

ORIGINAL ARTICLE

Consumption trends for specific drugs used to treat dementia in the region of Madrid (Spain) from 2002 to 2012^{☆,☆☆}



M.C. de Hoyos-Alonso^{a,*}, E. Tapias-Merino^b, C.M. Meseguer Barros^c,
M. Sánchez-Martínez^d, A. Otero^d

^a Servicio Madrileño de Salud, Centro de Salud Pedro Laín Entralgo, Alcorcón, Madrid, Spain

^b Servicio Madrileño de Salud, Centro de Salud Comillas, Área Centro, Madrid, Spain

^c Servicio Madrileño de Salud, Subdirección General de Compras de Farmacia y Productos Sanitarios, Consejería de Sanidad, Comunidad de Madrid, Spain

^d Departamento de Medicina Preventiva y Salud Pública, Universidad Autónoma de Madrid, Madrid, Spain

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Abstract

Introduction: Analysing drug consumption in large population groups lets us observe consumption trends and compare them between different settings.

Objective: To analyse the time trends for consumption and costs of specific drugs used to treat dementia in the region of Madrid (Spain) and compare trends by sex and age cohort.

Methods: Descriptive study of cholinesterase inhibitors (N06DA) and memantine (N06DX01) dispensed in Madrid between 2002 and 2012 and covered by the Spain's national health system. Consumption was calculated by analysing changes in DDD (defined daily doses) to find total and yearly increases. The cost was estimated based on DDD price. To compare consumption rates by age and sex, we calculated DDD per 100 inhabitants/day.

Results: Between 2002 and 2012, consumption of drugs used to treat dementia increased six-fold. During this period, cholinesterase inhibitors accounted for 76.70% of the drugs consumed and memantine, 23.30%. The estimated cost rose by a factor of 5.7 over 11 years (or by a factor of 4 taking into account the use of generic drugs).

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* Corresponding author.

E-mail address: mcanto.hoyos@salud.madrid.org (M.C. de Hoyos-Alonso).

PALABRAS CLAVE

Demencia;
Anticolinesterásicos;
Memantina;
Farmacoepidemiología;
Uso de fármacos;
Coste

In 2012, 2.42% of the patients aged 65 or over consumed cholinesterase inhibitors (women 2.82%, men 1.83%) and 0.90% consumed memantine (women 1.10%, men 0.61%). Consumption increased in age cohorts up to 86 to 90 (5.84% for cholinesterase inhibitors and 2.33% for memantine) and declined thereafter.

Conclusions: Consumption of cholinesterase inhibitors and memantine gradually increased, but consumption in 2012 did not reach levels equivalent to dementia prevalence figures. Pharmaceutical expenditure restraint measures may temporarily slow the cost increase temporarily but if the same trend of consumption persists, costs will rise.

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Evolución del consumo de fármacos específicos para la demencia en la comunidad autónoma de Madrid durante el periodo 2002-2012

Resumen

Introducción: El análisis del consumo de fármacos en grandes grupos poblacionales permite ver tendencias de consumo y comparar diferentes ámbitos.

Objetivo: Analizar la tendencia temporal de consumo y costes de fármacos específicos para la demencia en la comunidad autónoma de Madrid (CAM) y comparar por grupos de edad y sexo.

Métodos: Estudio descriptivo, seleccionando anticolinesterásicos (N06DA) y memantina (N06DX01) dispensados en la CAM del 2002 al 2012 con cargo al Sistema Nacional de Salud. El consumo se calculó analizando la evolución de las dosis diarias definidas (DDD), con incrementos totales y anuales. El coste se estimó por precio de DDD. Para comparar el consumo por edad y sexo, se calcularon las DDD por 100 habitantes-día.

Resultados: Del 2002 al 2012 se multiplicó por 6 el consumo de fármacos para la demencia. El 76,70% de los fármacos consumidos en este periodo fueron anticolinesterásicos y el 23,30% memantina. La evolución del coste estimado se multiplicó por 5,7 en 11 años (por 4 considerando utilización de fármacos genéricos).

En 2012, el 2,42% de los mayores de 65 años consumió anticolinesterásicos (2,82% mujeres, 1,83% hombres) y el 0,90% memantina (1,10% mujeres, 0,61% hombres). El consumo aumentó hasta los 86-90 años (5,84% en anticolinesterásicos; 2,33% en memantina), disminuyendo posteriormente.

Conclusiones: El consumo de anticolinesterásicos y memantina aumentó progresivamente, sin alcanzar en 2012 cifras equivalentes a la prevalencia poblacional de demencia. Las medidas de contención de gasto farmacéutico pueden frenar el aumento del coste, aunque este volverá a crecer si persiste la misma tendencia temporal de consumo.

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Introduction

Dementia prevalence is approximately 6.4% in patients older than 65 years, and it increases with age, from 0.8% in patients aged 65 to 69, 10% in patients older than 70 years, and 25% to 54% in the group of patients aged 90 or older.¹⁻³ Alzheimer disease (AD) is the most frequent type of dementia and the main cause of disability among elderly patients. It places a significant burden on caregivers and generates social costs which increase as the disease progresses.^{4,5} Researchers estimate that some 600,000 people have dementia and 400,000 people have AD in Spain.² According to the ECO study,⁶ the average monthly cost per patient is 1425 euro. Almost 88% of the cost of illness corresponds to informal care, which is borne by the patient's own family. This percentage is higher than the European average, which is about 56%.⁷ Healthcare costs include pharmacological treatments, as well as diagnostic tests, office visits, hospitalisation, and institutionalisation.

