ORIGINAL RESEARCH

Use of antidepressants in the treatment of major depressive disorder in primary care during a period of economic crisis

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Objective: To describe antidepressant (AD) use in the treatment of major depressive disorder during a period of economic crisis.

Patients and methods: This was a retrospective, observational study using population-based databases. Two periods were considered: 1) 2008–2009, precrisis, and 2) 2012–2013, economic crisis. Certain inclusion/exclusion criteria were taken into account for the study (initiation of AD treatment). Patients were followed up for 12 months. The main measures were use (defined daily doses), epidemiologic measures, strategies used and treatment persistence, referrals, and use of resources. Statistical significance was set at $P < 0.05$.

Results: In the precrisis period, 3,662 patients were enrolled, and 5,722 were enrolled in the period of economic crisis. Average age was 58.8 years and 65.4% were women. Comparing the two periods, major depressive disorder prevalence was 5.4% vs 8.1%, $P < 0.001$. During the period of economic crisis, AD use rose by 35.2% and drug expenditures decreased by 38.7%. Defined daily dose per patient per day was 10.0 mg vs 13.5 mg, respectively, $P < 0.001$. At 12-month follow-up, the majority of patients (60.8%) discontinued the treatment or continued on the same medication as before, and in 23.3% a change of AD was made.

Conclusion: Primary health care professionals are highly involved in the management of the illness; in addition, during the period of economic crisis, patients with major depressive disorder showed higher rates of prevalence of the illness, with increased use of AD drugs.

Keywords: consumption, antidepressants, economic crisis

Introduction

Since about 2007, the socioeconomic situation in most European countries has worsened, resulting in higher levels of national debt and a decline in gross domestic product.[1,2] The majority of European countries have been affected by the economic crisis, but Spain is one of the countries that has suffered the worst consequences, among which are high rates of unemployment and a deterioration in finances, with anticrisis policies based on a reduction of spending on social welfare.[3,4]

The economic crisis has negative effects on the physical and mental health of the population.[4] Also, unemployment and other associated factors (impoverishment, social isolation, or unhealthy behaviors) are related to a higher prevalence of mental disorders in general and to depressive disorder in particular.[5,6] Depression is a major public health problem because of its high prevalence and impact on the use of health resources and on the individual's productivity.[7] According to some studies, the estimated overall annual prevalence of major depressive disorder (MDD) in Spain is 3.9% and lifetime prevalence is estimated at 10.5%. A total of 14% of patients seen

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in primary care (PC) in Spain have MDD.[8] Some studies have shown a significant increase in this disorder since the financial crisis began. Lee et al[9] (Asia) described an increase in MDD between 2007 and 2009, from 8.5% to 12.5%, and observed that pattern and severity the symptom's of depression were similar in both periods. Economou et al[10] (Greece) showed that the impact of the economic crisis on the mental health of the population is widespread and that health services should consider prevention of MDD as well as its diagnosis and appropriate treatment as a priority. In our country (Spain), Gili et al[11] concluded that the economic recession has increased the prevalence of mental disorders and alcohol abuse among patients in PC, especially in families suffering from unemployment and unable to make their mortgage payments. Iglesias García et al[12] in a particular region, Asturias, showed that the variation in socioeconomic indicators during the economic crisis is not associated with any increase in the demand for care for mental disorders but that, nevertheless, there is a negative correlation between the unemployment rate and the demand for care.

Antidepressants (ADs) are the mainstay of pharmacological treatment for MDD in order to achieve sustained remission of the symptoms.[13] As a result, in parallel with the increase in the prevalence of MDD, a rise in AD drug consumption has been observed during the period of economic crisis, although it is unknown whether there have been any changes in the prescription's pattern.[14,15] The available evidence regarding prescribing patterns of these patients in routine clinical practice settings is scarce, so the conduct of this study may be of interest.

The aim of the study was to describe the prescribing patterns and long-term use of ADs as treatment for MDD, during a period of economic restriction, in the PC health setting and in a context of routine clinical practice. In addition, the referral to specialists' rate and persistence to treatment was assessed.

Patients and methods
Design and study population
A retrospective, longitudinal, multicenter, observational study was conducted, based on a review of the medical records (computerized databases with dissociated data) of patients followed up in an outpatient setting. The study population consists of patients treated at the seven PC centers and at the Hospital Municipal of Badalona (on an outpatient basis), under the management of Badalona Serveis Assistencials, a service provider under contract with the Catalan Health Service. The population served by these centers is predominantly urban and mainly industrial working class of lower-middle socioeconomic status.

Inclusion and exclusion criteria
All patients in the study population who were diagnosed with MDD according to International Classification of Primary Care-2 (ICPC-2)[16] code P76, either as a first recurrent episode or prevalent and who started on a new AD treatment regimen during 2008–2009 (precrisis period) or 2012–2013 (period of economic crisis) were included in the study. These patients (in the two study periods) had to meet the following characteristics: 1) age ≥18 years; 2) be treated with an AD in the N06A subgroup (as per Anatomical Therapeutic Chemical codes);[17] 3) must not have received any AD treatment within 12 months prior to the diagnosis (to be sure that it was a new episode in prevalent cases); 4) the prescription had to fulfill criteria for minimum adequate treatment length (at least 60 days of treatment after the first AD prescription); 5) had to be active patients in the database for a minimum of 12 months before a new AD treatment; 6) had to be enrolled in the long-term medication prescription program with a record of daily doses, time interval, and duration of each treatment being administered; two or more prescriptions during the follow-up period; and 7) a regular follow-up of these patients during the course of the study period had to be ensured (two or more health data entries in the computer system). Excluded from the study were 1) patients transferred to other centers or those who were registered elsewhere and 2) patients who were permanently institutionalized.

