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Use of health care resources and loss of productivity in patients with depressive disorders seen in Primary Care: INTERDEP Study

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Introduction. The InterDep Study analyzes the characteristics of patients with a depressive disorder who, in the last years, have received health services at Primary Care in an specific health care area. The InterDep Study evaluates the use of heath care resources attributable to depression (direct costs) and loss of productivity (indirect costs). It also analyzes these patients' referral to the specialist.

Methods. A retrospective, multicenter observational study was conducted using computerized medical records collected in an anonymized database of 22,795 patients who received health care services between 2005 and 2009 for a new episode of depressive disorder in a specific Primary Care Area of the Madrid Health Service (Community of Madrid) (former Area 6).

Results. A 74.5% of the patients with depressive disorders were women, mean age 54 years (SD 17.7). According to the ICPC classification, depression was the most frequently diagnosed disorder (48.4%), followed by anxiety (35.4%) and adjustment disorder (16.2%). A 88.5% were treated with selective serotonin reuptake inhibitors (SSRIs) (N06AB). The average total annual cost (both direct and indirect costs) was 725.2 Euros. Loss of productivity was the major cost in depressed patients treated in primary care (501.0 Euros), especially among those patients on disability. A 29.7% of the patients were referred to specialized care.

Conclusions. The prevalence and the socio-sanitary impact of depressive disorders in primary care require adequate clinical competence from the physician to guarantee proper disease management thus, minimizing the significant direct (health care resources) and indirect (loss of productivity) cost.

Keywords: Anxiety, Specialized Care, Primary Care, Depression, Health costs, Adjustment disorder

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Uso de recursos sanitarios y pérdida de productividad en pacientes con trastornos depresivos atendidos en atención primaria: Estudio InterDep

Introducción. El estudio InterDep analiza las características de los pacientes con trastorno depresivo que en los últimos años han recibido atención sanitaria en las consultas de atención primaria de un área sanitaria. Además, evalúa el uso de recursos sanitarios imputables al trastorno depresivo en este ámbito (costes directos) y la pérdida de productividad (costes indirectos). Se analiza además, la derivación a atención especializada.

Métodos. Estudio observacional multicéntrico, retrospectivo realizado a partir de los registros informatizados de las historias clínicas recogidas en una base de datos anonimizada de 22.795 pacientes atendidos, entre 2005 y 2009, por un nuevo episodio de trastorno depresivo en los centros de salud de la antigua Área 6 de Atención Primaria del Servicio Madrileño de Salud de la Comunidad de Madrid.

Resultados. El 74,5% de los pacientes con trastornos depresivos analizados son mujeres, con una edad media de 54 años (DE 17,7). Según la clasificación CIAP, la depresión fue el diagnóstico más frecuente en la población analizada (48,4%), seguida de ansiedad (35,4%) y trastorno adaptativo mixto (16,2%). El 88,5% estaba tratado con inhibidores selectivos de la recaptación de serotonina ISRS (N06AB). El coste total anual promedio (costes directos y costes indirectos) fue de 725,2 euros. La pérdida de productividad labo-

ral representó el principal coste en pacientes con depresión atendidos en atención primaria (501,0 euros), principalmente en aquellos pacientes que causaron baja laboral. El 29,7% de los pacientes fue derivado a atención especializada.

Conclusiones. La prevalencia e impacto socio-sanitario de los trastornos depresivos en atención primaria requiere del médico de familia una competencia clínica apropiada para garantizar un correcto manejo de la patología, minimizando así el importante coste directo (recursos asistenciales) e indirecto (bajas laborales).

Palabras clave: Ansiedad, Atención especializada, Atención primaria, Depresión, Costes sanitarios, Trastorno adaptativo mixto

INTRODUCTION

The presence of any mental health disorder accounts for about 25% of the medical visits in primary care[1]. Specifically, in Spain, at least one out of every five visits received by the General Practitioner is related to some psychological or psychiatric problem.[2]

The most frequent mental disorder is the major depressive episode. According to the World Health Organization (WHO), there are more than 350 million persons in the world suffering from depression, although only half of them receive the care they need.[3] In Europe, life-prevalence of depressive disorders varies from 2.6% to 17.1% depending on the country.[4,5] Thus, in Spain, the annual prevalence is estimated to be 4.0% and 10.5% in one's lifetime.[6]

Depression, characterized by a state of profound sadness and loss of interest or pleasure lasting for at least two weeks and present most of the day, is a disease that generates high disability affecting the quality of life of the patient and his/her family, the social and work life.[7,8]

The objective of the treatment of depression is the total remission of the symptoms and not only partial improvement.[9] Thus, the recommended therapies combine pharmacological and non-pharmacological treatments.[10,11] The pharmacological treatments, which should be maintained for a minimum period of 4-9 months to assure the success of the treatment,[12] include first generation antidepressants (tricyclic antidepressants and monaaminooxidase inhibitors) and newer drugs, such as selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-noradrenaline reuptake inhibitors (SSNRIs) and others.

