Gozzo L, Benfatto G, Giorgianni F (2020) 03: 68-78
https://doi.org/10.36118/pharmadvances.03.2020.01

OPINION PAPER **Open Access**

Beyond the budget silo approach: estimating health system sustainability for future dementia drugs

L. Gozzo[1], G. Benfatto[1], F. Giorgianni[2], J. Sultana[2], E. Rossi[3], L. Longo[1], S. Mansueto[1], D. C. Vitale[1], C. Savoca[4], F. Caraci[5,6], M. De Rosa[3], G. Trifirò[2], F. Drago[1,4]

[1] A.O.U. Policlinico Vittorio Emanuele, Catania, Italy
[2] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[3] CINECA, Interuniversity Consortium (Health Service), Bologna, Italy
[4] Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy
[5] Department of Drug Sciences, University of Catania, Catania, Italy
[6] Oasi Research Institute, IRCCS, Troina, Italy

E-mail: f.drago@unict.it

Summary
Aim of the study: to analyze the impact of a hypothetic disease-modifying drug (DMD) on the estimated costs of dementia sustained by the National Health System (NHS) based on current real-world data.
We performed our analysis on the Caserta Local Health Unit (LHU) database and the ARNO Observatory, which include data from 19 Italian LHUs. Participants with at least 1 year of database history and a diagnosis of dementia were identified using the ICD-9CM codes for dementia in the hospital discharge diagnosis, specific exemption codes and prescriptions of anti-dementia drugs. An assessment of the actual healthcare costs was performed using available data on all healthcare services reimbursed by the NHS in the reference period. Finally, we made prevalence projection for Caserta's and for ARNO's population and estimated the number of new cases avoided by decreasing the incidence of 20% and 40% five years after the introduction of DMD in 2025.
Average annual cost per patient with dementia equaled € 2,193 for the Caserta LHU and € 4,356 for the ARNO LHUs. The NHS 5-years savings was equal to € 4,057,050 and € 8,116,293 for Caserta, and € 96,563,808 and € 193,127,616 for ARNO, considering a 20% and 40% reduction of dementia incidence after the introduction of the hypothetical new anti-dementia drug in 2025.
Our study forecasts the impact of future prevalence on health management based on real-world prevalence and expenditure data and provides a useful model to project theoretical savings after the introduction of a new DMD for dementia and for other unmet medical needs. Although comparable by sample type and selection criteria, the estimated difference in disease expenditures from the two databases indicates that the method of generating costs could be linked to a distinct health management in LHUs.

Introduction

Pharmaceutical cost is the main public healthcare expenditure target for cost controls due to its rapid growth in recent years and being easy to calculate. However, treating pharmaceuticals as a separate

category for cost-containment according the so called "silos approach" may lead to greater expenditures on other inputs, such as hospital care, reducing the overall efficiency of the healthcare system (1). An alternative methodology for managing system sustainability emerged in the possibility of adopting the "disease or therapeutic area budget" in which costs related to health services are globally considered. In this case, an increase in pharmaceutical expenditures following the approval of a breakthrough therapy could be acceptable if its use results in a reduction of the other expenditure items for the same populations in the brief and/or long term. Hence, the adoption of policies that extend beyond the silos approach should be encouraged and promoted (2). Italy has used several methods to make pharmaceutical costs more sustainable as well as adequate access to medications, such as managed entry agreements (MEAs) (3).

Despite research advances, there are still many highly disabling and/or fatal diseases lacking disease-modifying drugs (DMDs), which would change their natural history. According to the European Medicine Agency (EMA) and the Food and Drug Administration (FDA), a drug is disease modifying when it can delay or arrest the underlying pathophysiological process that drives the disease (4). Such innovative drugs may have a major impact not only on public health but also on the expenditure sustained by the National Health Systems (NHSs). This happened with the new antivirals for hepatitis C chronic infection, a breakthrough treatment which obtained an eradication rates > 95% (5). However, the high price and the large number of people who needed to be treated made their use unsustainable for public health systems, and this gave rise to a debate on cost-effectiveness and on patients' prioritization (6,7). It is likely that such a situation will rise every time a highly innovative therapy for critical unmet medical need will be introduced on the market. In this context, projections of epidemiologic and economic data are useful to be prepared for rational resources allocation, and real-world data are the best starting point to make these predictions reliable.