Study populations and follow-up periods
There were two study groups: 1) patients who started AD treatment during the 2008–2009 period (precrisis) and 2) those who started AD treatment during the 2012–2013 period (period of economic crisis). Patients were followed up for 12 months from the date the AD drug was initially prescribed. The patients were included in separate groups.

Diagnosis of MDD
The records of patients who were diagnosed with MDD according to ICPC-2 (code P76) were obtained.[16] Only MDD of P76 code was included.

Sociodemographic and comorbidity variables
The sociodemographic variables studied were age (continuous and ranges), occupational status (active worker/pensioner),

sex, and years since onset of the disease (only recurrent cases).

The comorbidity variables as well as personal history based on ICPC-2[16] classification were hypertension (K86, K87); diabetes mellitus (T89, T90); dyslipidemia (T93); obesity (T82); active tobacco abuse (P17); alcohol abuse (P15, P16); any type of organ failure (heart, liver, and kidney); ischemic heart disease (K74, K75, K76); cerebrovascular accident (K90, K91, K93); dementia or memory disturbances (P70, P20); neurological diseases: Parkinson's disease (N87), epilepsy (N88), multiple sclerosis (N86), and other neurological diseases (N99); and malignant neoplasms (all types: A79, B72–75, D74–78, F75, H75, K72, L71, L97, N74–76, T71–73, U75–79, W72–73, X75–81, Y77–79). The following comorbidity summary measures were used for each patient treated: 1) the Charlson Comorbidity Index[18] as an indicator of the severity of the patient's condition and 2) an index of comorbidity (the Adjusted Clinical Groups System), which classifies patients according to isoresource consumption group.[19] The software includes the resource utilization bands that are used to rank patients on the basis of their overall morbidity and group the individuals into one of five mutually exclusive categories (1: healthy or very low morbidity, 2: low morbidity, 3: moderate morbidity, 4: high morbidity, and 5: very high morbidity).

Medications given, persistence with treatment, and resource use

Active ingredients (molecule) from the N06A subgroup AD drugs indicated for the treatment of MDD according to the Anatomical Therapeutic Chemical classification system[17] were obtained, as well as those of the concomitant medications including sedatives/hypnotics (N05C) and antipsychotics (N05A). The information was obtained from the medication dispensing records on file in the CatSalut (Catalan Health Service) electronic prescription system through the *Registro Central de Medicamentos y Productos Sanitarios*. The choice of drug for each individual patient was determined by the attending physician according to routine clinical practice. AD use was obtained through the defined daily dose (DDD) and also from expenditures (retail price of each package prescribed).[17]

The following options were considered as possible strategies for treatment discontinuation (completion) and/or change in AD treatment by the PC or specialist physician: 1) change in AD treatment (selection of a new drug); 2) adding another AD (combination) or adding a new drug without any intrinsic AD properties (an AD booster, such as lithium and atypical antipsychotics), and 3) an increase in the dose of the initial AD.

Persistence with treatment was defined as the length of time, measured in months (discontinuation or switch) at least 60 days after the initial prescription. In order to assess direct resource use, the number of and reasons for referral to a psychiatrist specialist and/or mental health referral center were obtained. It was found that the main reasons were 1) the severity of the episode, 2) lack of response to treatment, and 3) other reasons. The number of visits in PC and specialized care (psychiatry) were also recorded. The number of days of temporary disability were recorded as indirect resource use.

Confidentiality of information

The confidentiality of the records (which are anonymous and unlinked) has been respected in this study, in accordance with Organic Law 15/1999, of December 13, concerning the protection of personal data. The study was classified by the Spanish Agency for Medicines and Health Products (SAMHP) and received approval from the Clinical Research Ethics Committee of the Hospital Universitari Germans Trias i Pujol in Badalona.

Statistical analysis

To ensure the quality of the records, data validation was performed. Univariate descriptive statistical analysis was performed by which mean values, typical/standard deviation, 95% confidence intervals, and interquartile range (median and 25–75 percentiles) were calculated. Normality of the distribution was tested using the Kolmogorov–Smirnov test. Analysis of variance, chi-squared test, and Pearson's linear correlation test were used. SPSS/Win version 17.0 was used, and threshold for statistical significance was set at $P < 0.05$.