The economic costs associated to depressive disorders are high, both the direct ones, derived from use of health care resources related to the diagnosis, treatment, prevention, rehabilitation and care, as well as the indirect ones, caused by loss of employment, lower work productivity or premature death.[13,14]

A study performed in Spain, in 2004, showed that patients with mental disorders have a greater use of health care resources at all levels, regardless of age, gender and possible comorbidity, with an annual cost per patient being 851.50 Euros versus 519.20 Euros in the rest of the patients.[15] The same author, in a population study, showed that the total costs divided into health care (direct) and loss of work productivity (indirect) accounted for 32.9% and 67.1%, respectively. Specialized care accounted for 41% of the health care cost and the remaining 59% was attributed to primary care.[16]

Depression is a frequent disorder in the primary care (PC) setting, reaching an estimated point prevalence (total cases detected/total patients surveyed) between 14% and 17%.[17,18] Primary care physicians are the ones treating mental disorders and screening the referral of patients to specialized care, where many of the referred patients already have a psychopharmacological treatment prescribed by the General Practitioner. However, there are studies that indicate that mental disorders are underdiagnosed by the General Practitioner,[19,20] and that, when recognized and referred, this is not always correctly done since up to 20-30% of the patients referred because of a mental disorder do not have any mental disease which could be diagnosed according to the specialist consultant.[21-23] Thus, there is low agreement between the diagnoses issued by these two levels of care. According to a study conducted in Barcelona, the lowest coincidence percentages are found in the detection of affective (37%), anxiety (42%) and adjustment disorders (79%).[24]

The characteristics of the referred patients and the reasons behind their referral have not been studied enough in our setting and, the results can vary based on the study consulted.[25] Elderly age of the patients, presence of suicidal ideas and greater severity of the symptoms seem to be some of the factors that could determine the referral to the specialist.[26,27]

The current study proposes to increase the knowledge around the referrals to specialist care in patients with depressive disorders seen at primary care, analyzing a wide and representative population of patients seen by primary care physicians in a health care area of the Community of Madrid and assess the associated costs (direct and indirect) that these disorders represent for the National Health System and for the society.

Thus, as specific objectives, the study is aimed to describe the profile of the patient on disability and the profile of the patient referred to specialized care, identifying the differential characteristics, and to describe the pharmacotherapeutical management in primary care as well as to evaluate the annual economic impact.

METHODOLOGY

Study design

In order to achieve the objectives indicated in the previous section, a retrospective, observational, multicenter, epidemiological study was performed on the basis of the computerized registries of the clinical records collected in the Primary Care data base of the Madrid Health Service. The study was evaluated and approved by the Ethics Committee (EC) of the University Hospital Puerta de Hierro (Madrid).

Characteristics of the data base

The computerized clinical records registered in the OMI-AP computer program of the health centers of the former Primary Care Area 6 of the Madrid Health Service made up for the study data base.

In a first phase of the project, those General Practitioners with indicators of good registry in the electronic clinical record (ECR) were identified. To do so, criteria were established that made it possible to deduce which physicians of the Health Area used the ECR more frequently and with greater reliability that made it possible to elaborate a ranking of physicians who's ECRs were chosen for the next study phase. A list of global indicators was elaborated in order to measure the quality of the ECRs in their multiple dimensions to be able to analyze the quality of the ECR records and thus be able to identify the practices of "good register" and the percentage of compliance with the selected indicators. The OMI-AP computer program works with standardized classifications such as the International Classification of Primary Care (ICPC) and the International Classification of Diseases - ninth edition (ICD-9). The adequate use of these classifications and their relation with the different components of the ECR served as indexes of appropriate use of these classifications and therefore, as criteria of 'good registry'. The indicators were the disability without correct coding or discharge date, the episodes pending labeling during a long time period, erroneous ICPC coding and prescriptions that were not placed in the episode that favored them. A low score on these indicators was assimilated to a good register standard.

Processing of the data was performed, always assuring the anomyzation of the centers, their patients and health care professionals related to the clinical records analyzed in the study. The data were obtained by SQL (*Structure Query Language*) queries aimed at the clinical data base of the 28 data servers of the different health centers so that, in order to obtain the defined indicators, only the necessary fields of some tables of the data bases found in the health center servers were identified and selected.

