

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Variability and trends in dementia drug consumption in Castilla-La Mancha (Spain). Estimated prevalence of Alzheimer's disease

J.J. Criado-Álvarez^{a,*} and C. Romo Barrientos^b

^aUnidad Docente de Medicina Familiar y Comunitaria, Gerencia de Atención Primaria de Talavera de la Reina, SESCAM, Toledo, Centro de Estudios Universitarios de Talavera de la Reina, Universidad de Castilla-La Mancha, Toledo, Spain

^bUnidad de Salud Mental, Hospital Nuestra Señora del Prado, Talavera de la Reina, SESCAM, Toledo, Spain

Received on 13th March 2009; accepted on 28 December 2009

KEYWORDS

Alzheimer's disease;
Drug utilisation study;
Pharmacoepidemiology;
Prevalence;
Variability medical

Abstract

Background: Alzheimer's disease (AD) is one of the most prevalent degenerative disorders in the population over 65 years. We believe that the prevalence in Spain is between 4 and 11% for the population over 65 years old. Drugs are currently available to treat this disease in its different phases.

Material and methods: We estimated the prevalence of AD by calculating the defined daily doses per 100 inhabitants over 65 years old and days of dementia drugs (therapeutic group N06DA and N06DX) for the years 2004-2008 for each of the provinces of Castilla-La Mancha (Spain). We have provided the data requirements specified by the Regional Health Service of Castilla-La Mancha.

Results: The prevalence of AD is than 2.98 per 100-days for the whole region, there is variation in drug use and consumption, with a predominance of donepezil in all provinces except Guadalajara. On the whole, the consumption of these drugs has increased by 8% annually.

Conclusions: The consumption of dementia drugs is used to estimate the distribution of AD in Castilla-La Mancha (Spain). These figures still do not accurately estimate the prevalence of the disease, despite the increase in consumption. We can establish the variability in medical practice for this disease.

© 2009 Sociedad Española de Neurología. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE

Enfermedad
de Alzheimer;
Estudio de utilización
de medicamentos;

Variabilidad y tendencias en el uso de fármacos contra la demencia. Estimación de la prevalencia de la enfermedad de Alzheimer en Castilla-La Mancha

Resumen

Introducción: La enfermedad de Alzheimer (EA) es uno de los trastornos degenerativos más importantes en la población mayor de 65 años. Se estima que la prevalencia en Es-

*Corresponding author.

E-mail: jjcriado@sescam.jccm.es (J.J. Criado-Álvarez).

Farmacoepidemiología;
Prevalencia;
Variabilidad en la
práctica médica

paña está en el 4-11% en esa población. En la actualidad hay fármacos para el tratamiento de esta enfermedad en sus diferentes fases.

Material y métodos: Se estima la prevalencia de EA mediante el cálculo de las dosis diarias definidas/ 100 habitantes mayores de 65 años y día de fármacos contra la demencia (grupo terapéutico N06DA y N06DX), durante los años 2004-2008, para cada una de las provincias de Castilla-La Mancha. Se ha dispuesto de los datos de las prescripciones indicadas por el SESCOAM.

Resultados: La prevalencia mínima de EA es de 2,98/ 100 habitantes y día para el conjunto de la región, con variabilidad en su uso y consumo, y predominio del donepezilo en todas las provincias, excepto Guadalajara. En su conjunto, el consumo de estos fármacos se ha incrementado un 8% anual.

Conclusiones: El consumo de fármacos contra la demencia permite estimar la distribución de EA en Castilla-La Mancha. Las cifras obtenidas no permiten todavía estimar con precisión la prevalencia de la enfermedad, pese al aumento en su consumo. Sí se puede establecer la variabilidad en la práctica médica frente a esta enfermedad.