Results
General characteristics

Out of an initial population of 89,353 people aged ≥18 years, a total of 74,163 were seen during the preeconomic crisis period (2008–2009). A total of 4,005 of these patients had a diagnosis of MDD, and in the final analysis, there were a total of 3,662 patients who met the inclusion/exclusion criteria and were able to be followed for the duration of the study period (Figure 1). During the period of economic crisis (2012–2013), out of an initial population of 90,831 people aged ≥18 years, 74,758 were seen. A total of 6,055 patients were diagnosed with MDD and, at the end, a total of 5,722 were analyzed (Figure 1).
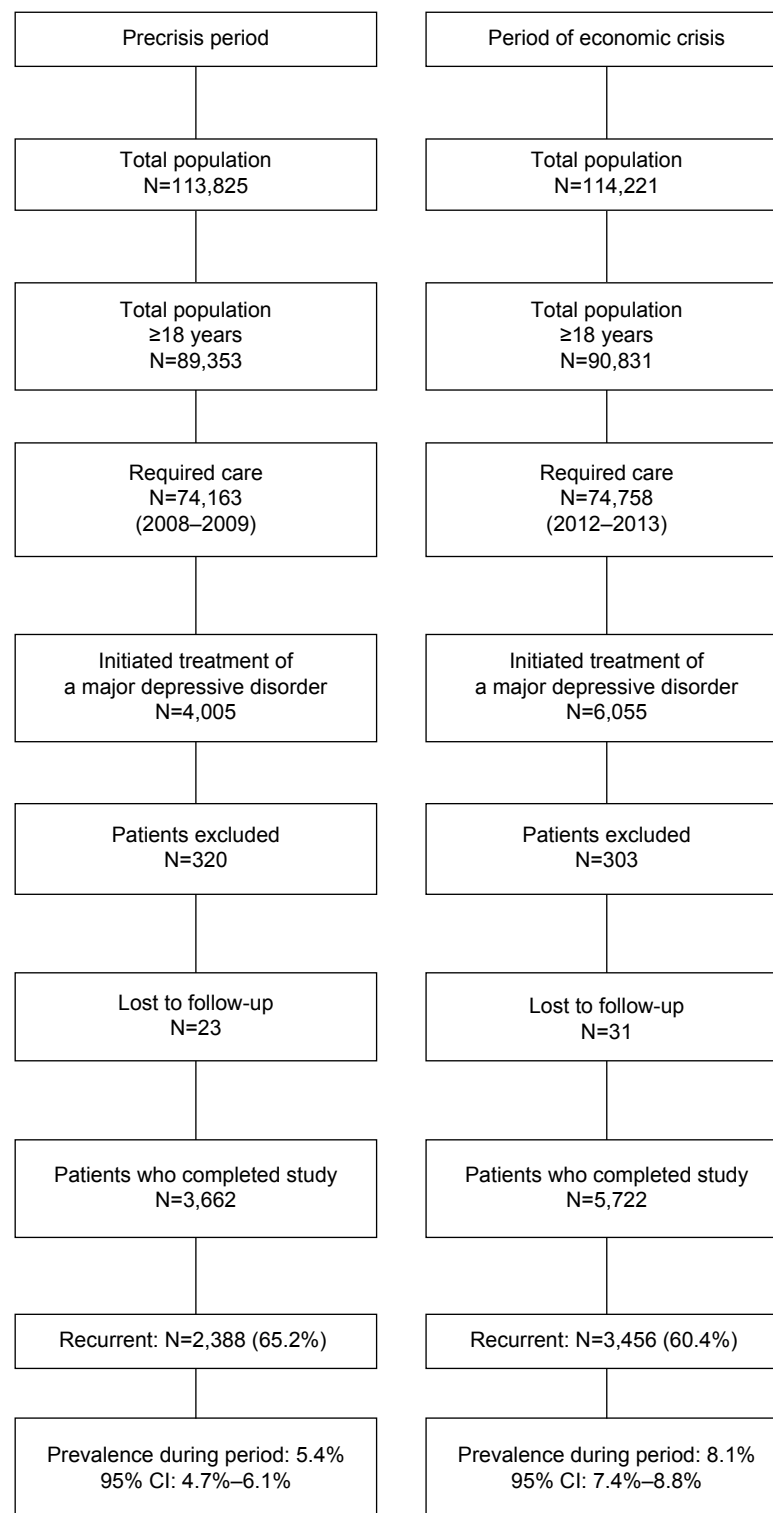
Figure 1 General outline of the study.
Abbreviation: CI, confidence interval.

A comparison of the two periods showed that the prevalence of diagnosed MDD was 5.4% (95% confidence interval: 4.7%–6.1%) in the precrisis period, as opposed to 8.1% (95%: 7.4%–8.8%), $P<0.001$ in the period of economic crisis.

Table 1 shows the baseline characteristics of the patients with a new episode of MDD in each study period. Mean age was 58.8 years, 65.4% were women, and resource utilization band score was 2.7 points. Generally speaking, dyslipidemia (53.9%), hypertension (41.2%), and obesity (22.3%) were the

