) e Agência Nacional de Vigilância Sanitária (ANVISA), bem

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como os pareceres da National Institute for Health and Care Excellence (NICE) e Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC). Sete medicamentos foram identificados, sendo quatro sintomáticos e três modificadores. Todos os sintomáticos foram aprovados pelas agências regulatórias. Entre as terapias modificadoras, apenas o donanemabe apresentou aprovação convergente nas três agências, enquanto aducanumabe e lecanemabe não receberam aprovação da EMA e ANVISA, sendo o aducanumabe rejeitado devido à gravidade dos eventos adversos e à incerteza clínica. Na análise de ATS, quatro das sete tecnologias (57%) receberam recomendação positiva simultânea pela NICE e CONITEC. Nenhuma terapia modificadora foi avaliada pela CONITEC, enquanto a NICE manteve aducanumabe com avaliação descontinuada e lecanemabe e donanemabe em avaliação. Foram identificadas diferenças entre decisões regulatórias e avaliações de ATS em relação às terapias modificadoras da doença.

PALAVRAS-CHAVE: Doença de Alzheimer. Avaliação de Tecnologias em Saúde. Avaliação de Medicamentos.

RESUMEN
La enfermedad de Alzheimer requiere una atención regulatoria y de Evaluación de Tecnologías Sanitarias (ETS) cada vez mayor. Objetivo: Analizar las aprobaciones regulatorias y las decisiones de ETS relacionadas con los medicamentos sintomáticos y modificadores indicados para la enfermedad. Métodos: Se realizó una revisión documental considerando las decisiones de la Food and Drug Administration (FDA), la European Medicines Agency (EMA) y la Agencia Nacional de Vigilancia Sanitaria de Brasil (ANVISA), así como los informes del National Institute for Health and Care Excellence (NICE) y de la Comisión Nacional para la Incorporación de Tecnologías al Sistema Único de Salud (CONITEC). Se identificaron siete medicamentos, cuatro sintomáticos y tres modificadores de la enfermedad. Todos los medicamentos sintomáticos fueron aprobados por las agencias reguladoras. Entre las terapias modificadoras de la enfermedad, solo donanemab presentó una aprobación convergente por parte de las tres agencias, mientras que aducanumab y lecanemab no recibieron la aprobación de la EMA ni de ANVISA. Aducanumab fue rechazado debido a la gravedad de los eventos adversos y a la incertidumbre clínica. En el análisis de ETS, cuatro de las siete tecnologías (57%) recibieron simultáneamente una recomendación positiva por parte de NICE y CONITEC. Ninguna terapia modificadora de la enfermedad había sido evaluada por CONITEC, mientras que NICE mantuvo suspendida la evaluación de aducanumab y continuaba evaluando lecanemab y donanemab. Se identificaron diferencias entre las decisiones regulatorias y las evaluaciones de tecnologías sanitarias en relación con las terapias modificadoras de la enfermedad.

PALABRAS CLAVE: Enfermedad de Alzheimer. Evaluación de Tecnologías Sanitarias. Evaluación de Medicamentos.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide and represents one of the major public health challenges (BRASIL, 2024). In 2021, the World Health Organization (WHO) published a report estimating that 55.2 million people were living with dementia in 2019, a figure similar to the estimate calculated by the Global Burden of Disease (GBD) study, which estimated 57 million cases (NICHOLS et al., 2022). Both studies showed that prevalence increases with age, doubling every five years from the age of 65 years onward. They also revealed

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that prevalence rates are higher among women than men and indicated that most people living with dementia reside in low- and middle-income countries, including Brazil. GBD estimates further indicate that, in 2019, approximately 1.8 million people were living with dementia in Brazil, with projections reaching 6.7 million by 2050.

