



Morbidity and costs associated with depressive syndrome in stroke sufferers in a population

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Abstract

Objective: To measure morbidity and the associated costs of depressive disorders (DD) in subjects who have had a stroke in a population treated by primary care settings under usual clinical practice conditions.

Method: Cross-sectional, retrospective studies. Adult stroke patients with DD were included in the study, and treated by 5 primary care settings (PCS) during 2006. A comparative group was formed with the rest of non-DD patients. The main measurements taken were: age, sex, history/co-morbidity, Charlson index, clinical parameters, and corresponding outpatient costs; drugs, diagnostic tests, referrals, and visits. Multiple logistic regression analysis and ANCOVA were used to correct the models.

Results: A total of 2566 stroke patients were assessed. Seventeen point seven percent (95% CI, 16.2-19.2) were identified as having DD; average age, 69.5 years (standard deviation, 12.6); 57.2% of those were female. In the correction of the model, females (OR, 2.1), obesity (OR, 1.1), and neuropathy (OR, 2.2), were significantly associated with DD in stroke patients. The adjusted total costs of DD were higher in most components, €2037.55 versus €1498.24, $P < .001$. Seventy three point four percent of the total cost was drugs-derived.

Conclusions: Prevalence of DD was higher in stroke patients, and was more associated with females, obesity, and neuropathy. The patient cost is high and patients use more health resources.

Key words: Depressive disorders. Stroke. Cost.

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Morbilidad y costes asociados al síndrome depresivo en sujetos con ictus en un ámbito poblacional

Objetivo: Medir la morbilidad y los costes asociados al síndrome depresivo (SD) en sujetos con ictus en población atendida por equipos de atención primaria y en condiciones de práctica clínica habitual.

Método: Estudio transversal de carácter retrospectivo. Se incluyeron pacientes adultos con presencia de ictus y de SD atendidos por 5 equipos de atención primaria durante el año 2006. Se formó una cohorte comparativa con el resto de pacientes sin SD. Las principales medidas fueron: edad, sexo, historial/comorbilidad, índice de Charlson, parámetros clínicos y costes totales (visitas, pruebas complementarias, derivaciones y medicamentos). Se efectuó un análisis de regresión logística y de ANCOVA para la corrección de los modelos.

Resultados: El total de pacientes atendidos con ictus fue de 2.566. Un 17,7% (intervalo de confianza del 95%, 16,2-19,2%) se identificaron con SD; promedio de edad: 69,5 años (desviación estándar: 12,6); el 57,2% eran mujeres. En la corrección del modelo, el sexo femenino (odds ratio [OR]: 2,1), la obesidad (OR: 1,1) y las neuropatías (OR: 2,2) se asociaron significativamente al SD en sujetos con ictus. Los costes totales ajustados del SD fueron superiores en la mayoría de sus componentes, 2.037,55 € frente a 1.498,24 €, $p < 0,001$. El 73,4% de los costes se derivó de los medicamentos.

Conclusiones: La prevalencia del SD en sujetos con ictus es elevada, se asocia al sexo femenino y a la presencia de obesidad y neuropatías. Los costes de estos pacientes son altos y ocasionan un elevado consumo de recursos sanitarios.

Palabras clave: Síndrome depresivo. Ictus. Coste.

INTRODUCTION

Stroke is one of the primary causes of disability, and morbidity and mortality in developed countries, and has a high economic and social cost. In western countries, it is the third cause of death after heart diseases and neoplasias, and constitutes 10% of causes of death. Overall prevalence is between 500 and 700 cases per 100 000 persons.^{1,2} Depressive disorders (DD) cause a change in mood and are characterized by a well-defined group of symptoms. This is one of the most frequent reasons for treatment in primary care settings and represents one of the most frequent psychiatric diagnoses in the general population.²⁻⁵ Prevalence in Spain is 10% of the adult population, and 21.3% of the female population.²

DD is the most frequent affective disorder occurring after a stroke and may have an adverse effect on functional recovery and survival of patients. Consequently, an early diagnosis and correct treatment are essential. The consulted bibliography shows some differences of DD prevalence in these patients based on the type of epidemiological study: population studies show lower prevalence (15%-40%) than studies from specific treatment or rehabilitation units (40%-60%).^{2,6-9}

Relevance of DD for stroke patients is associated with different comorbidity, health resources consumption, and consequently, different costs. Regarding this, the limited research information available in Spain and other countries which measure these variables holistically are of interest, and these would elucidate a hypothesis and relevance of the study.^{2,10,11} The study's objective was to measure morbidity and economic impact of DD for stroke patients, in a population treated by various primary care settings (PCS) under usual clinical practice conditions.