© 2009 Sociedad Española de Neurología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

Alzheimer's disease (AD) was first described in 1906¹. Despite the continuing advances in knowledge about it, treatment is still in its infancy, as existing drugs only limit the evolution of the disease and delay its natural progression. However, they cannot prevent or cure the disease; they were only approved for their symptomatic effect^{2,3}. In Spain, the aging process is occurring at an accelerated rate, and getting older is becoming a natural reality, in addition to increased mortality due to dementia⁴⁻⁶. Along with this aging process, appear added diseases, such as AD or age fragility, defined as the loss of physiological or homeostatic adaptation that leads to dependency, institutionalization and death. In 2002, in the province of Guadalajara it was observed that 22.6% of the frail elderly had cognitive impairment, 11.7% suffered disability according to the Barthel index, and 3.2% had dementia⁴. Because the prevalence of frailty and its comorbidity are so high, we must use all available means for its secondary prevention, coupled with early and effective treatment of AD in cases where it is indicated^{4,7}. The main drugs approved between 1998 and 2002 and used in Spain for mild-moderate AD are donepezil, rivastigmine and, in cases of moderate-severe disease, galantamine and memantine^{3,7-10}. We can consider these drugs as a specific treatment for all patients with AD, although with limitations (anticholinesterases are not indicated in cases of advanced disease, and memantine, in the incipient).

The aim of this work was to study the evolution of consumption of drugs against dementia in Castilla-La Mancha, between 2004 and 2008, and to estimate the prevalence of AD in the population over 65 years through this consumption.

Material and methods

The source of information used in this study was the drug database of the Pharmacy Area of the Health Service of

Castilla-La Mancha (SESCAM). This information system has regional coverage and records the consumption of outpatient drugs through official prescriptions by the National Health System (NHS). These drugs against dementia require, in most cases, medical inspection approval^{8,11}. Consumption according to this source is usually considered an acceptable approximation to real consumption¹²⁻¹⁴. We selected drugs from group N06DA of the Anatomical Therapeutic Chemical¹⁵ (anticholinesterases): donepezil, rivastigmine and galantamine; as well as other drugs for dementia (N06DX) such as memantine and *Ginkgo biloba* (which, although not specific to this disease, is used for it and is in the therapeutic group)^{7,8,10}.

We obtained the annual number of packages sold between 2004 and 2008 (data available), and from this figure, we calculated the total number of active ingredient milligrams per year, for the whole of Castilla-La Mancha and for each province. To measure consumption, we used the defined daily doses (DDD) of each drug. One DDD is the average daily dose of an active ingredient in its main indication, and is the technical measurement unit proposed by the Drug Utilization Research Group (DURG) of the WHO Regional Office of Europe. The number of DDD used has been proposed by the Nordic Council on Medicines^{12,16}. The DDD per day were calculated by dividing the number of DDD by 365, thus estimating, on average, the number of people receiving daily treatment with each active ingredient^{13,17,18}. To carry out geographical comparisons, we calculated DDD per 100 inhabitants and day (dose inhabitant day [DID]), which indicated the proportion (cases per 100 inhabitants) of the population receiving treatment with a given active ingredient as a daily average. The estimates from the consumption of these drugs must be considered as estimates of minimum prevalence or of the method of prescription in Castilla-La Mancha^{8,18}. Populations for the calculation of rates (DID) for each year were obtained from the TEMPUS database of the National Statistics Institute (www.ine.es). We used the age group over 65 years (DID65) because it is the population group at which these drugs are targeted and on which most studies are based, in addition to reducing

Table 1 Consumption of drugs for dementia in DID65 by province and year in Castilla-La Mancha. Estimated prevalence of Alzheimer's disease

Province	2004	2005	2006	2007	2008	$\Delta\%$	$\Delta a\%$	Prevalence (%)
Albacete	2.37	2.51	2.92	3.22	3.73	36.46	7.3	3.73
Ciudad Real	2.20	2.39	2.66	3.20	3.55	38.03	7.6	3.55
Cuenca	1.57	1.77	1.93	2.05	3.04	48.36	9.7	3.04
Guadalajara	1.82	2.16	2.58	2.86	3.14	42.04	8.4	3.14
Toledo	1.99	2.28	2.66	2.74	2.81	29.18	5.8	2.81
Castilla-La Mancha	2.04	2.27	2.60	2.95	2.98	31.54	6.3	2.98

DHD65: dose per inhabitant and day (cases or daily defined dose / 100 inhabitants / day in population over 65 years);

$\Delta t\%$ percentage increase between 2004 and 2008; $\Delta a\%$ annual percentage increase between 2004 and 2008.

the impact of aging on the population of Castilla-La Mancha (since it is expected that the majority of AD patients are in this age group). 95.4% of patients with specific AD treatment are over 65 years. This may increase the calculated prevalence by lowering the denominator; but if we maintain the potential and few cases of presenile AD, then a higher distortion will be originated⁹. We also estimated the annual percentage change between 2004 and 2008.