In addition, DATASUS data indicate that, between 2010 and 2019, hospital admissions due to AD increased by 87.7%, with the greatest increases observed among men (97.4%), individuals who self-identified as mixed race (pardos) (224%), people aged 80 years or older (115.1%), and residents of the Northeast (172.1%) and Central-West (144.2%) regions of Brazil. These findings reflect the growing demand for specialized diagnosis and care within the Brazilian Unified Health System (SUS). The increasing magnitude of this condition imposes a substantial clinical, social, and economic burden on health systems, particularly in settings where long-term care infrastructure is limited (MATA et al., 2025; MATA et al., 2024; WIMO et al., 2023).

Regarding the economic impact of AD in Brazil, Gutierrez et al. (2014) reported that the disease generates substantial costs per patient, including both direct expenditures, such as hospitalizations and formal care, and indirect costs associated with informal caregiving or institutionalization, corroborating DATASUS data. This scenario poses a significant challenge for families and public financing, particularly during the moderate and advanced stages of the disease, reinforcing the need for public policies that promote not only early diagnosis and rehabilitation but also the rigorous assessment of health technologies for the treatment of AD (CASTRO et al., 2010; MATA et al., 2025).

Because the disease has several proposed etiological mechanisms, its pharmacological management has traditionally relied predominantly on symptomatic agents, such as acetylcholinesterase inhibitors, including donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. These medications have modest efficacy and are used to alleviate cognitive and functional symptoms (HANSEN et al., 2008). Since 2021, however, new therapies known as disease-modifying therapies have been approved. These anti-β-amyloid monoclonal antibodies, represented by aducanumab, lecanemab, and donanemab, have significantly altered the regulatory and scientific landscape (CUMMINGS et al., 2024).

These emerging therapies have generated worldwide debate regarding their clinical effectiveness, safety profiles, and cost-effectiveness (BARBOSA et al., 2024). While regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have adopted accelerated approval approaches based on surrogate endpoints, Health Technology Assessment (HTA) agencies, such as the National Institute for Health and Care

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Excellence (NICE) and the National Commission for the Incorporation of Technologies into the Brazilian Unified Health System (CONITEC), have recommended greater caution in view of uncertainties regarding sustained clinical benefits, the risk of adverse events, and the sustainability of health systems. This divergence illustrates a critical interface between regulatory decision-making and HTA, particularly for high-cost innovative therapies supported by emerging evidence (BARBOSA et al., 2024; BROCKMANN et al., 2023; WRIGHT et al., 2023).

The role of HTA agencies is to provide technical and scientific evidence to support decision-making regarding the incorporation of health technologies into health systems, considering not only efficacy and safety but also cost-effectiveness, budget impact, and equity (RODRIGUEZ LLORIAN et al., 2023). In Brazil, CONITEC has played a central role in this process since its establishment in 2011, as provided for by Law No. 12,401/2011. Despite advances, studies have demonstrated that discrepancies between regulatory approvals and reimbursement or coverage decisions remain significant, particularly in fields such as oncology and neurology (DEBSARMA, 2022; NIÑEROLA; SÁNCHEZ-REBULL; HERNÁNDEZ-LARA, 2020). This raises questions regarding equitable access to innovation and the sustainability of the public health system (RODRIGUEZ LLORIAN et al., 2023).

Against this backdrop, understanding the relationship between regulatory approvals and HTA recommendations is essential for aligning public health policies, health technology management, and equitable access to therapies. Therefore, the present study aimed to comparatively analyze medications approved for AD by regulatory agencies and their respective recommendations by HTA agencies, discussing the reasons for the observed discrepancies and their implications for the incorporation of disease-modifying technologies in Brazil.

MATERIALS AND METHODS

This study was a comparative documentary review conducted between August and October 2025, in which regulatory approval and Health Technology Assessment (HTA) decisions concerning medications indicated for Alzheimer's disease (AD) were analyzed and compared.

Information was collected from official public sources available on the institutional websites of each agency, including databases, technical reports, assessment reports, and decision documents. The main international regulatory agencies were included: the *Food and Drug Administration* (FDA), United States; the *European Medicines Agency* (EMA), European Union; and the Brazilian Health Regulatory Agency (ANVISA), Brazil. The HTA agencies included were the *National Institute for Health and Care Excellence* (NICE), United Kingdom, and the National Commission for the Incorporation of Technologies (CONITEC), Brazil.