Since there is no curative treatment for dementia, treatment approach is focused on treating cognitive impairment symptoms, as well as behavioural and psychological symptoms. Its target is also to prevent complications and functional disability, and manage comorbidities. Acetylcholinesterase inhibitors (AChEI) are indicated as specific treatment for mild to moderate AD.⁸⁻¹⁰ These include donepezil (marketed in Spain since 1998), rivastigmine (since 2000), and galantamine (since 2001). Memantine, a non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist, was authorised in 2003 for use in mild to severe AD.⁸⁻¹⁰ AChEI and memantine can be administered in combination, but studies yield contradictory results.^{8,10-12} In addition to AD, both drugs can be used to treat vascular dementia, and diseases with Lewy bodies (dementia with Lewy bodies and Parkinson's disease), but they are not indicated to treat frontotemporal dementia.^{8,9}

Their effects are modest and temporary and not all patients respond to treatment.¹³ However, according to

clinical practice guidelines,⁸ treatment with these drugs should be started as soon as AD is diagnosed, considering that previous identification of patients who will respond to treatment is not possible.¹⁴ Spanish regulations establish that every first or maintenance prescription should be authorised by the medical inspection service after a neurologist, gerontologist, or psychiatrist issues the initial report confirming the disease and the treatment indication. There is no consensus on when to suspend treatment with these drugs,^{15–17} but some Spanish regions have established rules regarding use and continuity.¹⁸ The cost-benefit ratio of these treatments is currently being debated. Although several studies indicate that starting drug treatments, especially in mild-moderate stages, can delay disease progression, institutionalisation, and associated costs, results remain uncertain.^{19–21} Therefore, they should be interpreted considering those differences between public health systems that would influence cost distribution.¹⁴

Consumption of AChEI and memantine has increased progressively since they were introduced to the market,^{22–26} and they are listed among the 35 most expensive active ingredients for the Spanish Health System.²⁷ This increase, which may be partly due to the increased prevalence of dementia caused by population ageing, also depends on the higher percentage of dementia patients treated since these drugs began to be indicated habitually. Thus, a study performed in a primary care setting simultaneously with our own showed that the percentage of dementia patients treated with these drugs had increased from 23% in 2002 to 41% in 2011.²⁸

Regarding pharmacoepidemiological studies, quantitative studies of the consumption of drugs using prescription invoicing data and/or sales turnover figures show the actual consumption trends of the drugs in large populations. They also provide an overview of the actual costs of the disease and permit comparisons between different settings or populations.²⁹

The aim of our study is to analyse time trends of consumption and costs of cholinesterase inhibitors (AChEI) and memantine (specific drugs used to treat dementia) in the region of Madrid between 2002 and 2012. Consumption profiles by age and sex were also compared to one another.

Material and methods

A population-based descriptive study of the consumption of specific drugs used to treat dementia was performed between 1 January 2002 and 31 December 2012 in the region of Madrid. Our data source was the system for information and analysis on prescriptions and pharmaceutical services of the region of Madrid (Farm@drid), which serves as the database of official medical prescriptions dispensed by pharmacies in the region of Madrid and invoiced to the Spanish Health System.

We selected cholinesterase inhibitors belonging to the chemical subgroup N06DA and identified the active ingredients donepezil (N06DA02), rivastigmine (N06DA03), and galantamine (N06DA04). We selected memantine (N06DX01) from the N06DX subgroup but excluded ginkgo biloba (N06DX02) as it is not used specifically to treat dementia.

As variables associated with treatment, we analysed year of consumption, sex, and age group (in 9 categories: 51–55 years, 56–60 years, 61–65 years, 66–70 years, 71–75 years, 76–80 years, 81–85 years, 86–90 years, and older than 90 years).

To analyse drug consumption, we used the parameters 'defined daily dose' (DDD) and 'daily dose per inhabitant' (DDI) for each active ingredient.

DDD corresponds to the daily maintenance dose for a drug used for its main indication in adults and given by a specific route of administration.³⁰ We adhered to the DDDs defined by the World Health Organization: donepezil 7.5 mg, rivastigmine 9 mg (9.5 mg transdermally), galantamine 16 mg, and memantine 20 mg.³¹

We assessed trends in drug consumption during the study period by calculating the total number of DDD based on the total number of packages dispensed every year. To do this, we converted commercial formats in milligrams or grams to DDD. We analysed consumption trends for the DDD of each active ingredient and therapeutic chemical subgroup, the ratio between the end and the beginning of the period, and the yearly and total increase in DDD. To calculate the percentages of total increase for 2012 compared to the beginning of the study, we used the formula $\Delta_{2012-2002} = ([DDD_{2012} - DDD_{2002}] / DDD_{2002}) \times 100$ for AChEI, and $\Delta_{2012-2003} = ([DDD_{2012} - DDD_{2003}] / DDD_{2003}) \times 100$ for memantine (marketed since 2003).²⁹

Annual cost increases for each active ingredient were estimated by multiplying the number of DDD consumed each year by their sales price, calculated according to figures from the Nomenclátor Digitalis drug database.³² In our cost estimation, we considered commercial formats of maintenance doses exclusively. The price per milligram for each package format was obtained to later calculate the mean price per year of the different formats. Calculated DDD prices were between 4.39 and 4.04 euro for donepezil, 3.58 and 3.24 euro for rivastigmine, 3.84 and 3.53 euro for galantamine, and 3.8 euro for memantine. We performed an additional estimation after generic forms of donepezil became available in 2011 (DDD at 1.75 euro) and rivastigmine solution in 2012 (DDD at 2.65 euro). This estimation assumed that only generic drugs were used.