Dementia is one of the most appropriate examples to show the possible impact of a DMD. Almost 47 million people worldwide were affected by dementia in 2015, and this number is expected to reach 75 million by 2030 and 131 million by 2050 (8). Moreover, the global costs of dementia were estimated to be $ 818 billion in 2015, with an increase of 35% since 2010 (9). Disease costs in general increase with dementia severity, due to the decline of cognitive and functional status (10). Therefore, dementia presents several challenges from both medical and economic perspectives, since current drug therapies, such as cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and memantine, exert only symptomatic effects on cognitive dysfunction, while having no effect on disease progression. A novel DMD that targets the development of dementia is expected to have impact on disease progression before any substantial and irreversible functional loss occurs. Hence, this class of drugs preventing disease progression would improve morbidity and quality of life of millions and would save a great amount of money.

Drug development in Alzheimer's disease (AD) is particularly difficult, since a 99.6% failure rate has been previously reported (11). The success rate continues to be low, and several drugs in late phases of clinical development failed (12). Pipeline updated in 2019 according to data from clinicaltrials.gov included 132 agents, with more than 70% represented by DMDs (13-15). Several agents failed to meet pre-specified outcomes, e.g. BACE (β-site amyloid precursor protein-cleaving enzyme) inhibitors such as verubecestat (16) and lanabecestat and monoclonal antibody targeting Aβ fibrils solanezumab (17), gantenerumab and crenezumab (18).

Recently, the Food and Drug Administration (FDA) accepted to perform a priority review for aducanumab for Alzheimer's disease based on the post-hoc analysis of data from the trials to include patients who continued till March 2019, when the failure of

the two ongoing phase 3 studies was announced. The updated data of the EMERGE trial showed a 23% improvement on the primary outcome (changes in the Clinical Dementia Rating-Sum of Boxes - CDR-SB - score) compared with placebo (p=0·031), whereas the ENGAGE trial still did not show statistical significance (6% worsening compared with placebo, p=0·627) (19). However, the clinical relevance of the results of EMERGE trial is still uncertain, especially in light of the lack of effect in the ENGAGE one, being the relative difference on the CDR-SB equal to an absolute difference of about 0.4 points.

In 2015, the Alzheimer's Association published the document "Changing the Trajectory of Alzheimer's Disease" describing the current and future impact of AD and the effect of introducing a hypothetical treatment in 2025, which could delay the onset by five years (20). This report shows how this treatment would significantly reduce the costs of caring for people affected by dementia, estimating total savings of over $ 83 billion in 2030 and of $ 367 billion in 2050. These results are based on US epidemiological and expenditure data and on their long-term projections.

In sum, our aim was to analyze the impact of a new hypothetical DMD on the costs of dementia sustained by the Italian NHS.

Material and methods

We analyzed data from two healthcare databases:

a) Caserta Local Health Unit (LHU) database, which is a record linkage of electronic medical records from general practitioners and the claims databases of the same catchment area in Southern Italy covering a population of around 1 million inhabitants in 2009–2013;

b) ARNO Observatory (21), a population-based database including inhabitants of 19 Italian LHUs and of several Italian Regions (69.6% from the north, 11.0% from the central and 19.4% from the south of Italy). We accessed data of year 2016.

In both cases, available claims databases include data on health services reimbursement provided by the NHS to inhabitants residing in the respective catchment areas, such as hospital admissions, drugs dispensing, medical procedures, diagnostic tests, and specialists' visits (22).

Participants with at least 1 year of database history and a diagnosis of dementia were identified using the ICD-9CM codes for dementia (290* and 331*) as found in the hospital discharge diagnosis database as well as specific exemption code from payment healthcare services. In addition, dementia was identified using Anatomical Therapeutic Chemical (ATC) codes N06DA and N06DX, corresponding to the prescriptions of specific anti-dementia drugs in the drug-dispensing database.