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For the FDA and EMA, the *Drugs@FDA* and *European Public Assessment Reports* platforms, respectively, were used. For ANVISA, information was obtained through the institutional portal and the *Bulário Eletrônico* (Electronic Drug Compendium). NICE decisions were extracted from the *Technology Appraisal Guidance* repository, whereas CONITEC decisions were obtained from the panels of requested technologies and recommended technologies.

All medications with a label-approved indication for the treatment of AD were included, comprising both symptomatic therapies, represented by acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA receptor antagonist memantine, and disease-modifying therapies, represented by the anti-amyloid monoclonal antibodies aducanumab, lecanemab, and donanemab. Inclusion was based on the existence of a regulatory or HTA decision issued by October 31, 2025, regardless of local marketing status.

The variables analyzed were: year of regulatory approval; type of technology (symptomatic or disease-modifying); type of HTA decision (recommended, not recommended, or under assessment); technical justifications presented in the decisions, categorized according to clinical efficacy, safety, cost-effectiveness, and budget impact; and the presence of relevant adverse events reported in the assessment documents. Data extraction was performed independently by two researchers, and any discrepancies were resolved by consensus.

Data analysis was conducted descriptively and comparatively. Initially, a quantitative synthesis was prepared of the number of medications approved by each regulatory agency and recommended by the HTA agencies. Subsequently, a qualitative analysis of the justifications presented in the recommendation reports was performed to identify convergences and divergences among decision-making criteria, following a standardized approach (VAN DER WILT *et al.*, 2022).

In addition to the interagency comparison, a contextual analysis of the Brazilian scenario was conducted, considering the relationship between ANVISA and CONITEC. This stage sought to examine discrepancies between regulatory approval and the issuance of HTA recommendations, as well as the nature of the technical justifications presented by CONITEC. This analysis enabled the identification of potential regulatory, cost-effectiveness, and clinical uncertainty barriers.

RESULTS

Regulatory Status of the Included Medications

The seven medications with therapeutic indications for AD included in the study were identified, with approvals granted between 1996 and 2025. Table 1 summarizes the results

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regarding the year of regulatory approval, type of technology, and registration status with each agency.

Table 1. Regulatory approvals of medications for Alzheimer's disease (FDA, EMA, and ANVISA), according to type of technology and year of approval.

Drug	Technology type	FDA (USA)	EMA (EU)	ANVISA (Brazil)
Donepezil	Symptomatic (acetylcholinesterase inhibitor)	1996	1997	2002
Rivastigmine	Symptomatic (acetylcholinesterase inhibitor)	2000	1998	2004
Galantamine	Symptomatic (acetylcholinesterase inhibitor)	2001	2000	2005
Memantine	Symptomatic (NMDA receptor antagonist)	2003	2002	2008
Aducanumab	Disease-modifying (anti-β-amyloid antibody)	2021[a]	Not approved	Not approved
Lecanemab	Disease-modifying (anti-β-amyloid antibody)	2023	2025	Not registered
Donanemab	Disease-modifying (anti-β-amyloid antibody)	2024	2025	2025

Note[a]: Accelerated approval

Of the seven therapies identified, all symptomatic therapies were approved by the three regulatory agencies, whereas among the disease-modifying therapies, only donanemab has an approved regulatory status with the FDA, EMA, and ANVISA.

A pattern of greater caution by the EMA and ANVISA can be observed regarding the approval of innovative therapies based on surrogate endpoints, in contrast to the FDA, which has adopted accelerated approval mechanisms. The number and severity of reported adverse events were key determinants in non-approval decisions, as observed in the case of aducanumab (LARGENT *et al*., 2022; LAU; SEIFERT, 2025).