Daily dose per inhabitant refers to the mean number of inhabitants receiving daily treatment with a given drug.³⁰ DDI corresponds to the DDD typically calculated for 1000 inhabitants. In our study, we decided to use a DDI per 100 inhabitants to draw comparisons with dementia prevalence in the population, and with other prevalence studies on consumption of these drugs.^{23,28}

We used DDI to analyse consumption by age group and sex in 2012. We calculated DDI for both sexes and each age group, and for patients older than 60, 65, or 70 years, using the following formula: $number\ of\ DDI_{2012} = (number\ of\ DDD_{2012} / population_{2012}) \times (1/365) \times 100$. Only DDDs consumed by patients older than 50 years were considered. Populations used in calculating this rate were obtained from Farm@drid, according to health card holder records. Data were limited to patients older than 50 years since they constitute the reference population for these drugs. We calculated confidence intervals for both sexes and each age group.

Table 1 Changes in consumption of specific drugs to treat dementia (cholinesterase inhibitors and memantine) in the region of Madrid between 2002 and 2012, in defined daily doses.

Year	Cholinesterase inhibitors			Memantine			All anti-dementia drugs	
	DDD	Δ (%) ^a	%TDD ^b	DDD	Δ (%) ^a	%TDD ^b	DDD	Δ (%) ^a
2002	2 037 210		100	NM			2 037 210	
2003	2 656 311	30.39	90.29	285 712		9.71	2 942 024	44.41
2004	3 331 106	25.40	82.87	688 464	140.96	17.13	4 019 571	36.63
2005	3 877 923	16.42	80.17	959 370	39.35	19.83	4 837 294	20.34
2006	4 449 169	14.73	77.36	1 302 078	35.72	22.64	5 751 247	18.89
2007	5 274 603	18.55	76.09	1 657 862	27.32	23.91	6 932 465	20.54
2008	6 170 972	16.99	75.97	1 952 172	17.75	24.03	8 123 145	17.18
2009	7 041 935	14.11	75.42	2 295 350	17.58	24.58	9 337 285	14.95
2010	7 766 068	10.28	74.80	2 616 482	13.99	25.20	10 382 550	11.19
2011	8 497 908	9.42	73.31	3 094 222	18.26	26.69	11 592 130	11.65
2012	8 969 820	5.55	72.54	3 396 356	9.76	27.46	12 366 176	6.68
Total 2002-2012	60 073 025	340.30	76.70	18 248 068	1088.73	23.30	78 321 093	507.02
Beginning/end ratio ^c	4.40			11.89			6.07	

DDD, defined daily dose; NM, not on the market.

^a Δ (%), increase in the annual percentage with regard to previous year. Total reflects cumulative increase for 2012 with regard to the initial period (2002 for cholinesterase inhibitor-TDD, and 2003 for memantine).

^b %TDD, percentage of the total for anti-dementia drugs (cholinesterase inhibitor + memantine).

^c 2012/2002 ratio for cholinesterase inhibitors-TDD; 2012/2003 ratio in the case of memantine.

Data extracted from the Farm@drid digital record did not include variables that could identify patients; therefore, our study preserves data confidentiality.

Data were analysed with the SPSS statistical software, version 19.0; Excel® version 12.3.0 (110427); and Epidat 3.0.

Results

Consumption of the specific drugs used to treat dementia, cholinesterase inhibitors (AChEI) and memantine, increased by a factor of 6 between 2002 and 2012 in the region of Madrid. This meant a total increase in DDD of 507%. In this period, 76.7% of the drugs consumed to treat dementia were AChEI, with 23.3% corresponding to memantine (Table 1).

Half of the AChEI prescriptions filled during the study period were for donepezil. Galantamine consumption increased progressively up to 2008, when platformed off. Beginning in 2009, rivastigmine consumption increased until it made up 30% of all AChEI prescriptions in 2012. The increasing trend in consumption was more homogeneous for donepezil and memantine throughout the 11-year study period (Fig. 1).

In 2012, 12.3 million DDDs of specific drugs used to treat dementia were consumed, 10.3 million more than in year 2002 (Table 1). Estimated costs increased by a factor of 5.7, from 8.2 million euro in 2002 to 47.6 million in 2012. If we consider prices for generic drugs only, the final cost amounts to 34 million, 4 times higher than at the beginning of the study period. Annual cost savings due to the use of generic drugs amounted to 12 million in 2011, and 13 million in 2013 (Fig. 2). Total costs during the 11-year period would be 300 million euro for brand-name drugs only or 275 million euro considering the generics that became available in 2011 and 2012.

After adjusting 2012 consumption data by age and sex, 2.42% of patients older than 65 years (95% CI, 2.39-2.45) consumed AChEI, and 0.90% took memantine (95% CI, 0.88-0.92). Consumption increased for both drug groups in patients between 65 and 90 years old; 5.84% consumed AChEI (95% CI, 5.68-6.00), and 2.33% took memantine (95% CI, 2.23-2.43). Consumption decreased in patients older than 90 (Table 2 and Fig. 3).