In these study populations, an assessment of the actual healthcare costs sustained by the NHS in the reference period was performed using available data about healthcare services provided. We used this data to calculate average annual cost for patients with dementia in several Italian settings. As patients with dementia who are captured using claims databases about services provided in secondary healthcare settings likely have more severe dementia than those identified using primary-care electronic medical records, we included both Caserta and ARNO databases to fully capture the range of severity.

Moreover, we used dementia prevalence found in these samples as our starting point for prevalence projections. An estimate of dementia prevalence up to year 2050 was calculated in two study groups, based on previously reported data (8,20,23).

The curves were normalized according to the expected increase of people aged > 65 years foreseen by the Italian National Institute of Statistics (ISTAT) report (24). Considering the variation in the 5-year period after the introduction of the drug, the curves were built through a point-to-point correlation with the literature data, corrected and weighed by aging trend. Considering regional differences, we normalized the Caserta sample projec-

tion according to the age of population in southern Italy, and the ARNO sample projection according to the age of all Italian regions. We hypothesized that a DMD, which delays the onset of dementia by five years, will be introduced in 2025. To predict the impact of the hypothetic DMD, curves of prevalence for each case study were developed. Based on the calculated prevalence curves, we simulated two scenarios in which the drug could delay — by five years — the onset of dementia, reducing the incidence by 20% and 40%, respectively. We considered a fixed average incidence of 3,57/1.000 weighed by age (25). Finally, Caserta's LHU and ARNO database-related savings after the introduction of the drug were calculated multiplying the number of patients avoided by the average annual cost per patient.

Results

Caserta and ARNO populations are classified by age, sex and dementia prevalence in **table I**. Using the selection criteria previously described, 2,420 (1.76%) and 29,680 (1.68%) patients with dementia aged > 65 years were identified in Caserta LHU and ARNO Observatory databases. The average annual costs per patient with dementia were equal to € 2,193 and € 4,356, respectively. Costs per category are detailed in **table II**. Prevalence projection curves are shown in **figure 1** for Caserta's population and **figure 2** for ARNO's population.

Table I. Caserta and ARNO populations by age, sex, and dementia prevalence.

	Caserta population	**ARNO population**
Total population	908,928	7,224,871
Population aged ≥ 65 years	137,479	1,761,836
Patients with dementia aged ≥ 65 years	2,420	29,680
Prevalence of dementia in those aged ≥ 65 years	**1.76%**	**1.68%**
Men	37.6%	43.9%
Women	62.4%	56.1%

Table II. Average annual dementia costs per patient stratified by expenditure items. LHU = Local Health Unit.

Cost	Caserta LHU costs per patient (€)	ARNO costs per patient (€)
Hospital admissions	1,402 (63.9%)	3,064 (71%)
Medical examinations	197 (9%)	401 (9%)
Pharmaceutical	594 (27.1%)	891 (20%)
Total	**2,193 (100.0%)**	**4,356 (100.0%)**

Figure 1. Curve of prevalence predictions related to Caserta's sample population; estimate of dementia prevalence up to year 2050 was calculated based on data reported in the literature (Alzheimer's Association 2015; Lobo et al. 2000) and normalized according to the expected increase of people aged > 65 years related to the southern Italy population foreseen by the ISTAT report (ISTAT 2018).
In blue, the expected curve without a disease-modifying drug; in green, the curve obtained with the introduction of a drug able to reduce dementia incidence of 20%; and, in red, the expected curve obtained with the introduction of a drug able to reduce dementia incidence of 40%.