Study population

The study population was made up of 22,795 patients with a new episode of depressive disorder who were seen in the health centers of the former Primary Care Area 6 of the Madrid Health Service during the study period and who met the selection criteria.

Patients included in the study had to be 14 years or older (using the date of the first episode as reference), have some of the diagnoses corresponding to depression/ depressive disorders (P76: depression, P74: adjustment disorder and P73: endogenous depression) and/or symptoms corresponding to depression and/or anxiety (P01: anxiety, P02: relation of grief and P03: depressed/depressive) of the International Classification of Primary Care (ICPC); receive treatment with any drug from the therapeutic group of antidepressants (N06A) during the 12 months following the diagnosis, and have a primary care clinical history including some type of clinical follow-up for the mental disorder during the 12 months following the diagnosis.

To guarantee that it was indeed a first episode of depression, patients with any prescription of antidepressants (N06A therapeutic group) during the 6 months prior to the depressive disorder were excluded from the study.

The definition of new episode of depressive disorder in the study responded to diagnostic criteria and treatment with antidepressants. It is stressed that if a patient had more than one depressive episode during the observation period, only the data from the first episode were assessed.

Study period and follow-up

The study period included from 31 January 2005 to 31 January 2009, although for evaluation purposes, it was necessary to obtain the data starting 31 July 2004, in order to evaluate the criterion "new episode of depressive disorder". Thus, since a 12-month follow-up was conducted for each patient of this cohort from the date of the first episode of depression, data were obtained up to 31 January 2010.

Study variables

The socio-demographic characteristics, characteristics of the infrastructure of the center and available income, comorbidities, number of prescriptions of the N06A therapeutic group recorded and duration of the treatment, concomitant treatments, use of health care resources (visits to primary care, referrals to specialized care and diagnostic tests) and loss of productivity (number of days of disability) -in order to calculate the direct annual costs (use of health care resources) and indirect costs (number of days on

disability) of the depression episode-were the variables analyzed in the present study.

The holders (affiliated to the Social Security) were considered "workers" and therefore susceptible of being on disability. Pensioners or the beneficiaries were not considered susceptible of being on disability.

Statistical methodology

At all times, the reliability and strictness of the analyses were guaranteed, descriptive statistics was performed for all the variables analyzed. In quantitative variables, measurements of the central tendency (mean, median and mode) and the dispersion (standard deviation) with a 95% confidence interval were shown while for qualitative variables, absolute and relative frequencies were shown. For comparison of subgroups of patients, parametric tests (Student's T or ANOVA) or nonparametric ones (Mann-Whitney or Kruskal-Wallis) were used for quantitative variables, according to the characteristics per se of the study variables. The Chi-square test was performed for qualitative variables.

Direct health care costs were calculated by applying their unit price to each one of the health care resources obtained from the list of public prices to be paid for the service by the health care services corresponding to the year 2009. The price of the medications was obtained from the national catalog of official prices of medications published by the General Counsel of Official Associations of Pharmacists (CGOCF).

In regards to the indirect health care costs, the value of one work day was obtained from the latest data published on the Wage Structure Survey of the National Institute of Statistics, where it was stated that the mean interprofessional salary in 2008 was 64.86 Euros per day of work (this unit cost was applied to one day of disability).

RESULTS

Patient data

Data were collected on a total of 22,795 patients seen in the Madrid Health Service's Primary Care Area (former Area 6) who presented a new episode of depressive disorder during the study period (Table 1). Of these, 13,857 were active social security holders (workers) and 8,938 were not (pensioners/beneficiaries of health care card). A total of 74.5% of the patients were women. Mean age was 54.0 (±17.7) years, patients in the workers' group (active holders) were younger (45.1 years) than the non-holders (67.8 years). When evaluating the third sociodemographic variable, the situation regarding Social Security showed a significant difference between workers (active holders) patients (69.1%) and pensioners (30.9%).

Regarding the **study condition,** according to the grouping of the ICPC diagnosis and symptoms shown in **study condition** shown in Table 1, depression was the most frequent disorder in the analyzed population (48.4%) followed by anxiety (35.4%) and adjustment disorder (16.2%). It was observed that anxiety symptoms (41.9%) and depressive disorder (39.4%) were predominant among the patients in the workers group, followed by adjustment disorder (18.7%), while depression was the most frequent disorder among the non-workers group (62.2%) versus 25.4% of anxiety symptoms and 12.4% of adjustment disorders.