METHODS

A transversal, multicentre, retrospective study was carried out based on data from medical records of adult patients treated under usual clinical practice conditions. The study population consisted of persons treated from 5 PCS (PCS Apenins-Montigalá, PCS Morera-Pomar, PCS Montgat-Tiana, PCS Nova Lloreda, and PCS La Riera) and carried out by Badalona Medical Assistance Services S.A., whose region of care covers an urban population of 110 000 persons, of which 15.8% are over 64 years. All patients recorded and treated during 2006 were included, and the following data were collected: age older than 14 years and an established diagnosis of a stroke before the study period. Subjects transferred to other PCS, those not treated by a centre, those who moved or were outside the geographical area, and those who only visited with associated specialists were excluded from the study.

The episodes treated in the population recorded and selected based on an established diagnosis of stroke and DD were obtained from the International Classification of Primary Care (ICPC-2 [Lamberts & Wood]; K90-K91-K92 [cardiovascular health problems] and P76 [psychological health problems]).¹² Diagnoses'

dates were not considered in the study. The standard scales used by the teams for screening/diagnosis of DD were from Goldberg (morbidity co-existence), Hamilton (intensity of depressive symptoms) and geriatric scales from Yesevage. The stroke record (ischemic or haemorrhagic), registered in the PCS, generally came from respective reports from other levels of care. The following overall variables were collected: age (continuous and by ranges), sex, personal antecedents or comorbidities according to ICPC-2 standards, the Charlson index (severity of patients), and particular biochemical parameters for cardiovascular control (Table 1). Neuropathies were defined as the group of pathologies including Parkinson's disease, and demyelinating and neurodegenerative diseases.

The health resources used were obtained from the records of each centre and came from electronic medical records, and these were: visits or appointments made in the PCS, costs from using referenced specialists, additional supporting exams, and drug prescription from CatSalut (the Catalan Health Service). Expenditure in the profit and loss account under general accounting was adjusted in accordance to the costs under cost accounting and was carried out in 2 stages: *a*) conversion of normal expenses into costs, and *b*) assignment and classification of costs. Accounting entries from the following expenditures were defined as normal costs: personnel (salaries), consumer goods (medications and health materials), and a collection of expenses associated with external services of structuring and management (repayment and taxes), according to the general accounting plan for health care centres. Assignment and classification of costs was carried out in the second stage. Fixed or semi-fixed costs (allocation criteria: indirect costs) and variable costs (allocation criteria: direct costs) were considered according to their dependence on the volume of activity developed in the centres.^{13,14} Fixed/semi-fixed costs (structure), personnel related costs (salaries), consumer products, and a collection of expenses related to external services were considered, according to the general accounting plan for health care centres. Direct costs were those related to diagnostic or therapeutic forms, or costs incurred by the centre's professionals. The different aspects of the study and their financial assessment were the following: *a*) additional testing (laboratory—average cost per request—), conventional radiology (cost per test requested), supporting tests (cost per test requested); *b*) consultations between specialists, or referrals to specialists or hospitals (cost adjusted according to referral); and *c*) prescriptions (acute, chronic, or on request medical prescriptions; sales price per package to the public). Various distribution alternatives to possible financially assisted and non-assisted centres were assessed through primary distribution to the end GP and paediatrics services of each centre. An average cost per visit was obtained based on a final direct distribution from semi-fixed and fixed costs. Therefore, the cost per patient (Cp), based on the final service assigned, was: $Cp = (\text{average cost per visit} \times \text{number of visits} [\text{indirect costs: fixed/semi-fixed}]) + (\text{variable costs} [\text{direct costs}])$.