Results

Considering these drugs as specific treatment for all patients with AD, we estimated a regional prevalence in the population over 65 years of 2.04 cases per 100 in 2004 and 2.98 cases per 100 in 2008. This represents an average increase of 6.3% annual change (31% throughout the period) (table 1). This also represents, in absolute figures for Castilla-La Mancha, between 7,407 cases in 2004 and nearly 11,000 cases in 2008 of mild to severe AD patients. Nevertheless, there are differences per province, with a maximum in Albacete (3.73%) and a minimum in Toledo (2.81%) (fig. 1). In general, drug consumption has increased throughout the period in all

provinces by 23-36% although this is not statistically significant; it goes from 2.04 in 2004 to 2.98 in 2008 ($\chi^2 = 0.35$; $p > 0.05$). There is an increase in the consumption of all drugs, except for memantine, whose consumption has decreased from 2.04 to 1.76 throughout Castilla-La Mancha. However, the drug with minimum consumption varies from one province to another (fig. 1). The most widely consumed drug is donepezil in all provinces (11 DID in 2008), except in Cuenca, where memantine is the most widely consumed, with a 9.84 DID in 2008 (figs. 1 and 2).

Discussion

By determining the DID applied to the prescription of drugs against dementia, we estimated that the prevalence of AD in Castilla-La Mancha in 2008 was 2.98% of the population over 65 years. This figure doubles that found in Aragon using the same methodology (1.47% in 2004)⁸. If we assume that 34.17% of patients with AD are being treated, the final prevalence estimated in Castilla-La Mancha would be 2.46% although other authors find patterns of 64.3% thus giving a figure of 4.63% so the range is broad: 2.46 to 4.63%¹¹.

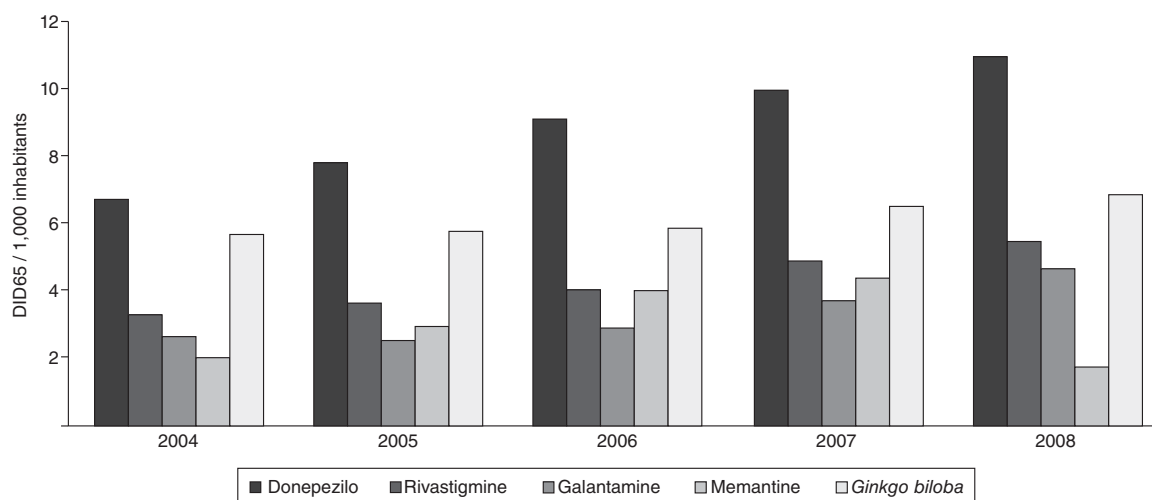


Figure 1 Consumption of drugs against dementia in doses per inhabitant and day in population over 65 years (DID65) in Castilla-La Mancha between 2004 and 2008.