When the **concomitant conditions** were evaluated, the mean of the associated chronic conditions (arterial hypertension, diabetes, hyperlipidemia, chronic obstructive pulmonary disease, etc.) was lower in the group of workers (0.5±0.8) than in non-workers (1.1±1.0), this difference being statistically significant (p<0.0001).

Antidepressive treatments' data

Once the patient data were evaluated, the authors studied the therapeutic management used in the 12 months following the onset of the new depressive disorder episode. To do so, qualitative (type of drug used) and quantitative variables (treatment duration and cost) were evaluated.

The **most used antidepressants** among the study patients were selective serotonin reuptake inhibitors (SSRIs) (N06AB), mainly paroxetine (37.7%), fluoxetine (22.1%) and escitalopram (20.4%) (Table 2). Table 3 shows the data of the drugs used based on whether the patient was on disability or not due to the study condition.

Regarding the **duration of the antidepressive treatments (days per year),** patients were on treatment with SSRIs (N06AB) an average of 117.19±118.89 days/year (Table 2). In relation with the fact of being on disability or not due to the study condition, the highest number of days on treatment per year was for venlafaxine, paroxetine, sertraline and citalopram (Table 4).

Finally, Table 5 shows the differences in **annual cost of antidepressive treatment**, statistically significant differences between the group with disability due to the study condition and the group without disability were found. According to the ATC code, the group on selective serotonin reuptake inhibitors (SSRIs) (N06AB) had the highest cost, followed by the group with other antidepressants (N06AX), both being greater in the group with disability, and to a larger degree, in the N06AX. The cost of the non-selective monoamine re-

Table 1 Demography and clinical characteristics based on type of user

Variable		Total (n=22,795)	Workers (n=13,857)	Non-workers (n=8,938)	*p-value*
Infrastructure of the center[1]	Low	1,429 (10.3%)	1,429 (10.3%)	1,088 (12.2%)	
	Middle	5,540 (40.0%)	5,540 (40.0%)	3,238 (36.2%)	0.2174[a]
	Very high	6,888 (49.7%)	6,888 (49.7%)	4,612 (51.6%)	
Income available	Low	3,092 (22.3%)	3,092 (22.3%)	1,909 (21.4%)	
	Middle	2,611 (18.8%)	2,611 (18.8%)	2,066 (23.1%)	<0.0001[b]
	High	3,263 (23.5%)	3,263 (23.5%)	2,155 (24.1%)	
	Very high	4,891 (35.3%)	4,891 (35.3%)	2,808 (31.4%)	
Sex	Woman	9,941 (71.8%)	9,941 (71.8%)	7,040 (78.9%)	<0.0001[c]
	Man	3,914 (28.2%)	3,914 (28.2%)	1,887 (21.1%)	
Age	Mean (SD)	45.1 (10.3)	45.1 (10.3)	67.8 (17.9)	<0.0001[d]
Work status	Active	13,756 (99.3%)	13,756 (99.3%)	1,994 (22.3%)	<0.0001[c]
	Pensioner	101 (0.7%)	101 (0.7%)	6,943 (77.7%)	
Grouped diagnosis (ICPC)	Depression (P76 + P03 + P73)	5,464 (39.4%)	5,464 (39.4%)	5,560 (62.2%)	
	Anxiety (P01)	5,807 (41.9%)	5,807 (41.9%)	2,272 (25.4%)	<0.0001[c]
	Adjustment disorder (P74 + P02)	2,586 (18.7%)	2,586 (18.7%)	1,106 (12.4%)	
Number of associated chronic conditions	0 (none)	8,710 (62.9%)	8,710 (62.9%)	2,885 (32.3%)	
	1-2	4,654 (33.6%)	4,654 (33.6%)	5,082 (56.9%)	<0.0001[a]
	3 or more	493 (3.6%)	493 (3.6%)	971 (10.9%)	
	Mean (SD)	0.5 (0.8)	0.5 (0.8)	1.1 (1.0)	<0.0001[d]

Values expressed in frequency and percentage or mean (SD)
SD: standard deviation; *p-value*: statistical significance
[1]Administrative personnel; total/partial opening; urban/rural; type of network connection; number of users
ICPC: International Classification of Primary Care. Symptoms; P01: anxiety; P02: relation of grief; P03: sadness; Diagnosis: P73: endogenous depression; P74: adjustment disorder; P76: depression
[a]Exact-Mantel-Haenszel. [b]Mantel-Haenszel. [c]Exact-Fisher. [d]Independent Student's T. [e]Chi-Square

uptake inhibitors (N06AA) was similar between those with disability and those without it.