A statistical, descriptive, and univariate analysis was carried out, and distribution normalcy was proven using the Kolmogorov-

Table 1. Distribution of general variables, clinical parameters, and antecedents according to groups with presence or absence of depressive disease (DD) in stroke subjects

Study variables	Absence of DD	Presence of DD	Total	P	OR ^a	95% CI
Subjects in study (%)	2113 (82.3)	453 (17.7)	2566 (100.0)			
<i>General</i>						
Age, mean (SD), y	70.2 (13.6)	69.5 (12.6)	70.1 (13.4)	NS		
Age ranges, y						
15-44	5.0%	4.0%	4.8%			
45-64	24.8%	30.0%	25.8%			
65-74	58.4%	57.4%	58.2%			
>74	11.8%	8.6%	11.2%	.045		
Sex (women)	39.0%	57.2%	42.2%	.000	2.1	1.7-2.6
Average of episodes/year (SD)	7.6 (4.2)	9.5 (4.9)	7.9(4.4)	.000		
Average of Charlson index (SD)	0.9 (0.6)	0.8 (0.6)	0.9 (0.6)	NS		
Average of visits/year, SD	14.9 (14.0)	17.8 (17.3)	15.5 (14.6)	.000		
<i>Antecedents or associated comorbidities</i>						
Arterial hypertension	59.0%	60.0%	59.2%	NS		
Diabetes mellitus	28.9%	30.0%	29.1%	NS		
Dyslipidemia	44.2%	47.9%	44.8%	NS		
Obesity	39.2%	44.6%	40.2%	.044	1.1	1.0-1.2
Smokers	17.6%	15.9%	17.3%	NS		
Alcoholism	3.9%	2.6%	3.7%	NS		
Ischemic cardiopathy	18.4%	18.1%	18.3%	NS		
Liver, heart, kidney failure	14.6%	16.3%	14.9%	NS		
Bronchial asthma	3.2%	4.6%	3.5%	NS		
COPD	9.8%	11.5%	10.1%	NS		
Neuropathies (Parkinson's, etc)	1.3%	2.9%	1.6%	.017	2.2	1.1-4.3
Dementias	4.0%	6.0%	4.3%	.043		
Organic and affective psychosis	0.8%	0.4%	0.7%	NS		
Malignant neoplasias	7.8%	8.4%	7.9%	NS		
<i>Clinical parameters</i>						
BMI (SD), kg/m ²	28.4 (4.7)	29.2 (5.6)	28.6 (4.9)	.003		
SBP (SD), mmHg	134.1 (17.5)	132.9 (18.0)	133.9 (17.6)	NS		
DBP (SD), mmHg	75.3 (9.6)	76.2 (11.1)	75.5 (9.9)	NS		
Basal glycemia (SD) mg/dL	109.4 (37.3)	106.4 (35.4)	108.9 (37.0)	NS		
Serum triglycerides (SD) mg/dL	128.5 (88.2)	130.9 (80.0)	129.0 (86.8)	NS		
Total cholesterol (SD) mg/dL	194.6 (39.9)	198.0 (43.0)	195.2 (40.5)	NS		
HDL-C (SD), mg/dL	54.6 (17.5)	55.2 (17.0)	54.7 (17.4)	NS		
LDL-C (SD), mg/dL	115.1 (36.3)	117.4 (37.3)	115.5 (36.5)	NS		

Values expressed as percentage or average (standard deviation [SD]).

BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; CI, confidence interval; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NS, not significant; OR, odds ratio; SBP, systolic blood pressure.

^aLogistic regression model.

Smirnov test. The bivariate analysis included the Student *t* test (Mann Whitney *U* test, if the application conditions were not fulfilled) and the χ^2 test. A logistic regression analysis was carried out (enter procedure) for statistically significant variables from the bivariate analysis, and DD was used as the dependent variable. The method of association for the bivariate and multivariate analysis of costs, as a dependent variable, was carried out without logarithmic

transformation and following the recommendations described by Thompson and Barber.¹⁵ For correction of cost components and comorbidities among the 2 groups of patients, a covariance analysis was carried out (ANCOVA) with the Bonferroni correction (marginal averages, comparisons by pairs) for multiple comparisons. The SPSS for Windows (version 12) was used, and this established statistical significance for the values $P < .05$.