Table 1 Baseline characteristics of the patients in each study period

Study groups	Precrisis period	Period of economic crisis	Total	P-value
Number of patients				
N (%)	3,662 (39.0)	5,722 (61.0)	9,384 (100)	
Sociodemographic characteristics				
Mean age, years	58.0 (15.7)	59.3 (15.6)	58.8 (15.6)	<0.001
18–44 years	20.5%	19.6%	19.9%	
45–64 years	45.0%	45.2%	45.2%	
65–74 years	17.0%	18.8%	18.1%	
>74 years	17.5%	16.4%	16.8%	0.091
Sex (women)	64.7%	65.8%	65.4%	0.257
Occupational status, retired	44.6%	46.0%	45.5%	0.200
Overall morbidity				
Mean Charlson's index	0.5 (0.7)	0.5 (0.7)	0.5 (0.7)	0.804
Mean RUBs	2.8 (0.7)	2.7 (0.7)	2.7 (0.7)	0.101
1 (very low comorbidity)	1.4%	2.5%	2.1%	
2 (low comorbidity)	32.0%	37.7%	35.4%	
3 (moderate comorbidity)	55.8%	50.5%	52.6%	
4 (high comorbidity)	9.2%	8.2%	8.6%	
5 (very high comorbidity)	1.6%	1.1%	1.3%	0.071
Associated comorbidities				
Hypertension	40.0%	42.0%	41.2%	0.053
Diabetes mellitus	17.8%	18.3%	18.1%	0.560
Dyslipidemia	53.1%	54.4%	53.9%	0.193
Obesity	21.8%	22.7%	22.3%	0.314
Active smokers	23.6%	22.1%	22.7%	0.090
Alcohol abuse	3.8%	3.1%	3.4%	0.082
Ischemic heart disease	6.5%	5.8%	6.1%	0.187
Cerebrovascular accident	11.3%	11.3%	11.3%	0.917
Cardiovascular events	15.7%	15.4%	15.5%	0.681
Organ failure	15.9%	16.2%	16.1%	0.771
Asthma	8.1%	7.3%	7.6%	0.205
COPD	7.8%	8.8%	8.4%	0.109
Neurological diseases	2.1%	2.1%	2.1%	0.896
Dementia (all types)	5.5%	5.2%	5.3%	0.450
Malignant neoplasms	11.9%	10.6%	11.1%	0.071
Characteristics of the illness				
Evolution of the illness, years	4.8 (4.0)	5.5 (5.0)	5.2 (4.7)	<0.001
Prevalent cases (N=5,844)	65.2%	60.4%	62.3%	<0.001

Notes: Values are expressed as percentage or mean (standard deviation). P indicates statistical significance.
Abbreviations: RUBs, resource utilization bands; COPD, chronic obstructive pulmonary disease.

most frequent comorbidities. Of the 9,384 episodes of MDD (start of treatment), 3,662 (39.0%) occurred in the precrisis period and 5,722 (61.0%) in the period of economic crisis. Overall, the two groups were comparable.

AD drug use

Table 2 provides the total AD drug use and expenditure during the two study periods. During the period of economic crisis, the total consumption of ADs (measured in DDD) rose by 35.2% (precrisis: 26,728,274 mg; period of economic crisis 56,446,109 mg). This increase in total AD consumption was mainly due to the other ADs (44.2%) and selective serotonin reuptake inhibitors (SSRIs, 37.4%) class groups, whereas there was a decline in the use of tricyclic ADs (−42.2%). Overall, the rate of consumption per patient was

higher (DDD/patient/day; 10.0 mg vs 13.5 mg, $P<0.001$). Per active ingredient, increases in the percentage of use of sertraline (12.1% vs 15.3%, $P<0.001$), escitalopram (12.7% vs 13.2%, $P=0.001$), and duloxetine (7.8% vs 9.7%, $P<0.001$) were noted. These differences between the two periods were statistically significant.

During the period of economic crisis, pharmaceutical spending on ADs per patient decreased in comparison to the precrisis period (€392 as opposed to €241, difference: −38.7%, $P<0.001$). Percentagewise, by active ingredient, the highest expenditure was on duloxetine (17.8% in the precrisis period compared to 29.8% in the period of economic crisis, $P<0.001$).

Drug consumption, in general, as well as use of ADs as first line of treatment (initial prescription) per patient during

Table 2 Total pharmaceutical spending and consumption of antidepressants during the two study periods