Consumption was higher in women than in men. In the group of patients older than 65 years, 2.82% of the women (95% CI, 2.78-2.87) consumed AChEI versus 1.83% of the men (95% CI, 1.79-1.87). Memantine was consumed by 1.10% of the women (95% CI, 1.07-1.12) versus 0.61% of the men (95% CI, 0.59-0.64). We found significant differences between sexes in patients older than 65 years regarding consumption of AChEI, and of memantine in patients older than 71 years. Increased consumption with age and

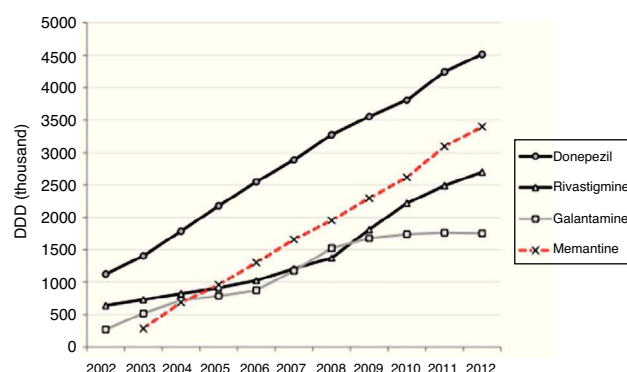


Figure 1 Changes in consumption of specific anti-dementia drugs (cholinesterase inhibitors and memantine) in the region of Madrid between 2002 and 2012, given as defined daily doses. DDD, defined daily dose.

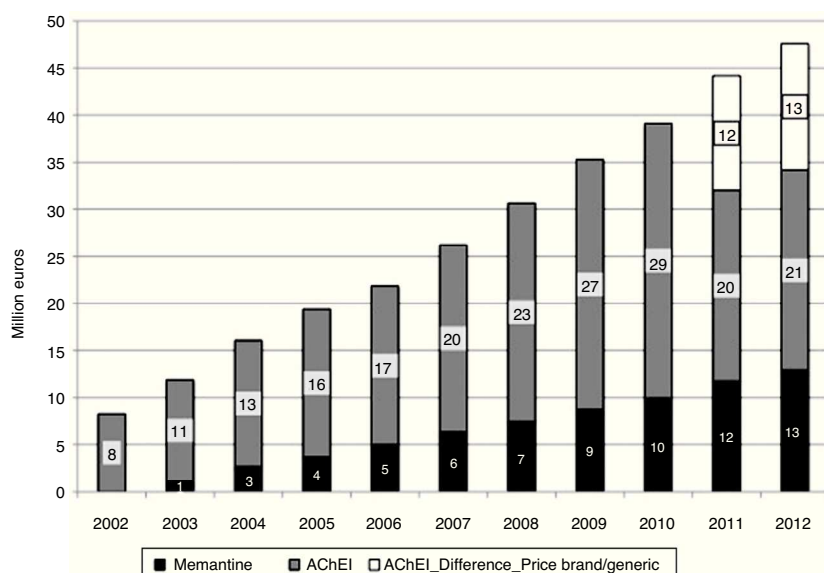


Figure 2 Estimation of cost changes for specific drugs used to treat dementia (cholinesterase inhibitors and memantine) in the region of Madrid between 2002 and 2012. AChEI_Difference_Price brand/generic, price difference between brand name and generic drug.

decreased consumption in patients older than 90 years was observed both in men and women (Table 3, Figs. 3 and 4).

The most widely used active ingredient in 2012 in both men and women of all ages was donepezil; the least used was galantamine. Rivastigmine was the drug with the least pronounced sex difference; differences in use by sex were only identified in patients aged 76 to 90.

Discussion

Overall consumption of specific drugs used to treat dementia in the region of Madrid increased by a mean of 50% annually between 2002 and 2012. Mean annual increase during the first 6 years (2002-2007) was 48% versus 15% for the last 6 years (2007-2012). Compared to similar periods, the consumption increase in the region of Madrid was higher than

that reflected by other studies performed in Spain using the same analysis methods. For example, DDD consumption around Madrid increased by 25% annually from 2004 to 2008, while in Castilla-La Mancha this increase reached 11.5% (in a study which included ginkgo biloba²³). Likewise, the annual increase between 2006 and 2011 was 20% in the region of Madrid, versus 12% in the Basque country during the same period, as reported by a study in patients older than 60.²⁴

Donepezil was the most widely used active ingredient in the region of Madrid throughout the study period, a tendency that was also observed in other Spanish studies^{22,23,28,33,34} as well as in international studies.^{26,35,36} This trend has been linked to the drug's ease of use and low rate of adverse effects.¹⁴ However, the literature shows considerable variability in the proportions and consumption trends for these drugs.^{23,24,34,37}

The standstill in galantamine consumption in the region of Madrid coincides with the increase in the use

Table 2 Age distribution of consumption of cholinesterase inhibitors and memantine in the region of Madrid in 2012.