Cost data

After evaluating data regarding the characteristics of the patients and the antidepressant treatments received, the authors analyzed the direct costs (health care resources used: pharmacological and visits), indirect cost (disability) and the total costs generated (Table 6).

Regarding **health care resources used** (drugs and visits), the average pharmacological and visits cost was 46.00±73.30 Euros and 178.30±195.80 Euros, respectively. It stands out that these were greater in the referred to specialized care group (p<0.0001). When comparing the use of health care resources in workers regarding whether the patient was or was not on disability because of the study condition, the annual medical costs of the visits to the General Practitioner and the Specialist consultant was higher in the group on disability (191.80±186.30 Euros versus 144.20±156.40 Euros, p<0.0001).

The mean annual **productivity cost** in Euros of all the patients (22,795 patients) was 501.00±1.865.00 Euros (69% of the total annual cost). In the workers group on disability due to anxiety-depressive episodes it was 2,373.10±3,469.20 Euros.

The average **total annual cost** (pharmacological,medical care cost and productivity cost) of all the patients was 725.20±1,922.40 Euros. In the workers group, these costs were statistically significantly greater (p<0.0001) (2,616.00±3,575.60 versus 181.60±179.60 Euros).

Table 2 Most used antidepressants and total duration (days/year) according to referral to specialized care

	Total (n=22,795)	No referral (n=16,019)	Referral (n=6,776)	*p-value*
Individual drugs				
Paroxetine	8,594 (37.7%)	5,756 (35.9%)	2,838 (41.9%)	<0.0001[a]
Fluoxetine	5,029 (22.1%)	3,452 (21.5%)	1,577 (23.3%)	0.0044[a]
Escitalopram	4,644 (20.4%)	2,834 (17.7%)	1,810 (26.7%)	<0.0001[a]
Citalopram	4,023 (17.6%)	2,810 (17.5%)	1,213 (17.9%)	0.5182[a]
Venlafaxine	2,660 (11.7%)	1,489 (9.3%)	1,171 (17.3%)	<0.0001[a]
Sertraline	2,705 (11.9%)	1,842 (11.5%)	863 (12.7%)	0.0087[a]
Mirtazapine	2,336 (10.2%)	1,343 (8.4%)	993 (14.7%)	<0.0001[a]
Duloxetine	1,561 (6.8%)	851 (5.3%)	710 (10.5%)	<0.0001[a]
Pharmacological groups				
Selective serotonin reuptake inhibitors (N06AB)	20,173 (88.5%)	14,062 (87.8%)	6,111 (90.2%)	<0.0001[a]
Other antidepressants (N06AX)	6,286 (27.6%)	3,755 (23.4%)	2,531 (37.4%)	<0.0001[a]
Non-selective monoamine reuptake inhibitors (N06AA)	1,644 (7.2%)	1,100 (6.9%)	544 (8.0%)	0.0023[a]
Duration (days/year)				
Selective serotonin reuptake inhibitors (N06AB)	117.1 (118.8)	114.6 (118.9)	122.9 (118.3)	<0.0001[b]
Other antidepressants (N06AX)	107.4 (126.1)	106.3 (125.2)	109.1 (127.4)	0.3810[b]
Non-selective monoamine reuptake inhibitors (N06AA)	77.8 (99.9)	83.0 (104.8)	67.4 (88.4)	0.0016[b]

Values expressed in frequency and percentage
p-value: statistical significance
[a]Exact-Fisher
[b]Independent Student's T

Patients referred to specialized care

Of the 22,795 patients seen in primary care, 29.7% (6,776 patients) were referred to specialized care (5,181 workers and 1,595 non-workers) (Table 7). In the group of patients diagnosed with depression, only 25% were sent to specialized care (2,749/11,024), while in the group with anxiety disorders, 33.5% (2,708/8,079) were referred, the referral was similar for patients with adjustment disorders (35.7%; 1,319/3,692).

SSRIs (N06AB) were used by 88.5% of all the patients, this percentage was higher in patients referred to specialized care than those not referred (90.2% and 87.8%, respectively, $p<0.0001$). Average duration (days per year) of these drugs was 117.1 days, this was also greater in the group of patients referred to the specialist (Table 2).