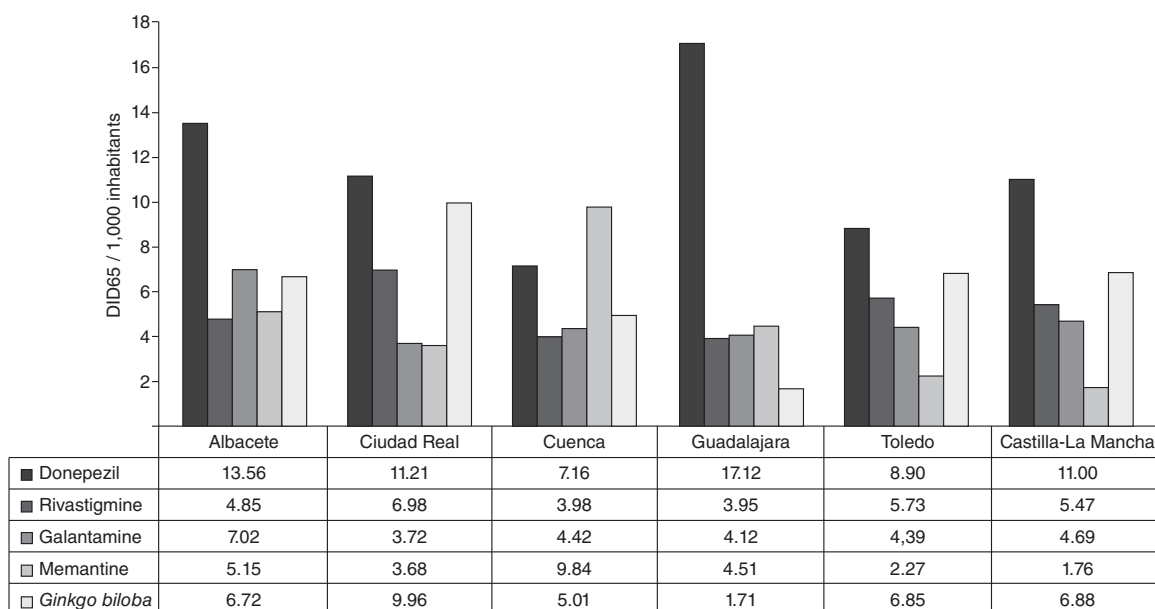


Figure 2 Consumption of drugs against dementia in doses per inhabitant and day in population over 65 years (DID65) by provinces and Castilla-La Mancha in 2008.

According to population studies, the figure for prevalence in Zaragoza and EURODEM study countries is 4.3%¹⁹⁻²¹. Comparing the figures obtained in the province of Toledo in 2008 (2.81%) with those found in the 2001 Toledo Study (4.6%) for AD, we obtain an underestimation of 41%. However, it is similar if we do the same with the final estimated prevalence of 2.46 to 4.63%². In the Girona Study, prevalence was 16.3% although if we consider the moderate-severe types of AD, prevalence becomes 5.3% an intermediate figure with our results, but close to that of the Basque Country (6.9%)^{21,23,24}.

The NHS, given its wide coverage and monitoring of drug prescription and availability, meets the conditions for determining DID consumption. In the case of AD, the prescription specificity of these drugs (except for *Ginkgo biloba*) makes it possible to deduce the prevalence of AD (although their use in other dementias is not ruled out)^{8,11}. The prescription profile in Castilla-La Mancha is similar to that found in other studies, with donepezil used in the first place, followed by rivastigmine, galantamine and memantine^{8,9,11,25,26}, although in our case there are some provincial differences (fig. 1). The validity of the data is supported by the control of these patients by specialists, the consensus in the treatment with DDD standards and the almost exclusive use of these drugs in this disease, together with approval by pharmaceutical inspection^{8,11}.

The consumption of these drugs is increasing in Castilla-La Mancha due to changes in the population pyramid, with almost 20% of the population being over 65 years old. Therefore, even maintaining the same consumption, the rates have increased^{5,14,23}. The population covered by the NHS has also increased, as has life expectancy, and there is greater access to specialised medical services and improved quality of drug prescription, with more therapeutic consensus and greater maintenance doses of drugs. The rate of patients with combination therapies is below 5% with only the

mixture of donepezil and memantine being accepted^{3,7,9,11}.