Age group	Population	DDD-AChEI	DDD-memantine	DDD-AChEI	DDD-memantine
51-55 years	400 388	15 368	6412	0.01	<0.01
56-60 years	330 706	60 865	32 648	0.05	0.03
61-65 years	305 295	158 585	66 324	0.14	0.06
66-70 years	258 342	362 895	145 866	0.38	0.15
71-75 years	203 281	827 404	306 450	1.12	.41
76-80 years	192 145	2 026 917	703 456	2.89	1.00
81-85 years	142 660	2 697 101	970 434	5.18	1.86
86-90 years	81 317	1 733 167	692 378	5.84	2.33
>90 years	40 147	450 817	194 378	3.08	1.33
Total >70 years	659 550	7 735 406	2 867 096	3.13	1.16
Total >65 years	917 892	8 098 301	3 012 962	2.42	0.90
Total >60 years	1 223 188	8 256 885	3 079 286	1.85	0.69

DDD, defined daily dose; DDI, defined dose per 100 inhabitants per day; AChEI, cholinesterase inhibitors.

Table 3 Age and sex distribution of consumption of specific anti-dementia drugs (cholinesterase inhibitors and memantine) in the region of Madrid in 2012.

Age group	DDI donepezil		DDI rivastigmine		DDI galantamine		DDI AChEI		DDI memantine	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
51-55 years	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	0.01	<0.01	<0.01
56-60 years	0.02	0.03	0.01	0.02	0.01	0.01	0.05	0.05	0.03	0.03
61-65 years	0.07	0.07	0.05	0.04	0.03	0.03	0.14	0.14	0.06	0.06
66-70 years	0.16 ^a	0.23 ^a	0.12	0.13	0.07	0.06	0.34 ^a	0.42 ^a	0.13	0.18
71-75 years	0.44 ^a	0.66 ^a	0.32	0.38	0.18 ^a	0.20 ^a	0.94 ^a	1.25 ^a	0.31 ^a	0.49 ^a
76-80 years	1.19 ^a	1.65 ^a	0.81 ^a	0.94 ^a	0.51 ^a	0.57 ^a	2.51 ^a	3.16 ^a	0.79 ^a	1.15 ^a
81-85 years	1.95 ^a	2.96 ^a	1.30 ^a	1.68 ^a	0.91 ^a	1.14 ^a	4.15 ^a	5.78 ^a	1.40 ^a	2.13 ^a
86-90 years	2.31 ^a	3.35 ^a	1.28 ^a	1.74 ^a	1.04 ^a	1.30 ^a	4.64 ^a	6.38 ^a	1.63 ^a	2.65 ^a
>90 years	1.38 ^a	1.73 ^a	0.76	0.87	0.46 ^a	0.63 ^a	2.61 ^a	3.22 ^a	0.89 ^a	1.46 ^a
Total >70 years	1.21 ^a	1.90 ^a	0.78 ^a	1.05 ^a	0.53 ^a	0.70 ^a	2.52 ^a	3.65 ^a	0.84 ^a	1.41 ^a
Total >65 years	0.87 ^a	1.47 ^a	0.57 ^a	0.81 ^a	0.38 ^a	0.53 ^a	1.83 ^a	2.82 ^a	0.61 ^a	1.10 ^a
Total >60 years	0.65 ^a	1.15 ^a	0.43 ^a	0.63 ^a	0.29 ^a	0.42 ^a	1.37 ^a	2.20 ^a	0.4 ^a	0.86 ^a

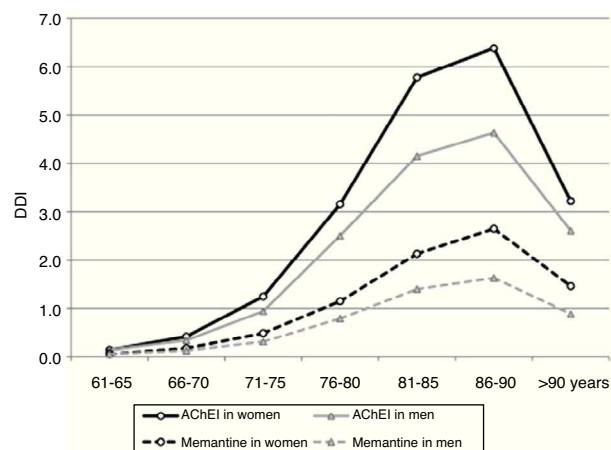
DDI, defined dose per 100 inhabitants per day.

^a Significant differences ($P < .05$) between men and women in this section.

of rivastigmine. Increased use of rivastigmine during the past few years was also observed by other consumption studies^{24,26} and may be explained by the marketing of rivastigmine transdermal patches in 2008.

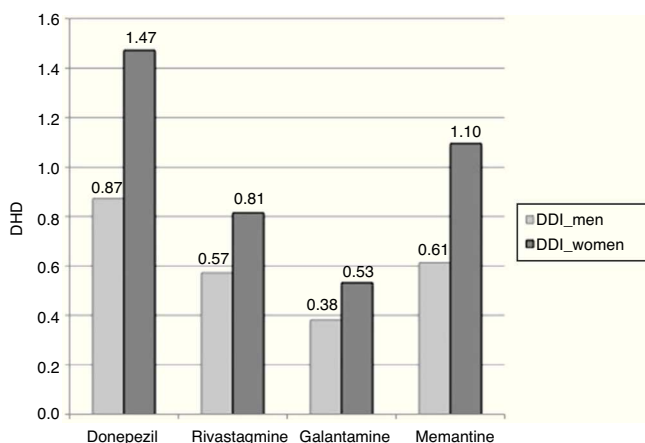
The indication of memantine for moderate to advanced dementia suggests that the prescription profile might show a use curve tending more towards advanced ages than is the case for AChEI. However, as in other studies of overall consumption,²⁸ the memantine consumption profile by age group was similar to that of AChEI in 2012. This might indicate that memantine could be used in the same progression stages of dementia, whether in combination treatment or as sole treatment in cases of moderate dementia with a contraindication of AChEI. Testing this hypothesis would require a different study design.