In the evaluation of the **direct costs,** mean annual costs of the visits in primary care was greater in the referral group (217.4±212.5 Euros *vs* 161.80±185.80 Euros; $p<0.0001$). Regarding **the productivity costs,** the average cost was also greater in the referral group (1,037.70±2,687.20 Euros) than in the non-referral group (273.90±1,312.30 Euros), the difference being statistically significant ($p<0.0001$). The **total average annual cost** in the referral group was 1,312.90±2,761.30 Euros versus 476.60±1,351.20 Euros in the non-referral group ($p<0.0001$) (Table 6).

DISCUSSION

Within the study condition, depression was the most frequent disorder in the Primary Care centers of the Former Area 6 (Madrid Health Service) (48.4%). The most common

Table 3 Most used antidepressants in workers based on disability due to study condition

	Total (n=13,857)	Without disability (n=9,045)	Disability (n=4,812)	*p-value*
Individual drugs				
Paroxetine	5,705 (41.2%)	3,556 (39.3%)	2,149 (44.7%)	<0.0001[a]
Fluoxetine	3,263 (23.5%)	2,170 (24.0%)	1,093 (22.7%)	0.0926[a]
Escitalopram	3,021 (21.8%)	1,777 (19.6%)	1,244 (25.9%)	<0.0001[a]
Citalopram	2,189 (15.8%)	1,389 (15.4%)	800 (16.6%)	0.0533[a]
Venlafaxine	1,685 (12.2%)	893 (9.9%)	792 (16.5%)	<0.0001[a]
Sertraline	1,311 (9.5%)	799 (8.8%)	512 (10.6%)	0.0006[a]
Mirtazapine	1,271 (9.2%)	676 (7.5%)	595 (12.4%)	<0.0001[a]
Duloxetine	970 (7.0%)	541 (6.0%)	429 (8.9%)	<0.0001[a]
Pharmacological groups				
Selective serotonin reuptake inhibitors (N06AB)	12,496 (90.2%)	8,090 (89.4%)	4,406 (91.6%)	<0.0001[a]
Other antidepressants (N06AX)	3,633 (26.2%)	2,027 (22.4%)	1,606 (33.4%)	<0.0001[a]
Non-selective monoamine reuptake inhibitors (N06AA)	893 (6.4%)	592 (6.5%)	301 (6.3%)	0.5368[a]

Values expressed in frequency and percentage
p-value: statistical significance
[a]Exact-Fisher

Table 4 Duration (days/year) of antidepressant treatment in workers based on disability due to study condition[a]

	Total (n=13,857)	Without disability (n=9,045)	Disability (n=4,812)	*p-value*
Individual drugs				
Paroxetine	89.1 (100.0)	90.2 (102.7)	87.3 (95.4)	0.2790[b]
Fluoxetine	92.2 (102.2)	93.4 (104.5)	89.8 (97.5)	0.3263[b]
Escitalopram	84.0 (94.2)	84.6 (94.6)	83.1 (93.6)	0.6508[b]
Citalopram	72.0 (88.9)	71.9 (88.6)	72.2 (89.5)	0.9489[b]
Venlafaxine	92.5 (101.9)	91.3 (103.0)	93.9 (100.7)	0.6084[b]
Sertraline	85.4 (96.3)	88.5 (101.4)	80.5 (87.4)	0.1271[b]
Mirtazapine	61.9 (80.3)	58.9 (79.3)	65.2 (81.3)	0.1643[b]
Duloxetine	78.0 (85.0)	75.8 (83.8)	80.6 (86.4)	0.3823[b]
Pharmacological Groups				
Selective serotonin reuptake inhibitors (N06AB)	107.3 (112.5)	105.0 (112.4)	111.5 (112.5)	0.0020[b]
Other antidepressants (N06AX)	95.4 (114.1)	89.9 (111.0)	102.4 (117.5)	0.0012[b]
Non-selective monoamine reuptake inhibitors (N06AA)	63.7 (84.4)	64.6 (86.4)	61.9 (80.3)	0.6440[b]

Values expressed in mean (SD)
SD: standard deviation; p-value: statistical significance
[a]Duration calculated in number of days of antidepressant treatment per year
[b]Independent Student's T

Table 5 Mean annual cost (in Euros) of antidepressant treatment in workers based on disability due to study condition[a]