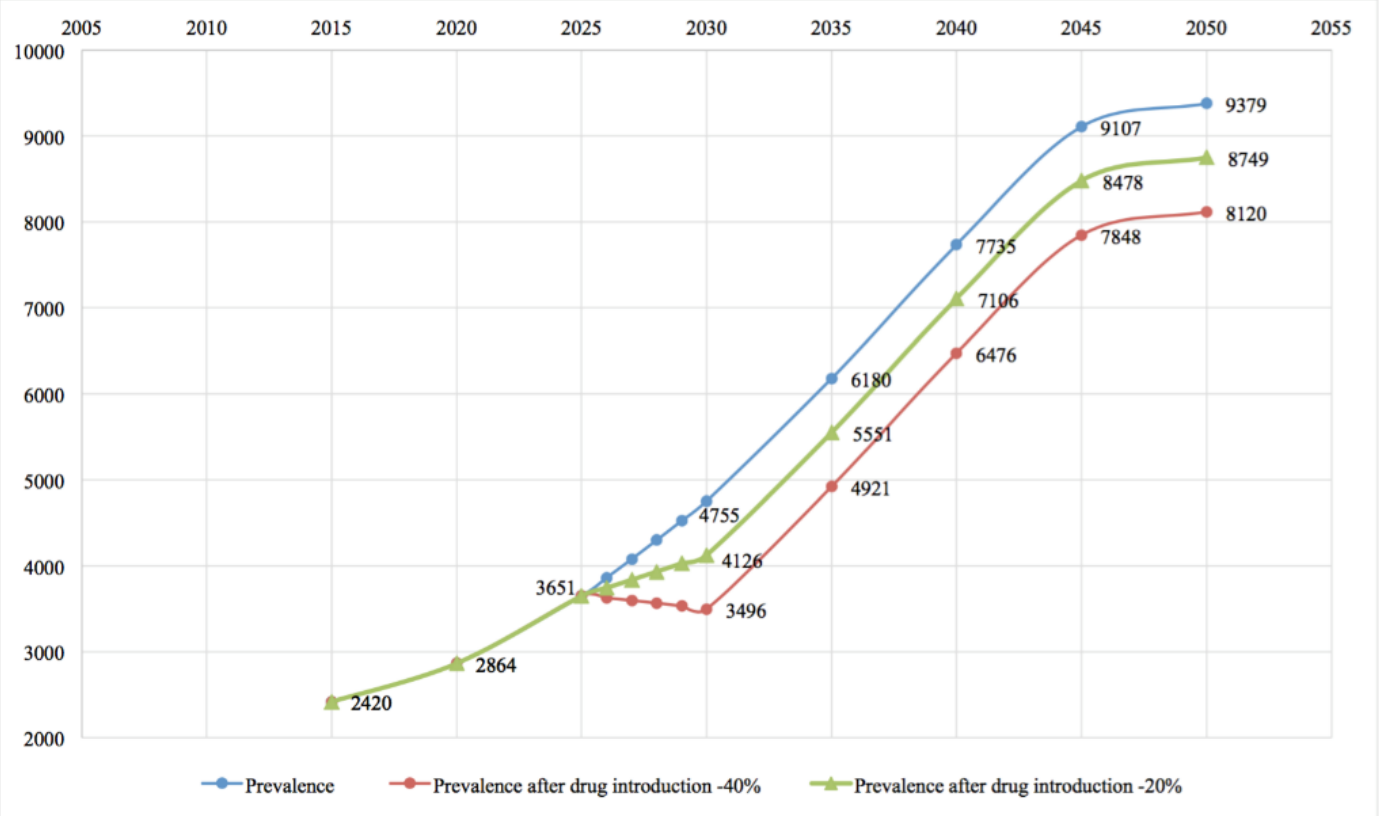
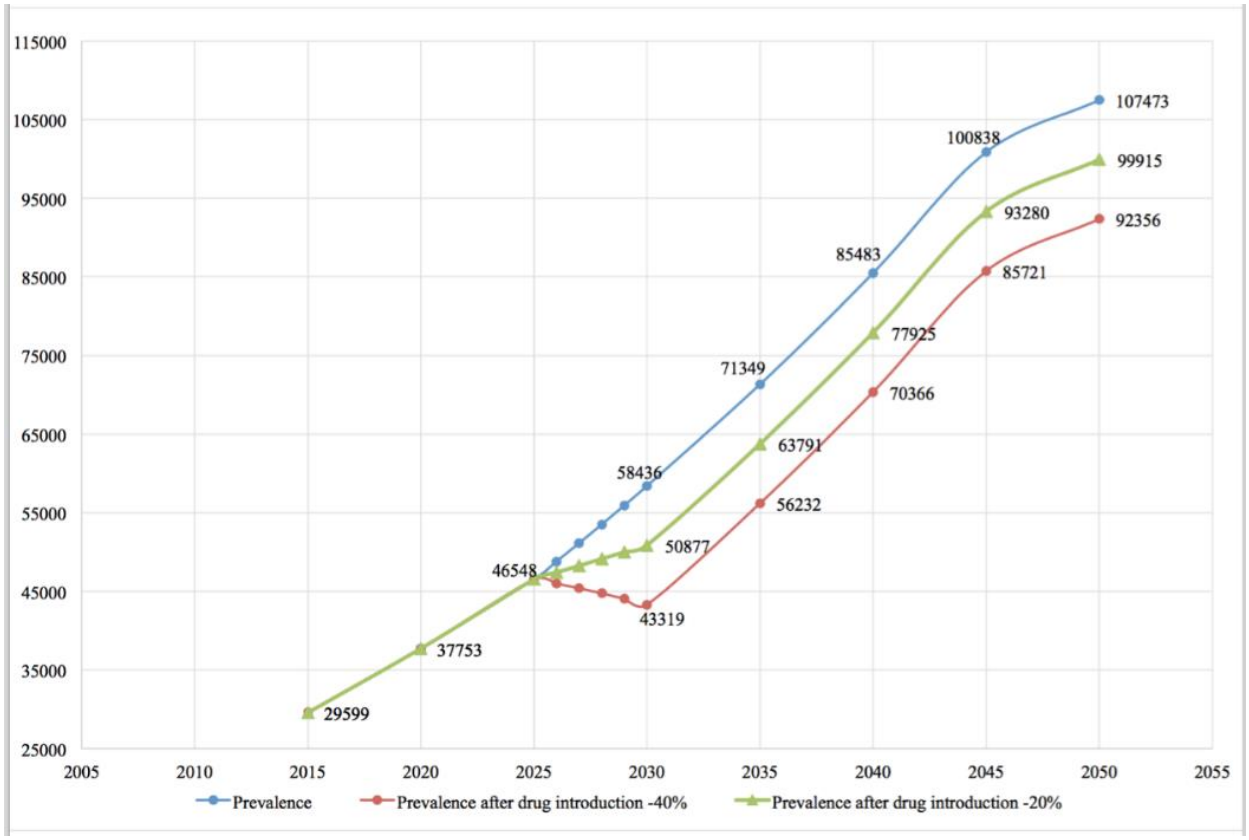