RESULTS

From an initial selection of 63 525 patients treated, 4.0% (95% of confidence interval [CI], 3.8-4.2) presented with a stroke ($n=2566$); average age was 70.1 years (standard deviation [SD], 13.4), and 42.2% were women. From these, 453 (17.7%; 95% of CI, 16.2-19.2) were diagnosed with DD; with an average age of 69.5 years (SD, 12.6); 57.2% were women. Overall, 75.2% of strokes were ischemic, 15.3% haemorrhagic, and the rest of the cases were not conclusive in this regard. DD presence was not significantly associated with age, general comorbidity, Charlson index, or metabolic control parameters (Table 1). Nevertheless, DD patients presented with a higher body mass index: 29.2 versus 28.4 kg/m², $P=.003$, and average episodes/patient: 9.5 (SD, 4.9) versus 7.6 (SD, 4.2), $P<.001$. After the adjustment, females (OR, 2.1), obesity (OR, 1.1), and neuropathies (OR, 2.2), were significantly associated with DD in stroke subjects.

Quantification of costs was 4 million euros (Table 2), with a distribution of 17.7% in fixed and semi-fixed costs and the rest in variables (costs for specialists, 7.0%, and drug prescription, 73.4%). Stroke with DD was associated with a higher use of health resources. After correcting for the effect of age, sex, comorbidity, and severity of the disease, stroke with DD was associated with significantly higher costs; 1498.24 versus 2037.55 euros, $P<.001$.

DISCUSSION

Epidemiological studies are indispensable for finding factors associated with diseases and therefore being able to exercise a certain degree of control over various aspects of prevention.^{2,4} In our study, the dates of initial diagnoses were not considered, and

also, time sequence was not considered as part of the study design (if the DD was before or after the stroke), nor was the degree of general relation between the DD and stroke considered. This circumstance is mainly due to various aspects: *a)* the type of study used; *b)* the difficulty of finding the chain of occurrences and/or the certainty of diagnosis in daily practice in the PCS, regarding the longitudinal follow-up of the patient's symptoms; and *c)* the existence of various little known physiopathologic hypotheses on the disease's associations. Some authors consider post-stroke DD patients to be carriers of major depression, and these include various diseases such as: bipolar disorder, organic mood disorder, or dementia with depression (categories defined in the DSM-IV). On the other hand, patients with an adjustment disorder (depressed mood, or mixed anxiety, and depressed mood), dysthymia, and major depressive disorder in remission, are sometimes grouped as having minor depression.^{2,8,16,17} In the etiology of DD, multiple genetic, biological, and psychosocial factors contribute to a significant neurochemical imbalance in noradrenergic, serotonergic, and dopaminergic transmission. The consumption of certain drugs (glucocorticoids, oral contraceptives, propranolol, anabolic steroids, reserpine, etc) and toxic substances (alcohol, cocaine, and amphetamine abstinence), or the presence of other somatic diseases (tumors, diabetes, collagen disease, Parkinson's, multiple sclerosis, or dementias) are some of the factors associated with DD.^{2,6,7,16} In general, the different methodologies used for measuring some variables in the studies reviewed, especially the different classification systems of patients and evaluation criteria, scales and types of neuropsychiatric diagnoses, make comparisons difficult and require caution when stating external validity of results. In our study, the following cannot be ruled out: an underassessment of the disease, the existence of a younger population makeup or the possible difficulties diagnosed in

Table 2. Distribution of gross annual costs (in euros) and adjusted costs (ANCOVA) per patient according to presence or absence of depressive disease (DD) in stroke subjects

Distribution of costs	Absence of DD		Presence of DD		Total		P			
	Average	SD	Average	SD	Average	SD				
Fixed/semi-fixed cost (distribution: visits)	272.23	254.10	323.26	315.59	281.24	266.63	.000	721	666.40	17.7
Variable cost	1227.55	1121.34	1701.09	1318.66	1311.15	1172.34	.000	3 364	400.16	82.3
Laboratory cost	20.11	23.44	22.34	23.33	20.50	23.43	NS	52	610.68	1.3
Image diagnosis cost	6.20	11.48	6.95	11.72	6.34	11.52	NS	16	255.68	.4
Additional tests cost	1.63	4.27	2.12	4.73	1.72	4.36	.030	4415.31		.1
Cost for use of specialists	106.07	145.58	140.77	184.36	112.19	153.67	.000	287	886.50	7.0
Drug prescription cost	1091.90	1083.73	1526.79	1267.62	1168.67	1130.36	.000	2 998	816.68	73.4
Total cost in primary care	1499.78	1260.41	2024.35	1441.88	1592.39	1309.37	.000	4 086	066.56	100.0
Adjusted cost ^a (95% CI)	1498.24		2037.55							
	(1445.65-1550.84)		(1925.62-2149.49)							