	Total (n=13,857)	Without disability (n=9,045)	Disability (n=4,812)	*p-value*
Individual drugs				
Paroxetine	8.9 (19.0)	8.7 (19.0)	9.5 (18.8)	0.0111[b]
Fluoxetine	2.2 (6.3)	2.2 (6.5)	2.0 (6.0)	0.0662[b]
Escitalopram	5.8 (17.6)	5.2 (16.9)	6.7 (18.8)	<0.0001[b]
Citalopram	2.5 (9.8)	2.5 (9.6)	2.7 (10.1)	0.2309[b]
Venlafaxine	5.7 (23.8)	4.6 (21.6)	7.9 (27.4)	<0.0001[b]
Sertraline	1.6 (7.6)	1.5 (7.6)	1.7 (7.4)	0.2773[b]
Mirtazapine	3.2 (17.2)	2.5 (15.2)	4.6 (20.3)	<0.0001[b]
Duloxetine	9.7 (53.1)	8.0 (48.3)	12.7 (61.1)	<0.0001[b]
Pharmacological groups				
Selective serotonin reuptake inhibitors (N06AB)	21.1 (26.0)	20.2 (25.7)	22.8 (26.6)	<0.0001[b]
Other antidepressants (N06AX)	20.3 (65.8)	16.5 (59.1)	27.6 (76.3)	<0.0001[b]
Non-selective monoamine reuptake inhibitors (N06AA)	0.7 (5.9)	0.7 (5.6)	0.8 (6.4)	0.2885[b]

Values expressed in mean (SD)
SD: standard deviation; *p-value*: statistical significance
[a]According to the data of the national list of official prices of medicinal products published by the General Council of the Association of Official Pharmacists.
Annual costs (€)
[b]Independent Student's T

pharmacological treatment were the SSRIs (N06AB). The aim of the depression treatment is the total remission of the symptoms and treatment should be maintained at least 4-9 months to assure its success.[12] In the InterDep study, average number of days for the mostly used drug was 117.1 days (3.9 months).

The results highlight the costs of care for patients with a new episode of depression, both direct ones (health care cost) and indirect ones (productivity costs) in the former Area 6 of the Community of Madrid. They also highlight the fact that disability, due to the study condition, and referral to specialized care increase these costs.

In Europe, in 2010, the total cost of brain disorders (neurological and psychiatric) was 798 billion (295 billion Euros were direct medical costs, 186 billion non-direct medical costs and 315 billion indirect costs).[28] These data agree with published studies that demonstrate that in Spain the cost attributed to depression reaches 5,005 million Euros (29% of direct costs).[16,29,30] The results obtained in this study are in line with these data. A 31% of the total annual cost of treating these patients is due to direct costs (pharmacological and visits costs).

In a National Health System, the cost arising from depression basically falls on medical care and pharmacological care. Most patients with depression go to the primary care physician seeking help, although they are not always correctly diagnosed or treated. In fact, the lowest percentages of agreement occur in the detection of affective, anxiety and adjustment disorders.[24] Being able to rely on effective care for mental health problems in primary care will be a great advance for our Health System.[31] If the estimates of the WHO, stating that depression will become one of the three main causes of disability worldwide in the year 2030[32] is added to this fact, the importance of improving the population's education about mental health problems and training primary care physicians in the management of this disease becomes clear. The role of the general practitioner is also very important, not only to assure better care for patients with a new episode of depression, but also to do so with the most sustainable possible view, both for public and private Health Care.

One of the greatest advantages in this study has been working with a very extensive database that made possible to reach a large number of patients with the study condition (n=22,795).

Table 6 Mean annual costs (in Euros) of the management of the patient due to the study condition

			Referral to specialized care		
		Total (n=22,795)	No referral (n=16,019)	Referral (n=6,776)	*p-value*
Direct costs	Pharmacological costs[a]	46.0 (73.3)	40.9 (65.9)	57.9 (87.1)	<0.0001[d]
	Visits costs[b]	178.3 (195.8)	161.8 (185.8)	217.4 (212.5)	<0.0001[d]
Indirect costs	Productivity costs[c]	501 (1,865.0)	273.9 (1.312.3)	1,037.7 (2,687.2)	<0.0001[d]
Total costs (direct + indirect)		725.2 (1,922.4)	476.6 (1.351.2)	1,312.9 (2,761.3)	<0.0001[d]
			Disability		
		Total workers (n=13,857)	Without disability (n=9,045)	Disability (n=4,812)	*p-value*
Direct costs	Pharmacological costs[a]	42.2 (70.1)	37.4 (63.1)	51.2 (81.0)	<0.0001[d]
	Visits costs[b]	160.7 (168.9)	144.2 (156.4)	191.8 (186.3)	<0.0001[d]
Indirect costs	Productivity costs[c]	824.1 (2.335.7)	0.0 (0.0)	2,373.1 (3,469.2)	<0.0001[d]
Total costs (direct + indirect)		1,027.0 (2,409.1)	181.6 (179.6)	2,616.0 (3,575.6)	<0.0001[d]