Figure 2. Curve of prevalence predictions related to ARNO population; in this case, estimate of dementia prevalence up to year 2050 was normalized according to the expected aging of all Italian regions foreseen by the ISTAT report (ISTAT 2018).
In blue, the expected curve without a disease modifying drug; in green, the curve obtained with the introduction of a drug able to reduce incidence of 20%; and, in red, the expected curve obtained with the introduction of a drug able to reduce incidence of 40%.



The final prevalence projected in 2050 is 4.44% for Caserta and 4.20% for ARNO.
In both cases, we estimated the number of new cases avoided by decreasing the incidence of 20% and 40% (**tables III**, **IV**) five years after the introduction of the new hypothetical drug in 2025.
Finally, we estimated savings after five years by multiplying the average annual costs per patient for the number of patients who avoided a dementia diagnosis (**table V**).

Table III. Estimate of patients with dementia in Caserta LHU population with and without the hypothetic disease-modifying drug reducing incidence of 20% and 40% introduced in 2025 *[Patients (n) - Incidence < 20%]; §[Patients (n) - Incidence < 40%]. LHU = Local Health Unit.

Year	Patients (n)	Incidence < 20%	Patient gap < 20%*	Incidence < 40%	Patient gap < 40%§
2015	2,420	2,420		2,420	
2020	2,864	2,864		2,864	
2025	3,651	3,651	0	3,651	0
2026	3,862	3,744	118	3,625	237
2027	4,078	3,838	240	3,597	481
2028	4,299	3,933	366	3,566	733
2029	4,525	4,029	496	3,533	992
2030	4,755	4,126	629	3,496	1,259
		Total patient gap after 5 years	1,850		3,701

Table IV. Estimate of patients with dementia in ARNO population with and without the hypothetic disease-modifying drug reducing incidence of 20% and 40% introduced in 2025. *[Patients (n) - Incidence < 20%]; §[Patients (n) - Incidence < 40%].