ATC code – antidepressant	Precrisis period (2008–2009)						DDD/patient	Period of economic crisis (2012–2013)					DDD/patient
	DDD (mg)	Amount (mg)	Amount/DDD	%	Spending	%		Amount (mg)	Amount/DDD	%	Spending	%	
Tricyclic antidepressants													
N06AA02 – Imipramine	100	8,633,600	86,336	0.3	898	0.1	23.6	23,830,750	238,308	0.4	1,424	0.1	41.6
N06AA04 – Clomipramine	100	54,116,640	541,166	2.0	9,293	0.6	147.8	62,643,000	626,430	1.1	16,997	1.2	109.5
N06AA06 – Trimipramine	150	387,200	2,581	0.0	44	0.0	0.7	6,637,620	44,251	0.1	11,703	0.9	7.7
N06AA09 – Amitriptyline	75	39,667,968	528,906	2.0	7,567	0.5	144.4	2,061,625	27,488	0.0	376	0.0	4.8
N06AA10 – Nortriptyline	75	1,936,400	25,819	0.1	435	0.0	7.1	1,145,500	15,273	0.0	107	0.0	2.7
N06AA21 – Maprotiline	100	6,433,200	64,332	0.2	958	0.1	17.6	17,657,100	176,571	0.3	2,506	0.2	30.9
Subtotal		111,175,008	1,249,141	4.7	19,195	1.3	341.1	113,975,595	1,128,321	2.0	33,113	2.4	197.2
SSRIs													
N06AB03 – Fluoxetine	20	79,952,128	3,997,606	15.0	55,555	3.9	1,091.6	157,567,920	7,878,396	14.0	39,383	2.9	1,376.9
N06AB04 – Citalopram	20	75,734,400	3,786,720	14.2	99,412	6.9	1,034.1	165,318,720	8,265,936	14.6	88,836	6.5	1,444.6
N06AB05 – Paroxetine	20	104,114,432	5,205,722	19.5	271,555	18.9	1,421.6	192,558,980	9,627,949	17.1	136,615	9.9	1,682.6
N06AB06 – Sertraline	50	162,328,320	3,246,566	12.1	70,868	4.9	886.6	431,292,500	8,625,850	15.3	88,013	6.4	1,507.5
N06AB08 – Fluvoxamine	100	868,800	8,688	0.0	475	0.0	2.4	30,990,000	309,900	0.5	2,227	0.2	54.2
N06AB10 – Escitalopram	10	33,987,904	3,398,790	12.7	236,029	16.4	928.1	74,593,360	7,459,336	13.2	165,563	12.0	1,303.6
Subtotal		456,985,984	19,644,093	73.5	733,894	51.1	5,364.3	1,052,321,480	42,167,367	74.7	520,638	37.8	7,369.3
Other antidepressants													
N06AX03 – Mianserin	60	3,161,120	52,685	0.2	1,438	0.1	14.4	8,781,400	146,357	0.3	2,145	0.2	25.6
N06AX05 – Trazodone	300	52,603,200	175,344	0.7	10,490	0.7	47.9	191,958,000	639,860	1.1	25,261	1.8	111.8
N06AX11 – Mirtazapine	30	29,672,640	989,088	3.7	85,788	6.0	270.1	5,191,710,000	1,730,570	3.1	71,377	5.2	302.4
N06AX12 – Bupropion	300	4,968,000	16,560	0.1	8,614	0.6	4.5	7,892,850,000	263,095	0.5	36,188	2.6	46.0
N06AX16 – Venlafaxine	100	248,391,408	2,483,914	9.3	316,899	22.1	678.3	47,967,484,000	4,796,748	8.5	219,825	16.0	838.3
N06AX18 – Reboxetine	8	206,976	25,872	0.1	2,926	0.2	7.1	71,736,000	89,670	0.2	4,371	0.3	15.7
N06AX21 – Duloxetine	60	125,212,416	2,086,874	7.8	255,084	17.8	569.9	32,740,995,000	5,456,833	9.7	410,073	29.8	953.7
N06AX22 – Agomelatine	25	117,600	4,704	0.0	2,596	0.2	1.3	68,220,000	27,288	0.0	53,128	3.9	4.8
Subtotal		464,333,360	5,835,041	21.8	683,836	47.6	1,593.4	1,140,069,350	13,150,421	23.3	822,368	59.8	2,298.2
Total		1,032,494,352	26,728,274	100	1,436,924	100.0	7,298.8	2,306,366,425	56,446,109	100	1,376,120	100.0	9,864.8

Abbreviations: ATC, Anatomical therapeutic chemical classification system; DDD, defined daily dose; SSRIs, selective serotonin reuptake inhibitors.

the two periods studied is described in Table 3. Average consumption of prescribed ADs per patient during the two periods was similar, so was the use of antipsychotics (quetiapine) and lithium. However, there was a slight decline in average use of sedatives/hypnotics per patient (68.8% vs 66.2%; *P*=0.008). Lorazepam (15.4%), alprazolam (11.9%), and lormetazepam (10.4%) were the most commonly prescribed drugs. With regard to the use of ADs as first line of treatment per therapeutic class, a slight increase in the frequency of use of other ADs (22.7% vs 23.8%; *P*<0.001) is to be noted, especially for prevalent patients.

Persistence to treatment

Table 4 shows the initial persistence to treatment with ADs, treatment strategies, referrals, and resource use during the two periods studied. At 6 months, persistence to treatment was 49.7% in contrast with 51.8%, in the precrisis and crisis periods, respectively (*P*=0.002). On the other hand, the strategies followed during the year of follow-up were similar for the two periods: 61.7% of patients discontinued their medications in the first period compared to 60.4% in the second. Of the patients whose initial treatment regimen was modified, 1,401 (38.3%) in the precrisis period and

2,316 (40.1%) in the period of economic crisis, the majority, 60.8%, switched to another medication, while dosage was increased in 23.3% of cases and in 15.9% the medication was boosted.

Resources use and therapeutic strategies

During the period of economic crisis, there was a higher proportion of referrals to a specialist (20.3% vs 23.8%; *P*<0.001). The average number of visits to PC also rose (8.2% vs 9.9%; *P*<0.001), although there were no significant changes in the average number of visits to specialist care. A lower average number of days of temporary disability was observed (13.6 as opposed to 8.9; *P*<0.001).

The therapeutic strategies used for AD treatment are described in Table 5. At 12-month follow-up, the majority of patients (60.8%) had discontinued their initial medication; in 23.3%, a change in AD prescription was made, 9.1% were given an additional AD, and in 6.5%, the AD dose was increased. There were no statistically significant (relevant) differences between the two periods analyzed (precrisis and period of economic crisis).