CI indicates confidence interval; NS, not significant; SD, standard deviation.

^aANCOVA model: estimations of adjusted total costs, covariables which appear in the model are evaluated in the following values: age = 70.1; Charlson index = 0.9. Every F-test contrasts the simple effect of depression in each combination of levels of the rest of the effects shown. These contrasts are based on comparisons by pair, linearly independent, among estimated marginal averages. Adjustment for multiple comparisons: Bonferroni, dependent variable: total cost in primary care; ANCOVA: multivariate analysis of variance.

screening cases, which could support these factors. Nevertheless, comparing prevalence, associated comorbidities and the use of resources for DD in the first studies reviewed indicates a certain variability, but this is more related to aspects of design than to regional variations or demographic structure.^{2,6-9,16,18,19}

Stroke disables individuals regarding independence in daily activities, causes a need for care and a need for institutionalization with considerable health and social costs. In the United States, it is estimated that this expense represents 25 000 dollars per patient per year. This includes treatment in the acute stage, rehabilitation, institutionalization expenses, and financial losses due to job loss and the loss of pensions of working age persons.^{2,6,7} The independent association of DD with neuropathy could be due to a statistical device, but the high degree of disabilities from these diseases could be the most consistent explanation. These results fit within the population prevalences observed.^{2,4,6,8} Also, this variable should be considered in stroke development and possibly for other diseases, because by itself, it is also associated with a significantly higher use of resources. There are results consistent with this in other series reviewed.^{2-4,6-8,10,11,16,17} In clinical practice, patients with DD have a greater risk of presenting with diseases, suffering from treatment failures and greater suffering or disability from a concurrent disease. The probability of death is higher due to an increased risk of suicide, accidents or fatal complications from another disease, or due to the development of other diseases commonly found with depression such as alcoholism and substance abuse (illicit or legal drugs).^{8,16} In the logistic model, obesity and female gender were associated with DD. Other morbidities showed no significant relationship. These results are consistent with the bibliography consulted.^{4,6,7,16,20} Nevertheless, variability of the methodologies used in various studies requires caution in generalizing the results obtained (factors for confusion). Our study reinforces the evidence related to association of antecedents and an increased use of resources for these patients.^{20,21}

Possible limitations of the study lie in the classification and measurement of costs, attributable to the information system developed, even though the ICPC-2 conversion with the International Classification of Diseases (9th edition, clinical modification) or the DSM-IV are not without difficulties. Furthermore, some indirect costs associated with the patient's quality of life were not considered. Direct costs related to the patient's hospitalization regimen were not considered, and socioeconomic consequences of the caregivers and their difficulties were not considered. In the article, limitations of retrospective studies are shown, for example the under-registering of the disease or the possible variability of professionals' regular use of different scales for screening clinical information. It is important to mention that one of the study's major limitations was the lack of information relevant to the collection some clinical variables. In this respect and regarding the example, it would have been of great interest to know the time duration from the initial stroke onward, relate the DD to the degree of residual disability and even locate the cerebral infarction. Future research should promote improvement in etiological knowledge of the disease and its social consequences.

It would be important to promote coordination mechanisms between different levels of treatment for comorbidities of patients and make available greater development and applicability of information systems and classification of patients by iso-consumption of resources to better adjust the model.²² A practical application of our study may be that the high prevalence of DD in stroke survivors should promote involvement by different health professionals (neurologists, psychiatrists, family practitioners, nurses, etc) from primary and specialized care to find, prevent and treat this problem and its various risk factors which develop at any time in the patient. Also, all discharged patients should receive an adequate neuropsychiatric evaluation of psychosocial factors and disability from aftereffects, with the aim of carrying out a complete curative treatment and most importantly, preventive treatment.² In conclusion, prevalence of DD in stroke patients is high and is associated with females, and obesity, and neuropathies. Adjusted costs for these patients are higher, and they use more health resources.