3.2. Recommendations from HTA Agencies

Table 2 presents the type of HTA decision (recommended, not recommended, or under assessment), together with the technical justifications categorized according to the four analytical dimensions: clinical efficacy, safety, cost-effectiveness, and budget impact.

Of the seven technologies assessed, four (57%) received positive recommendations from both HTA agencies (all symptomatic medications). Regarding disease-modifying therapies, only one received a recommendation against incorporation, while the others are currently under

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assessment by NICE. In the Brazilian context, no disease-modifying therapy has been submitted for assessment by CONITEC. Positive decisions were concentrated on symptomatic therapies, whose efficacy and safety were considered acceptable and cost-effective. In contrast, disease-modifying therapies demonstrated limited clinical benefit, high costs, and the need for intensive monitoring, resulting in non-recommendation or the absence of an assessment.

Table 2. Health Technology Assessment (HTA) recommendations for medications for Alzheimer's disease, according to NICE and CONITEC and the analytical dimensions evaluated.

Drug	Technology type	NICE	CONITEC	Clinical efficacy	Safety	Cost-effectiveness	Budget impact
Donepezil	Symptomatic	Recommended	Incorporated	Cognitive and functional improvement	Good tolerability	Favorable	Sustainable
Rivastigmine	Symptomatic	Recommended	Incorporated	Effects similar to donepezil	Mild gastrointestinal effects	Favorable	Sustainable
Galantamine	Symptomatic	Recommended	Incorporated	Mild benefit	Good tolerability	Favorable	Sustainable
Memantine	Symptomatic	Recommended	Incorporated	Behavioral improvement	Good safety profile	Favorable	Sustainable
Aducanumab	Disease-modifying	Assessment discontinued	Not assessed	Uncertain cognitive benefit ($p > 0.05$)	Severe ARIA in 35%	Unfavorable	High impact
Lecanemab	Disease-modifying	Under assessment	Not assessed	Modest cognitive benefit	–	–	–
Donanemab	Disease-modifying	Under assessment	Not assessed	35% reduction in decline in *CDR-SB*	–	–	–

Note: ARIA = amyloid-related imaging abnormalities; CDR-SB = Clinical Dementia Rating–Sum of Boxes.

The qualitative analysis of the rationales identified four main domains underlying the decision-making process: clinical efficacy, safety, cost-effectiveness, and budget impact. NICE and CONITEC demonstrated convergence in prioritizing technologies that provide proven clinical

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benefit and economic feasibility within the thresholds established by their respective health systems, as well as in recognizing uncertainty regarding the efficacy of disease-modifying therapies. Both agencies classified the cognitive gains observed in clinical trials of disease-modifying therapies as statistically significant but clinically limited (Van Dyck et al., 2023).

The convergence observed between HTA agencies regarding the need for robust evidence for emerging technologies is consistent with the international literature. Drummond et al. (2008) highlight that agencies such as NICE, the Canada's Drug Agency (CDA), Canada, and the Institute for Quality and Efficiency in Health Care (IQWiG), Germany, have reinforced the central role of demonstrated clinical effectiveness and methodological consistency in assessments, particularly for high-cost innovative therapies. According to the authors, pressure for rapid adoption should not override the requirement for clinically meaningful outcomes and transparent economic analyses. This supports the findings of the present study by demonstrating the cautious approach adopted by HTA agencies toward disease-modifying therapies for Alzheimer's disease.

Regarding safety, the assessment reports highlighted the occurrence of adverse reactions specifically associated with disease-modifying therapies, particularly amyloid-related imaging abnormalities (ARIA), which are brain abnormalities detected by magnetic resonance imaging in patients with AD receiving certain anti-amyloid immunotherapies. These abnormalities are characterized by vasogenic edema (ARIA-E) and cerebral microhemorrhages (ARIA-H) (VAN DYCK et al., 2023). In clinical trials, aducanumab was associated with ARIA-E and ARIA-H in up to 35% of patients, frequently accompanied by headache, confusion, and hypertension. Lecanemab showed an incidence of 21% for ARIA-E and 17% for headache, whereas donanemab showed 25% incidence of ARIA-E, generally of mild to moderate severity. These adverse reactions, combined with the need for magnetic resonance imaging monitoring, were important factors in decisions against recommending these therapies (BUDD HAEBERLEIN et al., 2022; SIMS et al., 2023; VAN DYCK et al., 2023).