In the last year of our study period (2012), AChEI consumption per inhabitant and day among patients older than 65 years was 2.82%, versus 1.10% in the case of memantine.

**Figure 3** Distribution of cholinesterase inhibitor and memantine consumption in the region of Madrid in 2012, by age group and sex. DDI, defined dose per 100 inhabitants per day; AChEI, cholinesterase inhibitor.

Considering that combined treatment is used some patients, we have to assume that less than 3.92% of patients older than 65 consume specific anti-dementia drugs (consumption prevalence). Despite progressive increases in consumption, this percentage is lower than might be expected if we compare it to prevalences of AD (4.6%) or of dementia (5.8-7.6%)^{38,39} in patients older than 65, as reported by other population studies conducted in nearby settings. This difference is more pronounced if we consider only those patients older than 70, since consumption of AChEI (3.13%) and memantine (1.16%) indicate that 4.29% of all patients older than 70 consume these drugs. Meanwhile, the prevalence of dementia in that age group is much higher.²

Women older than 65 consume more AChEI and memantine than men, which may be explained by the higher prevalence of dementia among women. Likewise, consumption increases with age, since prevalence of dementia

**Figure 4** Consumption of specific drugs used to treat dementia (cholinesterase inhibitors and memantine) in patients older than 65 years in the region of Madrid in 2012. Sex distribution of dose per inhabitant and day. DDI, defined dose per 100 inhabitants per day.

displays the same tendency. However, consumption tapers off at more advanced ages, a trend that has also been observed in other studies in the general population^{28,40} and in institutionalised patients.^{41,42} The reason may be that dementia prevalence no longer increases exponentially in patients older than 90 years; the tendency may also result from decisions to limit treatment (due to comorbidities, potential toxicity, very advanced dementia), and therefore withdrawal and/or reduced use of these drugs in this age group.^{3,17}

Consumption of different active ingredients varies according to sex and age, which seems to indicate a sex-related prescription profile, as also observed in other studies.^{28,40} Confirming sex differences in how these drugs are prescribed will require further studies of consumption among patients with dementia to determine whether differences persist after adjusting by dementia subtype and stage of progression. Either one of these circumstances may determine which of the active ingredients is the most appropriate.

Costs of AChEI and memantine have been increasing since they were first marketed due to the progressive increase in consumption, considering that prices have remained relatively stable. These drugs' share of the pharmaceutical expenditure on prescriptions dispensed in the region of Madrid⁴³ also increased from 1.31% in 2003 to 3.04% in 2010 according to our results. This was in line with findings from the Basque country.²⁴ In the region of Madrid, this percentage has been increasing since 2011, despite expenditure have been contained by the appearance of generic versions of these drugs. Therefore, considering a total prescription expenditure amounting to 1.057 billion⁴³ in 2012, we estimate that 4.50% would correspond to these drugs (3.23% if we consider generic drugs). In return, appropriate use of AChEI and/or memantine could help reduce the indiscriminate use of other drugs used to treat cognitive impairment and dementia (such as ginkgo biloba, piracetam, or citicoline), which have shown no benefits for controlling symptoms in patients with dementia.

This study presents some inherent limitations. Firstly, data regarding AChEI and memantine consumption refer to the total population, without mentioning patients with a confirmed diagnosis of dementia.

Since we do not have data regarding combined treatment (AChEI with memantine), only an estimated prevalence of patients treated with specific anti-dementia drugs (AChEI and/or memantine) in the region of Madrid could be obtained, unlike in other studies.

The study does not include prescriptions given by private practices or within the framework of special healthcare programmes such as the general Spanish civil service mutual insurance company, general mutual insurance scheme for the judiciary, and the social insurance institute of the armed forces. These groups make up such a small percentage of the population living in the region of Madrid (0.87%) and covered by the Spanish Health System that they do not impact the validity of our data whether in terms of the number of prescriptions or in population figures.⁴⁴

Using DDD in our study involves the limitations inherent to this kind of indicator, considering that it is a technical unit of measurement that does not necessarily reflect the true prescribed dose.^{30,31} However, since these drugs are

only indicated for dementia and are used according to an established protocol, data reflect consumption quite reliably.

Yearly cost estimations were performed assuming similar consumption of all available commercial formats (capsules, solution, and patches). However, there is probably a tendency towards using one type more than others. The very low variation in the price of DDDs for each active ingredient during the 11-year period, before generic drugs became available, justifies our method.

Data regarding AChEI and memantine dispensed by pharmacies upon presentation of official prescriptions do not fully ensure treatment compliance among patients. However, since these drugs must be prescribed by a specialist and authorised by the medical inspection service, the statistics provide information about consumption that is quite reliable. This fact, in addition to having the consumption data for all drugs covered by the Spanish Health System and finding coherent results, lets us state that data accurately reflect consumption tendencies for specific drugs used to treat dementia in the region of Madrid.

The appearance of generic formats of these drugs beginning in 2011, approval of different regulations to rationalise drug use and thus control pharmaceutical expenditure (for example, prescribing active ingredients rather than brand names under Legislative Royal Decree 9/2011⁴⁵), and the changes applied to the reference price system in 2013 are all measures able to temporally reduce costs and slow the progressive increase in expenditure.