Year	Patients (n)	Incidence < 20%	Patient gap < 20%*	Incidence < 40%	Patient gap < 40%§
2015	29,599	29,599		29,599	
2020	37,753	37,753		37,753	
2025	46,548	46,548		46,548	
2026	48,823	47,413	1,410	46,003	2,820
2027	51,149	48,278	2,871	45,407	5,742
2028	53,527	49,144	4,383	44,761	8,766
2029	55,956	50,011	5,945	44,065	11,891
2030	58,436	50,877	7,559	43,319	15,117
		Total patient gap after 5 years	**22,168**		**44,336**

Table V. Savings after five years with a reduction of 20% and 40% of incidence.

Case study	Average annual cost per patient (€)	Savings < 20% (€)	Savings < 40% (€)
Caserta database	2,193	4,057,050	8,116,293
ARNO database	4,356	96,563,808	193,127,616

Discussion

An effective therapy for AD or dementia in general is one of the greatest unmet needs facing modern medicine (8). Considering the disease burden, there is an urgent need to discover and develop new drugs to prevent the disease, delay its onset, or slow its progression (13). Specific cellular and molecular mechanisms underlying AD pathogenesis have been identified; however, a better understanding of the pathophysiology is crucial for the identification of novel pharmacological targets and finally to develop safe and effective DMDs.

Even if an effective treatment seems to be still far from final approval (11,12,18), our analysis provides a framework for rational planning and impact prediction in managing innovation and balancing access and sustainability. In this study, we used real-world expenditure data reported in Caserta and ARNO databases to estimate the average costs saved per year after the introduction of a DMD for dementia. These costs were mainly due to hospital admissions, given that currently available drugs have a very low price.

The characteristics of the two populations were similar in terms of prevalence of dementia and sex, in the latter case in line with previous studies (26-29). However, we noted an important difference in the real expenditures coming from the two databases; specifically, they were higher for all items in the multi-regional one.

One explanation could be related to the possible discrepancy in data collection and extraction from the two databases, which may result in difference in patients' characteristics, such as more severe forms of dementia in the ARNO Observatory than in Caserta LHU where most patients are identified by general practitioners' medical records rather than through hospitalization records. Moreover, difference in average cost per patient could be related to variability in patient management between northern regions of Italy (the most represented in ARNO database) and other regions.

Although comparable by sample type and selection criteria, the estimated difference in disease expenditures from the two databases indicates that the method of generating costs could be linked to variability in health management in LHUs. A comparison of regional real-world data should be further investigated to provide new perspectives on how a medication or interventions could impact patient outcomes, as well as reduce expenditures in other care settings.

However, we do not consider this a limitation of our method, as we propose a procedure adaptable for different settings (see **figure 3**).

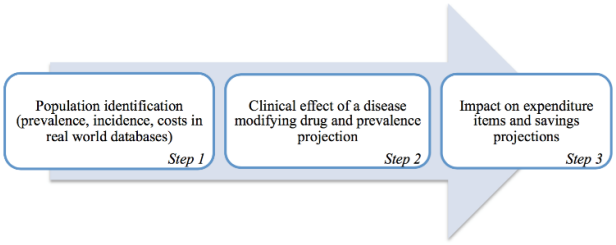
We hypothesized that a drug would delay the onset of dementia by five years, reducing the incidence by 20% and 40% in two scenarios; however, it is possible that future DMDs will have a different epidemiological impact. Further, the savings we projected could be useful to cover the costs of the DMD partially or totally, which we expect would have a critical impact on pharmaceutical expenditures.

Figure 3. Flow-chart describing method steps for making future projections about the impact of the drug.

Step 1- Population identification; population could refer to a subgroup of patients defined by symptoms or seriousness of the disease or to participants with risk factors.