Values expressed in mean (SD)
SD: standard deviation; *p-value*: statistical significance
[a]According to the data of the national list of official prices of medicinal products published by the General Council of the Association of Official Pharmacists.
[b]Health care resources are calculated by applying to each one of them their unit price obtained from the list of public prices to be paid for the health care service corresponding to the year 2009
[c]Value of one day of work in Euros obtained from the last data published on the Salary Structure Survey of the National Statistics Institute
[d]Independent Student's T

Table 7 Demographic and clinical characteristics based on referral

		Total (n=22,795)	Not referral (n=16,069)	Referral (n=6,776)	*p-value*
Worker	Yes	13,857 (60.8%)	8,676 (54.2%)	5,181 (76.5%)	<0.0001[c]
	No	8,938 (39.2%)	7,343 (45.8%)	1,595 (23.5%)	
Grouped diagnosis (ICPC)	Depression (P76 + P03 + P73)	11,024 (48.4%)	8,275 (51.7%)	2,749 (40.6%)	
	Anxiety (P01)	8,079 (35.4%)	5,371 (33.5%)	2,708 (40.0%)	<0.0001[c]
	Adjustment disorder (P74 + P02)	3,692 (16.2%)	2,373 (14.8%)	1,319 (19.5%)	
Number of associated chronic diseases	0	11,595 (50.9%)	7,636 (47.7%)	3,959 (58.4%)	
	1-2	9,736 (42.7%)	7,243 (45.2%)	2,493 (36.8%)	<0.0001[a]
	3 or more	1,464 (6.4%)	1,140 (7.1%)	324 (4.8%)	
	Mean (SD)	0.8 (1.0)	0.8 (1.0)	0.6 (0.9)	<0.0001[d]

Values expressed in frequency and percentage or mean (SD)
SD: standard deviation; *p-value*: statistical significance
ICPC: International Classification of Primary Care. Symptoms; P01: anxiety; P02: relation of grief; P03: sadness; Diagnosis: P73: endogenous depression; P74: adjustment disorder ; P76: depression
[a]Exact-Mantel-Haenszel. [b]Mantel-Haenszel. [c]Exact-Fisher. [d]Independent Student's T. [e]Chi-Square

Limitations of this study are subject to those of the design of a retrospective study. Some of them would be related to the quality of the health care providers registries in the clinical histories (infra-registry, over diagnosis due to lack of knowledge of the severity of the condition, intraprofessional variability, etc.), also to the lack of follow-up if the patients move to another health care area. Finally, there are limitations related to the data base because the information of the health care process is only collected in primary care. However, it should be stressed that a complete process was carried out in this study to assure good recording in the data base. A list of global indicators was developed that made possible to measure the quality of the electronic clinical histories and identification process of those General Practitioners with indicators of good recording in the clinical history.

Other possible limitations would be related to the classification of the disease and the definition of "new depressive disorder episode." The definition of a new depressive disorder episode in the study was based on diagnostic criteria and treatment with antidepressants criteria. Those patients with any of the diagnoses of depressive disorders/depression (P76, P74 y P73) and/or symptoms of depression and/or anxiety (P01, P02 y P03), who also had any prescription from the N06A therapeutic group following the diagnosis, were identified. Patients having a recording of any prescription from the N06A therapeutic group during the 6 months prior to the diagnosis of the new episode of depressive disorder or of the first episode, if they had more than one, were excluded.

Regarding the measurement of costs, the limitations are attributable to the information system per se that does not allow to evaluate all the costs related to the depression episode. Thus, some indirect costs, associated to the patient loss of quality of life or the socio-economic impact of the care-givers, were not considered.

However, these limitations do not invalidate the knowledge that is obtained from this type of studies, where it is possible to study, in routine clinical practice, the medical care and the associated costs of a disease in a large number of patients.

CONCLUSIONS

Within the study condition, depression was the most frequent diagnosis in the former Area 6 of Madrid Primary Care centers, the most common drug treatment being SSRIs (N06AB). Direct costs accounted for 31% of the total annual cost of caring for the patient and the remaining 69% was attributable to indirect costs (productivity costs). The total average annual cost for depressive disorders was 725.20 Euros and 1,027.00 Euros for workers (in the group with disability it was 2,616.00 Euros versus 181.60 Euros in the group without disability).

The health care and the social impact of depression treated in primary care requires appropriate clinical competence by the General Practitioner to assure an accurate management of the disease, thus minimizing the direct and indirect costs related to the management of depression disorders.

CONFLICT OF INTERESTS

The authors declare they have no conflict of interests.

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