Furthermore, the analysis of the assessment reports indicated that disease-modifying therapies had incremental costs exceeding £150,000/QALY, with a budget impact considered high. Estimated annual costs per patient ranged from US$25,000 to US$30,000, values considered incompatible with the cost-effectiveness thresholds adopted by HTA agencies. The main cost-effectiveness parameter used is the cost per quality-adjusted life year (QALY), a measure that expresses the gain in life expectancy weighted by the quality of health provided by an intervention (DRUMMOND et al., 2009).

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In the United Kingdom, NICE has traditionally considered a reference range of approximately £20,000 to £30,000 per QALY gained in cost-effectiveness assessments, although other factors are also considered in the decision-making process (MCCABE; CLAXTON; CULYER, 2008). In Brazil, CONITEC began adopting, in 2022, a reference parameter for the cost-effectiveness threshold, initially established at R$40,000 per QALY, with provision for annual adjustment according to changes in GDP per capita. In specific situations, an alternative threshold of up to three times the reference value may be considered. However, Brazilian health economics studies (LOURENÇÃO et al., 2023; RIBEIRO et al., 2017) have used, as an analytical reference, the historical parameter recommended by the World Health Organization (WHO), which considers interventions cost-effective when their cost is up to one to three times the gross domestic product (GDP) per capita per QALY. Based on the estimated GDP per capita for 2025, this range would correspond to approximately R$180,000 per QALY. Values above this level indicate technologies with unfavorable cost-effectiveness and potentially unsustainable budgetary impact for the Brazilian Unified Health System (SUS).

The economic impact associated with disease-modifying therapies for Alzheimer's disease is an increasing concern for health systems and is supported by the international literature. Ross et al. (2022) estimated that the cumulative costs of aducanumab and donanemab therapies, considering prices in the United States market, substantially exceed traditional cost-effectiveness thresholds, even under conservative assumptions regarding eligibility and efficacy. In settings with more limited resource availability, Price et al. (2025) demonstrated that pharmacological interventions for Alzheimer's disease tend to have a low probability of being cost-effective in middle-income countries when evaluated using local economic parameters. These findings reinforce that the barriers identified in HTA decisions reflect not only clinical uncertainties but also structural challenges related to financial sustainability, which is particularly relevant for health systems such as Brazil's.

3.3. Interagency Comparison

When comparing the dimensions assessed, regulatory processes may consider biomarkers and other endpoints used to support approval decisions, whereas HTA considers aspects related to clinical benefit, available evidence, safety, and the economic impact of technologies. In the Brazilian context, the incorporation of technologies into the Brazilian Unified Health System (SUS) is contingent upon sanitary registration with ANVISA, as established by current legislation. This requirement links the regulatory and technology incorporation assessment stages in the country and may influence the temporal sequence between sanitary

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registration and incorporation assessment, particularly for technologies that have been recently evaluated in other regulatory settings.

In contrast, the model adopted by NICE allows the assessment process to proceed in parallel with the regulatory review conducted by the EMA, requiring only that marketing authorization be in place at the time the final guidance is published. This mechanism provides greater agility in decision-making and reduces the interval between regulatory approval and the availability of technologies within the British public health system (DICKSON et al., 2018).