Generally speaking, patients for whom no changes were made in AD medications were new cases (precrisis: 40.6%;

Table 3 Consumption of medicines and use of antidepressants in first line of treatment (initial prescription) during the two study periods

Groups	Precrisis period	Period of economic crisis	*P*-value
Number of patients			
N (%)	3,662 (39.0)	5,722 (61.0)	
Consumption of medicines[a]			
Average number of antidepressants	1.4 (0.7)	1.4 (0.7)	0.559
One	68.8%	69.7%	
Two	24.2%	22.1%	
Three or more	7.0%	8.1%	0.071
Antipsychotics	10.7%	9.5%	0.074
Hypnotics/sedatives	68.8%	66.2%	0.008
Lithium	2.5%	2.6%	0.084
First line of treatment[b]			
Tricyclic antidepressants	8.0%	6.9%	0.089
N06AA04 – Clomipramine	1.8%	1.7%	
N06AA09 – Amitriptyline	5.3%	4.4%	
SSRIs	69.3%	69.3%	0.382
N06AB03 – Fluoxetine	14.0%	12.4%	
N06AB04 – Citalopram	15.2%	17.3%	
N06AB05 – Paroxetine	22.2%	19.8%	
N06AB06 – Sertraline	8.5%	9.3%	
N06AB10 – Escitalopram	9.4%	10.3%	
Other antidepressants	22.7%	23.8%	<0.001
N06AX05 – Trazodone	1.7%	2.5%	
N06AX11 – Mirtazapine	3.9%	3.9%	
N06AX16 – Venlafaxine	9.3%	9.5%	
N06AX21 – Duloxetine	7.0%	6.0%	

Notes: Values are expressed as percentage or mean (standard deviation). *P* indicates statistical significance. [a]Average use of antidepressants per patient during the two study periods. [b]Most commonly used medications in first line of treatment (initial prescription).

Table 4 Description of persistence, treatment strategies, referrals to specialist care and use of resources during the two study periods

Study groups	Precrisis period	Period of economic crisis	*P*-value
Number of patients			
N (%)	3,662 (39.0)	5,722 (61.0)	
Duration of treatment, months			
Mean (SD)	8.9 (3.7)	8.8 (3.8)	0.552
Median (P25–P75)	11.0 (5.0–12.0)	11.0 (5.0–12.0)	
Persistence with treatment			
Average, 6 months	74.3%	73.5%	0.371
95% CI	72.9%–75.7%	72.4%–74.6%	
Average, 12 months	49.7%	51.8%	0.002
95% CI	48.1%–51.3%	50.5%–53.1%	
Treatment strategy			
Discontinuation/no changes in medication	61.7%	60.4%	
Change in the initial regimen	38.3%	39.6%	0.444
Dosage increased	8.8%	9.4%	
Switch to another medication	23.0%	23.5%	
Medication boosted	6.4%	6.6%	0.597
Referrals to a specialist			
Rate of referrals	20.3%	23.8%	<0.001
95% CI	19.0%–21.6%	22.7%–24.9%	
Reasons for referral			
Lack of response to treatment	9.3%	11.0%	
Severity of the illness	7.9%	9.2%	
Other reasons/not specified	3.1%	3.6%	0.002
Use of resources			
Average number of primary care visits	8.2 (7.2)	9.9 (7.4)	<0.001
Average number of visits to a specialist	2.5 (1.8)	2.2 (1.7)	0.225
Average number of days of temporary disability	13.6 (60.9)	8.9 (48.5)	<0.001

Notes: Values are expressed as percentage or mean (mean [SD]). *P* indicates statistical significance. Persistence with treatment was defined as the length of time, measured in months (discontinuation or switch), at least 60 days after the initial prescription.
Abbreviations: CI, confidence interval; SD, standard deviation; P25–P75, 25th to 75th percentiles.

period of economic crisis: 43.3%), showed high persistence with treatment (precrisis: 58.2%; period of economic crisis: 61.2%), were treated with SSRIs (precrisis: 74.9%; period of economic crisis: 76.3%), and had a low rate of referral to a specialist (precrisis: 1.9%; period of economic crisis: 5.8%). Patients who had their AD doses increased showed low persistence with treatment (precrisis: 24.8%; period of economic crisis: 19.7%). The patients whose AD treatment regimen was changed were given a higher than average amount of AD (precrisis: 2.3; period of economic crisis: 2.3), had a higher rate of referral to a specialist (precrisis: 58.1%; period of economic crisis: 61.4%), more visits to a specialist (precrisis: 7.3; period of economic crisis: 6.6), and a higher number of days of temporary disability (precrisis: 18.5; period of economic crisis: 12.2).

Patients who were given a new AD or adjuvant treatment were for the most part prevalent cases (precrisis: 71.6%; period of economic crisis: 75.0%), with a higher percentage of referral to a specialist (precrisis: 58.1%; period of economic crisis: 51.8%), more visits to a specialist (precrisis: 6.3; period of economic crisis: 6.5), and higher percentage

use of other ADs (precrisis: 35.6%; period of economic crisis: 34.5%) and antipsychotics (precrisis: 97.9%; period of economic crisis: 92.9%). When comparing the period of economic crisis to the precrisis period, the most relevant changes were seen in patients whose AD treatment was switched or who were given additional treatment (Table 5). The medications most prescribed by specialists as second-line treatment (35.8% of the total) were 1) other ADs (22.7%), 2) SSRIs (13.1%), and 3) tricyclic ADs (3.3%). Duloxetine (6.5%), venlafaxine (5.4%), escitalopram (5.1%), citalopram (4.4%), and trazodone (2.7%) were the most commonly prescribed drugs.