The availability of data on drug consumption against dementia in SESCAM in the period 2004-2008 is comprehensive with regard to coverage. However, data availability is still limited as to time, making it difficult to study growth trends. Many patients (about 5%) in intermediate and moderately advanced stages take a combination of anticholinesterases and memantine, so the figures may vary slightly. The 5E study found that 20% of patients with moderate-advanced AD took a combined treatment; although this did not include incipient AD, this figure is far from the mentioned 5%. However, the disaggregated data per patient is not available, as required by the Organic Law on Data Protection. Its use in the estimation of AD prevalence is subject to all patients being treated with these drugs, which happens, in the best of cases, in 64.3%, due to its therapeutic effectiveness.⁷ It also depends on the patients following their therapeutic doses, which does usually occur because many of these patients have a caretaker who is responsible for administering and controlling drug intake²⁶. It is expected that all prescription medications are consumed, due to their cost and the magnitude and severity of the disease. It is unlikely that all the sick population attend health services, and that only mild or moderate cases benefit from treatment, because a certain therapeutic ineffectiveness can be considered in severe cases. A bias which is usually encountered in such studies is that drugs are purchased without a prescription, but this is not the case here^{11,18}. However, the universal coverage and the NHS reform undertaken in Spain and its regions through the process of health transfers in 2002 have permitted a greater closeness and accessibility to citizens. This may explain the rising trend in consumption, although it is likely to be an under-treated disease^{11,25,27}. The application of this model only becomes stable when sales data are stable over time, but the figures obtained by this method are always estimates^{11,13,14,18}. Nevertheless, these results are still far

from an accurate estimate of the prevalence of AD in Castilla-La Mancha if we compare the figures obtained (2.98%) with clinical and Spanish population studies, which estimate a prevalence around 4-7%. However, assuming a treatment rate of 64.3%, our estimated prevalence reaches 4.63%^{11,21-24}.

The results of this study enable us to determine the minimum prevalence of AD through the consumption of drugs in all its forms, and we can observe an interprovincial variability that is not due to medical causes as such^{17,25,28}. The implementation and review of clinical practice guidelines in Spain will prevent or diminish the differences found, increase the consumption of these drugs and help to improve care, expectations and quality of life for patients and their environment.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgements

We thank Ms Laura Jiménez López (Pharmaceutical Control Service) and Mr Ángel M. Martín Fernández Gallardo (Head of Pharmacy Department) of SESCOAM for providing drug prescription data in Castilla-La Mancha. We are especially grateful to the reviewers for their knowledge and their voluntary and anonymous work, with which the manuscript has been improved in its wording and possible biases.