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References

1. Baztan JJ, Pérez-Martínez DA, Fernández-Alonso M, Aguado-Ortega R, Bellando-Álvarez G, de la Fuente-González AM. Prognostic factors of functional recovery in very elderly stroke patients. A one-year follow up study. *Rev Neurol*. 2007;44:577-83.
2. Carod-Artal FJ. Post-stroke depression (I). Epidemiology, diagnostic criteria and risk factors. *Rev Neurol*. 2006;42:169-75.
3. Thomas MR, Waxmonsky JA, Gabow PA, Flanders-McGinnis G, Socherman R, Rost K. Prevalence of psychiatric disorders and costs of care among adult enrollees in a medicaid HMO. *Psychiatr Serv*. 2005;56:1394-401.
4. Haro JM, Palacín C, Vilagut G, Martínez M, Bernal M, Luque I, et al. Prevalence of mental disorders and associated factors: results from the ESEMeD-Spain study. *Med Clin (Barc)*. 2006;126:445-51.
5. Shvartzman P, Weiner Z, Vardy D, Friger M, Sherf M, Biderman A. Health services utilization by depressive patients identified by the MINI questionnaire in a primary care setting. *Scand J Prim Health Care*. 2005;23:18-25.
6. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke*. 2005;36:2296-301.
7. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. *Lancet Neurol*. 2005;4:371-80.
8. Politi P, Sciarini P, Lusignani GS, Micieli G. Depression and stroke: an up-to-date review. *Epidemiol Psychiatr Soc*. 2006;15:284-94.
9. Carota A, Staub F, Bogousslavsky J. Emotions, behaviors and mood changes in stroke. *Curr Opin Neurol*. 2002;15:57-69.
10. Carod-Artal FJ, González-Gutiérrez JL, Egido-Herrero JA, Varela de Seijas E. Post stroke depression: predictive factors at one year follow up. *Rev Neurol*. 2002;35:101-6.
11. González Torrecillas JJ, Mendlewicz J, Lobo A. Analysis of intensity of post-stroke depression and its relationship with the cerebral lesion location. *Med Clin (Barc)*. 1997;109:241-4.

12. Lamberts H, Wood M. Clasificación Internacional de la Atención Primaria (CIAP). Clasificación de razones de consulta. Barcelona: Masson/SG; 1990.
13. Orden de la Generalitat de Catalunya de 22 de diciembre de 1995. Diari Oficial de la Generalitat de Catalunya. 1995;2148:9689-90.
14. García Cardona F, Molins Pérez G, Farré Pradell J. La contabilidad de costes en atención primaria y cartera de servicios. *Aten Primaria*. 1995;16:141-5.
15. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? *BMJ*. 2000;320:1197-200.
16. Ros S, Agüera L, Gandara J, Rojo J, Pedro JM. Potentiation strategies for treatment-resistant depression. *Acta Psychiatr Scand*. 2005; 112:14-24.
17. Williams LS. Depression and stroke: cause or consequence? *Semin Neurol*. 2005;25:396-409.
18. Sackett D, Rosenberg W, Gray J, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71-2.
19. López de Munain J, Grandes G, Orueta JF. Importancia de la calidad de los datos en la validación del case-mix ACG. *Aten Primaria*. 1998;22:128.
20. Sicras Mainar A, Navarro Artieda R, Rejas Gutiérrez J, Blanca Tamayo M, Serrat Tarrés J, Llopart López JR. Comorbidity and related costs as a burden in the treatment of outpatients with depressive disorders in a primary care setting. *Fam Hosp*. 2007;31:101-5.
21. Alegría M, Frank R, McGuire T. Managed care and systems cost-effectiveness: treatment for depression. *Med Care*. 2005;43:1225-33.
22. Sicras Mainar A, Serrat Tarrés J. Measurement of relative cost weights as an effect of the retrospective application of adjusted clinical groups in primary care. *Gac Sanit*. 2006;20:132-41.