Step 2- Definition of the clinical effect of the new disease-modifying drug; this could be reported in pivotal clinical trials or be a desirable hypothetic effect. Curves of prevalence will be created with and without the drug introduction.

Step 3- Impact of the introduction of the disease-modifying drug on expenditure items (e.g., hospital admission, medical examinations, pharmaceutical) and savings predictions based on prevalence projections and costs from real-world databases.



However, the actual number and type of patients eligible for such treatment is not known: if we hypothesize to treat all patients with mild cognitive impairment (MCI) at high risk of dementia, considering a prevalence of 21% in aged ≥ 65 years and a 1 year-conversion rate to dementia of 4% as previously reported in an Italian multicentre population-based cohort study, more than 1,100 subjects of the Caserta population and almost 14,800 of the ARNO population would be eligible (30). Therefore, the 5-years estimated savings would enable to pay for the new DMD up to an annual cost per patient ranging between 740 € and 1,470 € for the Caserta case study and 1,300 € and 2,600 € for the ARNO case study.

However, we suggest that our projections may be useful for decision-making as they can be adapted based on the populations eligible to innovative treatment. Advantages of using real-world data include the sample width, the ability to perform long-term follow-up studies, and to provide information about "real" practice and cost.

However, several limitations should also be considered (22). First, given that this study was conducted on claims databases, an underestimation of the number of patients is possible. In particular, patients' identification through anti-dementia drug prescriptions could represent a potential risk of under-estimation of the disease, since not all affected patients are treated.

Second, some expenditure items may not have been collected (e.g., costs charged to citizens), which are expected to be a minimal component of the overall costs of patients with dementia. Third, to simplify the analysis, we considered all types of dementia without distinction between AD and other types, because it is often difficult to make a differential diagnosis using the study data sources; however, distinct forms of dementia could be managed differently and have variable costs. Lastly, it is difficult to generalize the results to countries other than Italy, but it is possible to apply the method in presence of similar sources of real-world data.

Conclusions

This study forecasts the future dementia prevalence and cost based on real-world data. Moreover, our results show how the impact of a hypothetic DMD for patients with dementia could be managed. This model is also useful for projections for other diseases, and it can support and guide decisions related to pharmaceutical governance.

Long-term data processing will allow rational planning of expenditures, ensuring access to innovative medicines and promoting the use of cost-effective drugs.