However, an increase in the number of dementia patients due to population ageing is to be expected, together with gradual growth in the percentage of dementia patients receiving treatment.²⁸ Both situations lead us to believe that the trend found by our study, i.e. increasing consumption of cholinesterase inhibitors and memantine, will continue. This being the case, it is also foreseeable that expenditure on these drugs will also increase in the next few years. It is therefore important to continue performing cost-benefit studies analysing the role of AChEI and memantine in the control of symptoms in different dementia stages. These studies should assess how these drugs contribute to reducing use of neuroleptics and to delaying disease progression and institutionalisation.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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References

1. Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, 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.
2. De Pedro-Cuesta J, Virués-Ortega J, Vega S, Seijo-Martínez M, Saz P, Rodríguez F, et al. Prevalence of dementia and major dementia subtypes in Spanish populations: a reanalysis of dementia prevalence surveys, 1990–2008. *BMC Neurol*. 2009;9:55.
3. Carrillo-Alcalá ME, Bermejo-Pareja F. Demencia en nonagenarios. Revisión sistemática de estudios poblacionales con datos de España. *Rev Neurol*. 2008;47:347–54.
4. Jönsson L, Wimo A. The cost of dementia in Europe: a review of the evidence, and methodological considerations. *Pharmacoeconomics*. 2009;27:391–403.
5. López-Pousa S, Garre-Olmo J, Turon-Estrada A, Hernández F, Expósito I, Lozano-Gallego M, et al. Análisis de los costes de la enfermedad de Alzheimer en función del deterioro cognitivo y funcional. *Med Clín (Barc)*. 2004;122:767–72.
6. Coduras A, Rabasa I, Frank A, Bermejo-Pareja F, López-Pousa S, López-Arrieta J-M, et al. Prospective one-year cost-of-illness study in a cohort of patients with dementia of Alzheimer's disease type in Spain: the ECO study. *J Alzheimers Dis*. 2010;19:601–15.
7. Wimo A, Jönsson L, Gustavsson A, McDaid D, Ersek K, Georges J, et al. The economic impact of dementia in Europe in 2008—cost estimates from the Eurocode project. *Int J Geriatr Psychiatry*. 2011;26:825–32.
8. Grupo de trabajo de la Guía de Práctica Clínica sobre la atención integral a las personas con enfermedad de Alzheimer y otras demencias. Guía de Práctica Clínica sobre la atención integral a las personas con enfermedad de Alzheimer y otras demencias. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad, Política Social e Igualdad. Agencia d'informació, Avaluació i Qualitat en Salut de Catalunya; 2010. Guías de Práctica Clínica en el SNS: AIAQS Núm. 2009/07.
9. O'Brien JT, Burns A, BAP Dementia Consensus Group. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol Oxf Engl*. 2011;25:997–1019.
10. National Institute for Clinical Excellence. Technology appraisal guidance 217. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111). Available from: www.nice.org.uk/guidance/TA217 [accessed 04.10.2013].
11. Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry*. 2009;80:600–7.
12. Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366:893–903.
13. Hogan DB, Bailey P, Black S, Carswell A, Chertkow H, Clarke B, et al. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. *Can Med Assoc J*. 2008;179:1019–26.
14. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;CD005593.
15. Hort J, O'Brien JT, Gainotti G, Pirttilä T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol Off J Eur Fed Neurol Soc*. 2010;17:1236–48.
16. Coll-de-Tuero G, López-Pousa S, Vilalta-Franch J. ¿Cuándo suspender el tratamiento farmacológico específico en el Alzheimer? *Aten Prim*. 2011;43:565–7.
17. Rodríguez D, Formiga F, Fort I, Robles MJ, Barranco E, Cubi D. Tratamiento farmacológico de la demencia: cuándo, cómo y hasta cuándo. Recomendaciones del Grupo de Trabajo de Demencias de la Sociedad Catalana de Geriatria y Gerontología. *Rev Esp Geriatria Gerontol*. 2012;47:228–33.
18. Instrucció X/2011; 2011. Available from: <http://tinyurl.com/oyklkbr> [accessed 10.10.13].
19. Cappell J, Herrmann N, Cornish S, Lanctôt KL. The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease. *CNS Drugs*. 2010;24:909–27.
20. Pouryamout L, Dams J, Wasem J, Dodel R, Neumann A. Economic evaluation of treatment options in patients with Alzheimer's disease: a systematic review of cost-effectiveness analyses. *Drugs*. 2012;72:789–802.
21. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. *Health Technol Assess Winch Engl*. 2012;16:1–470.
22. Villar Fernández I, Rabaneque Hernández MJ, Armesto Gómez J, García Arilla E, Izuel Rami M. Utilización de fármacos específicos para la enfermedad de Alzheimer. *Neurología*. 2007;22:275–84.
23. Criado-Alvarez JJ, Romo Barrientos C. Variabilidad y tendencias en el uso de fármacos contra la demencia. Estimación de la prevalencia de la enfermedad de Alzheimer en Castilla-La Mancha. *Neurología*. 2010;25:234–8.
24. Villanueva G, López de Argumedo M. Diagnóstico y consumo de fármacos para la enfermedad de Alzheimer en el País Vasco. Informe de Evaluación de Tecnologías Sanitarias: No EKU 12-03. Gobierno Vasco: Departamento de Sanidad y Consumo; 2012.
25. Hoffmann F, van den Bussche H, Glaeske G, Kaduszkiewicz H. Eight-year prescription trends of memantine and cholinesterase inhibitors among persons 65 years and older in Germany. *Int Clin Psychopharmacol*. 2010;25:29–36.
26. Sakshaug S, editor. Drug Consumption in Norway 2008–2012 (Legemiddelforbruket i Norge 2008-2012). Oslo: legemiddelstatistikk; 2013, 12013:1.
27. Subgrupos ATC y principios activos de mayor consumo en el Sistema Nacional de Salud en 2010. *Inf Ter Sist Nac Salud*. 2011;35:124–8.
28. Bonis Sanz J, de Hoyos Alonso MC, Llorente García A, Gil García M, Montero Corominas D, de Abajo Iglesias F. Prevalencia de uso de fármacos para el tratamiento de la enfermedad de Alzheimer y su evolución temporal: un estudio descriptivo con la base de datos de atención primaria BIFAP. *Alzheimer Real Invest Demenc*. 2013;54:20–7.
29. Alvarez Luna F. Farmacoe epidemiología. Estudios de utilización de medicamentos. Parte I: concepto y metodología. *Seguim Farm*. 2004;23:129–36.
30. Agencia Española de Medicamentos y Productos Sanitarios-Medicamentos de uso humano. Observatorio del Uso de Medicamentos de la AEMPS. Available from: <http://www.aemps.gob.es/medicamentosUsoHumano/observatorio/home.htm> [accessed 06.10.13].
31. WHO Collaborating Centre for Drug Statistics Methodology. Complete ATC/DDD Index 2012. Available from: <http://www.whocc.no/atc-ddd-index/?code=N06D> [accessed 16.09.13].
32. Nomenclátor Digitalis. Ministerio de Sanidad, Servicios sociales e igualdad; 2011. Available from: <http://www.msssi.gob.es/profesionales/farmacia/nomenclatorDI.htm> [accessed 21.09.13].
33. Portela Romero M, Pombo Romero J, Bugarín González R, Tasende Souto M, Represa Veiga S. Utilización de los inhibidores de la acetilcolinesterasa y la memantina para el tratamiento clínico de la demencia tipo Alzheimer. *Rev Esp Salud Pública*. 2005;79:665–72.