Discussion
The study reveals that during the period of economic crisis, there were higher prevalence rates of diagnosis of MDD along with a higher use of AD drugs in routine clinical practice settings. It is worth noting that in the absence of a standardized methodology, caution should be exercised when interpreting the results, which should be considered within the context of the health services provider's own setting, thus

Table 5 Therapeutic strategies used for antidepressant treatment

Groups	Discontinuation of the AD[a]		Increase in dose[b]		Change of AD[c]		Association with another drug[d]	
Study periods	Precrisis	Crisis	Precrisis	Crisis	Precrisis	Crisis	Precrisis	Crisis
Number of patients								
N (%)	2.261 (61.7)	3.458 (60.4)	323 (8.8)	539 (9.4)	842 (23.0)	1.345 (23.5)	236 (6.4)	380 (6.6)
Sociodemographic characteristics								
Mean age, years	57.9 (16.2)	58.5 (16.2)	57.2 (15.2)	59.2 (14.6)*	59.1 (14.7)	59.5 (14.4)	56.2 (15.2)	65.9 (13.9)*
Sex (women)	64.0%	64.5%	65.9%	63.2%*	65.4%	69.1%*	66.5%	69.6%*
Mean RUBs	2.7 (0.7)	2.6 (0.7)	2.8 (0.7)	2.7 (0.7)	2.9 (0.7)	2.8 (0.7)	2.8 (0.7)	2.8 (0.7)
Characteristics of the illness								
Evolution of the illness, years	4.3 (3.9)	5.1 (5.0)	6.0 (4.1)	6.6 (4.7)	5.5 (4.0)	5.4 (5.2)	6.3 (3.9)**	7.6 (4.7)**
Medication								
Duration of treatment, months	9.5 (3.5)**	9.8 (3.4)**	7.6 (3.2)	7.2 (3.1)	8.1 (4)	7.9 (4)	6.4 (3.8)	5.7 (4)
Persistence with treatment	58.2%**	61.2%*,**	24.8%*	19.7%*,**	42.4%	39.8%*	28.4%**	25.0%*,**
Mean number of antidepressants	1.0 (0.0)	1.0 (0.0)	1.7 (0.6)	1.7 (0.6)	2.3 (0.7)**	2.3 (0.8)**	1.6 (0.8)	1.7 (1.0)
Tricyclics	5.9%	5.3%	9.0%	8.1%	12.5%	11.5%	10.6%	6.6%*
SSRIs	74.9%**	76.3%*,**	60.4%	65.1%*	62.0%	55.7%*	53.8%	58.9%*
Other antidepressants	19.2%	18.4%	30.7%	28.8%	25.5%	32.8%*	35.6%**	34.5%*
Antipsychotics	0.0%	0.0%	3.3%	2.5%	45.7%	40.5%*	97.9%*,**	92.9%*,**
Sedatives/hypnotics	73.1%	69.3%*	61.0%	69.0%	65.9%	71.8%*	58.7%	69.5%*
Use of resources								
Rate of referrals	1.9%**	5.8%*,**	23.2%	25.6%*	58.1%*,**	61.4%*,**	58.1%**	51.8%*
Primary care visits	7.7 (6.8)	9.2 (6.9)*	7.4 (6.6)	9.3 (5.9)*	9.6 (8.6)	11.5 (8.9)*	9.8 (6.5)	10.8 (7.3)
Specialist care visits	0.2 (0.1)	0.6 (0.2)	2.9 (1.3)	2.7 (1.4)	7.3 (2.7)**	6.6 (2.4)**	6.3 (2.6)**	6.5 (2.1)**
Average number of days of temporary disability	11.0 (52.3)	8.8 (43.9)*	12.7 (52.8)	8.6 (52.2)*	18.5 (83.4)**	12.2 (56.9)*,**	11.0 (49.3)	7.8 (50.0)*

Notes: Values are expressed as percentage or mean (standard deviation). [a]Same treatment: no changes or discontinuation of treatment (no changes to initial prescription for 12 months). [b]Increase in the dose of the antidepressant. [c]Change of antidepressant medication. [d]Addition of another antidepressant or adjuvant treatment. *P<0.05 comparison of the two study periods (precrisis vs period of economic crisis). **P<0.05 compared to the total group in each study period.
Abbreviations: AD, antidepressants; RUBs, resource utilization bands; SSRIs, selective serotonin reuptake inhibitors.

compelling us to be very careful about the external validity of the findings. One of the strengths of the study relies on the large number of patients included in the study population, keeping in mind that few studies on this topic have been reported so far.

In our study, when comparing the two periods, the analysis showed that prevalence rose from 5.4% to 8.1% in the period of economic crisis. By way of example, Gili et al[20] and Bartoll et al[5] showed that the presence of an economic recession results in a higher frequency of mental health problems, especially in families suffering from unemployment and who face difficulties in making mortgage payments. Likewise, the study by Agudelo-Suárez et al[21] describes how mental health of immigrant workers has worsened in Spain during the economic crisis. In most countries, periods of economic crisis cause public health budgets to be reduced and, in general, mental health issues are considered as a low-priority area due to the stigma of mental illness, among other reasons. Nevertheless, the results are clear: mental health is adversely affected during periods of economic hardship. The study by Lee et al[9] shows that 1) the impact of the economic crisis on the mental health of the population is widespread; 2) there is a lack of population-based research on the relationship between economic uncertainty and specific mental disorders; 3) prevalence of MDD between 2007 (8.5%) and 2009 (12.5%) increased according to DSM-IV criteria; and 4) the pattern of symptoms and severity of episodes during the two periods were similar. Our results are consistent with those of these authors, although in our study the potential causes for MDD were not ascertained.