The difference observed between regulatory decisions and HTA recommendations for disease-modifying therapies for Alzheimer's disease has also been described in the literature. Lythgoe et al. (2022) reported that the FDA's approval of aducanumab considered the reduction of amyloid plaques as a surrogate endpoint, whereas the EMA adopted a different position, considering uncertainties related to clinical benefits and safety. Similarly, Ross et al. (2022) discussed the clinical effects and adverse events associated with aducanumab and donanemab, as well as aspects related to their economic evaluation. These findings are consistent with the results of the present study and suggest that differences between regulatory decisions and HTA assessments may occur in the context of innovative therapies, particularly when uncertainties remain regarding clinical benefits, safety, and associated costs.

Thus, this integrated analysis highlights a structural gap between innovation and access, driven by methodological and economic differences between regulatory assessment and HTA, reinforcing the importance of greater coordination between ANVISA and CONITEC. There is a need for early dialogue mechanisms between regulatory and HTA agencies so that clinical evidence, cost-effectiveness criteria, and implementation planning can be jointly considered (Eichler et al., 2015). Examples of transferable good practices include early-dialogue initiatives in the European Union involving the EMA and HTA networks. In addition, the adoption of adaptive assessment models, which allow reassessment as new data emerge, including real-world evidence, has been proposed as a strategy for addressing rapidly evolving innovations (EICHLER et al., 2015; NISTICÒ; BORG, 2021).

The need to incorporate real-world evidence into the HTA process is further supported by international comparative analyses. Makady et al. (2018), in a study involving five major HTA agencies, demonstrated that data derived from routine clinical practice are essential for reducing uncertainty regarding the effectiveness, safety, and appropriate use of complex technologies, particularly when clinical trials have methodological limitations or highly selected populations. Hampson et al. (2018) complement this perspective by discussing the challenges and opportunities associated with the use of real-world evidence in coverage decisions, highlighting

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that conditional coverage models, such as coverage with evidence development, may balance access and prudence in the presence of uncertainty. These considerations directly relate to the findings of the present study, supporting the potential adoption of adaptive models in Brazil to mitigate evidence gaps and support more dynamic decision-making.

Finally, it is important to highlight that the comparative assessment of regulatory approvals and HTA decisions is subject to several potential biases, which may be considered limitations of this study. These include unequal access to the publication of data from early development phases or post-marketing studies; differences in regulatory and coverage contexts across countries; and the limited availability of Brazil-specific data, which reduces the generalizability of the findings.

CONSIDERATIONS

A higher number of regulatory approvals than HTA recommendations was observed, particularly for disease-modifying therapies. This discrepancy reflects concerns regarding clinical uncertainty, safety, and cost-effectiveness, reinforcing the need to integrate regulatory evidence and real-world data into HTA analyses in order to balance innovation, access, and the sustainability of health systems.

The results indicate differences between the pace of regulatory approvals and that of HTA recommendations for disease-modifying therapies for Alzheimer's disease. From a regulatory perspective, agencies such as the FDA considered surrogate endpoints in some approval processes, whereas HTA assessments additionally considered the available evidence on clinical benefit, safety, and cost-effectiveness to inform decisions regarding incorporation into public health systems.

These differences reflect distinct assessment paradigms: regulatory processes seek to facilitate access to promising innovations, whereas HTA aims to ensure allocative efficiency and budgetary sustainability. In the case of Alzheimer's disease, whose prevalence is expected to increase substantially over the coming decades, the adoption of high-cost therapies with uncertain clinical benefits may affect the equitable allocation of healthcare resources. Thus, the cautious approach observed in HTA decisions should not be viewed solely as a barrier to incorporation, but also as a strategy for the responsible management of scientific and economic uncertainties.

In the Brazilian context, the findings highlight the importance of analyzing the interaction between regulatory and HTA processes, considering their different responsibilities, criteria, and decision-making stages. Experiences of early dialogue between regulatory bodies and HTA

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agencies, already adopted in some international settings, may provide a reference for studies on potential strategies for interaction between these institutions. In addition, the incorporation of real-world evidence represents a relevant approach for complementing the information available at the time of assessment. Future research could explore the use of such evidence, particularly in the Brazilian context, as well as monitor the evolution of HTA decisions and health technology incorporation processes.

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