34. Tapias Merino E, De Hoyos Alonso MC, Garrido Barral A. Atención a los pacientes con demencia en Atención Primaria de Salud. In: Libro Blanco sobre la demencia y enfermedad de Alzheimer en la Comunidad de Madrid. 1st ed. Madrid: Siglo SL; 2005. p. 27–43.
35. Mucha L, Shaohung S, Cuffel B, McRae T, Mark TL, Del Valle M. Comparison of cholinesterase inhibitor utilization patterns and associated health care costs in Alzheimer's disease. *J Manag Care Pharm JMCP*. 2008;14:451–61.
36. Truter I. Prescribing of drugs for Alzheimer's disease: a South African database analysis. *Int Psychogeriatr IPA*. 2010;22:264–9.
37. Villar-Fernández I, Bjerrum L, Feja C, Rabanaque MJ. Variability in the prescription of cholinesterase inhibitors and memantine. *Dement Geriatr Cogn Disord*. 2009;28:373–9.
38. García García FJ, Sánchez Ayala MI, Pérez Martín A, Martín Correa E, Marsal Alonso C, Rodríguez Ferrer G, et al. Prevalencia de demencia y de sus subtipos principales en sujetos mayores de 65 años: efecto de la educación y ocupación. Estudio Toledo. *Med Clin (Barc)*. 2001;116:401–7.
39. Bermejo-Pareja F, Benito-León J, Vega S, Olazarán J, de Toledo M, Díaz-Guzmán J, et al. Consistency of clinical diagnosis of dementia in NEDICES: a population-based longitudinal study in Spain. *J Geriatr Psychiatry Neurol*. 2009;22:246–55.
40. Villar Fernández I, Rabanaque Hernández MJ [tesis doctoral] Análisis de la utilización de fármacos específicos para la enfermedad de Alzheimer en Aragón; 2008. Zaragoza.
41. López Mongil R, López Trigo JA, Castrodeza Sanz FJ, Tamames Gómez S, León Colombo T. Prevalencia de demencia en pacientes institucionalizados: estudio RESYDEM. *Rev Esp Geriatria Gerontol*. 2009;44:5–11.
42. Parsons C, Briesacher BA, Givens JL, Chen Y, Tjia J. Cholinesterase inhibitor and memantine use in newly admitted nursing home residents with dementia. *J Am Geriatr Soc*. 2011;59:1253–9.
43. Ministerio de Sanidad, Servicios Sociales e Igualdad. Datos de Facturación de Recetas Médicas del Sistema Nacional de Salud (CC.AA. e Ingesa). Available from: <http://www.msssi.gob.es/profesionales/farmacia/datos/home.htm> [accessed 06.10.13].
44. Consulta interactiva del Sistema Nacional de Salud. Available from: <http://pestadistico.inteligenciadegestion.msssi.es/> [accessed 22.09.13].
45. Disposición 14021 del BOE n.º 200 del 2011-BOE-A-2011-14021.pdf. Available from: <http://www.boe.es/boe/dias/2011/08/20/pdfs/BOE-A-2011-14021.pdf> [accessed 27.09.13].