During the period of economic crisis, consumption of ADs for treatment of MDD increased by 35.2% while pharmaceutical spending decreased by 38.7%. This pattern is also consistent with the literature reviewed. In most countries, a trend over time toward a rise in prescription of ADs has been observed, although this may also be explained by the increase in the recurrence of mood disorders, by a higher rate of detection and diagnosis by PC physicians, as well as the approvals to extend therapeutic indications for these medications (adjustment disorders, chronic neuropathic pain, detoxication, etc).[7,8] In Spain, according to data published by the SAMHP in 2015, the use of AD drugs tripled between 2000 and 2013. The sharpest rise in spending on ADs was for SSRIs with, for example, escitalopram going from 20.4 daily doses per inhabitant in the year 2000 to 52.9 daily doses per inhabitant in 2013. SSRIs accounted for 70.4% of the total consumption of ADs in 2013. Similarly, the consumption of venlafaxine and duloxetine has also risen while there has

been a decline in the use of tricyclic ADs.[22,23] Our results are also consistent with these findings from the SAMHP with regard to the consumption of ADs for MDD.

Regarding the decline in pharma spending of AD drugs, the entry into effect of reference pricing for drugs in Spain may be the main reason for this reduction in pharmaceutical expenditures despite the increase in ADs consumption.

A high consumption of benzodiazepines is to be noted, in contrast with the results of studies in other countries where the use of this type of drugs is lower and where stricter prescribing rules are followed.[24,25] It might be that in our environment there is some discrepancy in clinical practice when it comes to following international recommendations and that patients are hard to persuade about the need to discontinue using this type of medication.

In our study, at 12-month follow-up, the majority of patients (60.8%) had discontinued their initial medication, a change in AD was made in 23.3% of cases, and in 6.5% the AD dose was increased. There were no significant differences between the two study periods studied. With respect to the attitude of PC physicians, our results highlight two aspects that contrast with the recommendations of Clinical Practice Guidelines: 1) a relevant number of patients continue with the initial treatment and 2) the percentage of patients who are prescribed an increase in the dosage of their AD medication is low. Patients whose AD medication was not changed tended to be those who started treatment (possibly with poor compliance) so they probably achieved some improvement, although not enough, and a more conservative attitude was adopted with them. This can be due to side effects or interactions with other medications, patient preferences, inadequate training of the practitioners in pharmacotherapy, associated medical conditions, or other effects not quantified in this study. Initiating concomitant treatment with lithium or other drugs is not standard clinical practice in PC. When there is no response to an AD after 6–8 weeks of treatment, the guidelines from the scientific associations recommend switching to another AD, first within the same class and later from a different class. Therefore, it seems that in the PC setting, there is little information based on data from studies about which strategies might be most appropriate for the management of treatment-resistant depression and what steps should be taken for the adoption of alternative therapies, which should always be individualized for each patient. However, the issue is open to debate. Substitution or change strategies are widely used, and some studies suggest that it may make sense to follow this type of strategy. Although Thase[26] described a response rate of 50% by switching from serotonergic drugs to tricyclic agents,

it seems that switching to venlafaxine may provide a higher rate of therapeutic response.[27] The truth of the matter is that there are no conclusive data as to what is the best available treatment alternative for treatment-resistant depression.[28]

During the period of economic crisis, there were more recurrent cases, patients showed a longer time from diagnosis, greater persistence with treatment, more referrals to a specialist, more visits, and fewer days of temporary disability. It is difficult to compare these results as so many different factors are involved, such as the training of health care professionals, the organizational models, resources available and services offered, the psychiatric comorbidities, and the type of patients. Furthermore, in our case, we have only included patients referred to a specialist or center for psychiatric care; referrals to psychotherapy services or social worker were not quantified. Our results are similar to those of Krahn et al[29] who observed that younger patients and those with suicidal tendencies (seriousness of illness) and recurrent MDD (prevalent cases) had consumed two or more AD (with a lack of response to treatment). With regard to rates of referral to specialist care, our results are similar to those described in the INTERDEP study, which was conducted in the Autonomous Community of Madrid (Spain).[30]

In this study, limitations inherent to population data-based studies apply, such as underrecording of the illness under investigation or potential variations in the registry of their condition by professionals and patients. Potential limitations of the study have to do with certainty in determining the diagnosis of the illness, possible inaccuracies in the diagnostic codes for MDD, and other comorbidities and also in measuring the remission of symptoms or treatment adherence. It is also possible that most severe cases have not been included in the study as these are usually managed at mental health care centers. Likewise, other biases should be considered such as failure to account for the presence or absence of psychotherapeutic interventions or consultations with other medical professionals providing care outside the national health system (private health) as well as the absence of some variables that could influence the final results, such as the patient's socioeconomic status or exposure to work and changes in drug dosage regimens, etc.

Future approaches with regard to this analysis should be focused on replicating the study in other health care institutions and making more studies of cost-effectiveness and treatment adequacy available. In the field of mental health, it becomes essential to strengthen protective factors from the impact of the crisis, especially for vulnerable subgroups such as children, young people, the elderly, and the unemployed or people with severe financial problems. Countries that have a strong social protection system require minor changes to reduce this impact.

Conclusion

To conclude, during the period of economic crisis, there were higher prevalence rates of diagnosis of MDD along with a higher use of AD drugs in routine clinical practice settings. In addition, primary health care professionals are highly involved in the management of the illness.

Disclosure

The authors report no conflict of interest in this work.

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