Impact statement

A rational planning of healthcare expenditures is required in order to guarantee access to highly innovative therapies and National Health Systems sustainability.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Garrison L, Towse A. The drug budget silo mentality in Europe: an overview. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. Jul-Aug 2003;6 Suppl 1:S1-9.
2. Drummond M, Jonsson B. Moving beyond the drug budget silo mentality in Europe. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. Jul-Aug 2003;6 Suppl 1:S74-77.
3. Navarria A, Drago V, Gozzo L, et al. Do the current performance-based schemes in Italy really work? "Success fee": a novel measure for cost-containment of drug expenditure. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. Jan 2015;18(1):131-136.
4. Ruthirakuhan M, Herrmann N, Suridjan I, Abraham EH, Farber I, Lanctot KL. Beyond immunotherapy: new approaches for disease modifying treatments for early Alzheimer's disease. Expert opinion on pharmacotherapy. Dec 2016;17(18):2417-2429.
5. Craxi L, Sacchini D, Refolo P, et al. Prioritization of high-cost new drugs for HCV: making sustainability ethical. European review for medical and pharmacological sciences. 2016;20(6):1044-1051.
6. Obach D, Yazdanpanah Y, Esmat G, et al. How to optimize hepatitis C virus treatment impact on life years saved in resource-constrained countries. Hepatology. Jul 2015;62(1):31-39.
7. Reau NS, Jensen DM. Sticker shock and the price of new therapies for hepatitis C: is it worth it? Hepatology. Apr 2014;59(4):1246-1249.
8. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet. Neurology. Apr 2016;15(5):455-532.
9. Wimo A, Guerchet M, Ali GC, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's & dementia : the journal of the Alzheimer's Association. Jan 2017;13(1):1-7.
10. Colucci L, Bosco M, Fasanaro AM, Gaeta GL, Ricci G, Amenta F. Alzheimer's disease costs: what we know and what we should take into account. Journal of Alzheimer's disease : JAD. 2014;42(4):1311-1324.
11. Cummings J, Feldman HH, Scheltens P. The "rights" of precision drug development for Alzheimer's disease. Alzheimer's research & therapy. Aug 31 2019;11(1):76.
12. Cummings J. Lessons Learned from Alzheimer Disease: Clinical Trials with Negative Outcomes. Clinical and translational science. Mar 2018;11(2):147-152.
13. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. Alzheimer's & dementia. 2019;5:272-293.
14. Caraci F, Iulita MF, Pentz R, et al. Searching for new pharmacological targets for the treatment of Alzheimer's disease in Down syndrome. European journal of pharmacology. Dec 15 2017;817:7-19.
15. Hampel H, Vergallo A, Aguilar LF, et al. Precision pharmacology for Alzheimer's disease. Pharmacological research. Apr 2018;130:331-365.
16. Egan MF, Kost J, Tariot PN, et al. Randomized Trial of Verubecestat for Mild-to-Moderate Alzheimer's Disease. The New England journal of medicine. May 3 2018;378(18):1691-1703.
17. Honig LS, Vellas B, Woodward M, et al. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. The New England journal of medicine. Jan 25 2018;378(4):321-330.
18. Loureiro JC, Pais MV, Stella F, et al. Passive antiamyloid immunotherapy for Alzheimer's disease. Current opinion in psychiatry. Jan 31 2020.
19. Schneider L. A resurrection of aducanumab for Alzheimer's disease. Lancet Neurol. 2020 Feb;19(2):111-112. doi: 10.1016/S1474-4422(19)30480-6. Epub 2019 Dec 4. PMID: 31978357
20. Association As. Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars. 2015. https://http://www.alz.org/documents_custom/trajectory.pdf. Accessed 20 Sept 2017.
21. Anziani OA. Il profilo della salute della popolazione over 65 anni. Rapporto 2018. https://http://www.cineca.it/sites/default/files/Rapporto-Arno-Anziani_DEF.pdf. Accessed 20 May 2018.
22. Trifiro G, Gini R, Barone-Adesi F, et al. The Role of European Healthcare Databases for Post-Marketing Drug Effectiveness, Safety and Value Evaluation: Where Does Italy Stand? Drug safety. Mar 2019;42(3):347-363.
23. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S4-9.
24. ISTAT. Il futuro demografico del paese. Previsioni regionali della popolazione residente al 2065. May 3 2018. https://http://www.istat.it/it/files/2018/05/previsioni_demografiche.pdf. Accessed May 2018.
25. WHO. WHO 2015. The epidemiology and impact of dementia current state and future trends. http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf. Accessed February 2017
26. Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease - the gateway to precision medicine. Nat Rev Neurol. 2018 Aug;14(8):457-469. doi: 10.1038/s41582-018-0032-9. PMID: 29985474.
27. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020 Aug 22;396(10250):565-582. doi: 10.1016/S0140-6736(20)31561-0. Erratum in: Lancet. 2020 Sep 5;396(10252):668. PMID: 32828189; PMCID: PMC7440877.
28. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: A call to ac-

tion. Alzheimers Dement. 2018 Sep;14(9):1171-1183. doi: 10.1016/j.jalz.2018.04.008. Epub 2018 Jun 12. PMID: 29907423; PMCID: PMC6400070.
29. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. Front Neuroendocrinol. 2014 Aug;35(3):385-403. doi: 10.1016/j.yfrne.2014.01.002. Epub 2014 Jan 13. PMID: 24434111; PMCID: PMC4087048.
30. Limongi F, Siviero P, Noale M, et al. Prevalence and conversion to dementia of Mild Cognitive Impairment in an elderly Italian population. Aging Clin Exp Res. 2017 Jun;29(3):361-370. doi: 10.1007/s40520-017-0748-1. Epub 2017 Mar 28. PMID: 28353219.