References

- Belart Alcalde R. El primer Alzheimer. *Rev Esp Geriatr y Gerontol*. 1993;28:178-82.
- Cummings JL. Alzheimer's disease. *N Engl J Med*. 2004;351:56-67.
- Mareque Ortega MA, Fernández Agüero L, Moreno Sánchez E, Martín Correa E. Abordaje farmacológico en el anciano con demencia. *Boletín Farmacoterapéutico de Castilla-La Mancha*. 2006;7:1-8.
- Urbina Torija JR, Flores Mayor MJ, García Salazar MP, Rodríguez Estremera E, Torres Buisan L, Torrubias Fernández RM. El anciano de riesgo en la provincia de Guadalajara. *Aten Primaria*. 2004;34:293-9.
- Criado-Álvarez JJ. ¿A qué edad se muere de viejo en Castilla-La Mancha? *Medicina Preventiva*. 2006;12:38-9.
- Puig X, Gispert R, Puigdefàbregas A, Pérez G, Mompart A, Domènech J. Mortalidad por demencia en Cataluña: un problema de salud emergente. *Med Clin (Barc)*. 2002;118:455-9.
- Loveman E, Green C, Kirby J, Takeda A, Flcot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. *Health Tech Assessment*. 2006;10: iii-iv, ix-xi, 1-160.
- Villar Fernández I, Rabanaque 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.
- Antoñanzas F, Rive B, Badenas JM, Gómez-Lus S, Guilhaume C. Cost-effectiveness of memantine in community-based Alzheimer's disease patients: an adaptation in Spain. *Eur J Health Econ*. 2006;7:137-44.
- Gandía L, Álvarez RM, Hernández-Guijo JM, González-Rubio JM, Pascual R, Rojo J, et al. Anticolinesterásicos en el tratamiento de la enfermedad de Alzheimer. *Rev Neurol*. 2006;42:471-7.
- 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.
- International Narcotics Control Board (2001). Psychotropic Substances. Statistics for 2001. Doc E/ INCB/ 2001/ 3.
- Provencio RM. Estudios de utilización de medicamentos. *Rev Neurol*. 1996;24:397-9.
- Criado-Álvarez JJ, Romo Barrientos C, Martínez Hernández J, González Solana I. Consumo de antiparkinsonianos en Castilla-La Mancha. Estimación de la prevalencia de la enfermedad de Parkinson. *Rev Neurol*. 1998;27:405-8.
- Boletín Oficial del Estado. Orden Ministerial de 13 de octubre de 1989, por la que se modifica el contenido del Anexo I de la Orden de 13 de mayo de 1985 por la que se actualiza la clasificación anatómica de medicamentos oficial de España. BOE n.º 257 de 26 de octubre de 1989. p. 1776-80.
- Nordic Council on Medicines. ATC Index with DDDs. WHO Collaborating Center for Drug Statistics Methodology. Oslo: WHO; 1999.
- Sartor F, Walckiers D. Estimate of disease prevalence using drug consumption data. *Am J Epidemiol*. 1995;141:782-7.
- Criado-Álvarez JJ, Romo Barrientos C. Variabilidad y tendencias en el consumo de metilfenidato en España. Estimación de la prevalencia del trastorno por déficit de atención con hiperactividad. *Rev Neurol*. 2003;37:806-10.
- Lobo A, Saz P, Marcos G, Día JL, De la Cámara C. The prevalence of dementia and depression in the elderly community in a southern European population. *Arch Gen Psychiatry*. 1995;52:497-506.
- Pocca WA, Hofman A, Brayne C, Breteler MM, Clarke M, Copeland JR, et al. Frequency and distribution for Alzheimer disease in Europe: a collaborative study of 1980-1990 prevalence findings. *Ann Neurol*. 1991;30:381-90.
- Barrio JL, Pedro-Cuesta J, Boix R, Acosta J, Bergareche A, Bermejo-Pareja F, et al. Dementia, stroke and Parkinson's disease in Spanish populations: A review of door-to-door prevalence surveys. *Neuroepidemiology*. 2005;24:179-88.
- García García FJ, Sánchez Ayala MI, Pérez Martín A, Martín Correa E, Marsal Alonso C, Rodríguez Ferrer G, et al. Prevalencia de demencia y sus subtipos en sujetos mayores de 65 años: efecto de la educación y ocupación. Estudio Toledo. *Med Clin (Barc)*. 2001;116:406-7.
- Vilalta-Franch J, López-Pousa S, Llinàs-Pegla J. Prevalencia de demencias en una zona rural. Estudio de Girona. *Rev Neurol*. 2000;30:1026-32.
- Fernández M, Castro-Flores J, Pérez de las Heras S, Mandaluniz-Lekumberri A, Gordejuela M, Zarranz J. Prevalencia de la demencia en mayores de 65 años en una comarca del País Vasco. *Rev Neurol*. 2008;46:89-96.
- Gil-Neciga E, Gobartt AL. Patrón de tratamiento de la enfermedad de Alzheimer con inhibidores colinesterásicos (estudio TRAIN). *Rev Neurol*. 2008;46:461-4.
- Dybiz SB, Keohane DJ, Erwin WG, McRae T, Shah SN. Patterns of cholinesterase-inhibitor use in the nursing home setting: A retrospective analysis. *Am J Geriatr Pharmacother*. 2006;4:154-60.
- Geldmacher DS. Treatment Guidelines for Alzheimer's Disease: Redefining Perceptions in Primary Care. *Prim Care Companion J Clin Psychiatry*. 2007;9:113-21.
- Meneu R. Variabilidad de las decisiones médicas y su repercusión sobre las poblaciones. Barcelona: Masson; 2002.