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A comparative cost-analysis of initiating pregabalin or SSRI/SNRI therapy in benzodiazepine-resistant patients with generalized anxiety disorder in Spain

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Objective: To compare the relative healthcare costs, from the perspective of the Spanish National Healthcare System (NHS), of initiating treatment with either pregabalin, or SSRI/SNRI, as add-on therapies, in patients with generalized anxiety disorder (GAD), who are resistant to benzodiazepine-based therapy (BR).

Methods: BR out-patients with GAD (DSM-IV) who were included in a 6-month, prospective, multicentre, observational cohort study were selected for this post-hoc economic analysis. BR was defined as insufficient response, with persistence of symptoms of anxiety (HAM-Anxiety scale≥16), after a 6-month course of benzodiazepines. Patients had not been previously exposed to pregabalin or SSRI/SNRI. Healthcare resource utilization (drugs, medical visits, hospitalizations, etc.) associated with GAD was collected at baseline and end-of-trial visits. Related costs were estimated at each visit and adjusted changes were compared using ANCOVA.

Results: A total of 128 patients with refractory GAD were treated with pregabalin and 126 SSRI/SNRI. Compared with SSRI/SNRI, pregabalin was associated with significantly lower percentage of benzodiazepines users; 57.0% *vs* 87.3%, p<0.001, and greater reduction in medical visits; -15.1 *vs* -13.0, p=0.029. Mean total healthcare resource utilization costs decreased significantly in the pregabalin cohort only; -€289 (p=0.003), although six months costs were not significantly different in both groups; €977 *vs* €822, respectively.

Conclusion: Initiating treatment with pregabalin was associated with significant reduction in medical visits and total health care resource costs of GAD compared to SSRI/SNRI in BR patients in the Spanish NHS setting. Compared with SSRI/SNRI, pregabalin therapy was accompanied by significantly less percentage of patients on concomitant benzodiazepines therapy.

Key words: Comparative cost analysis, Generalized anxiety disorder, Benzodiazepine-resistant patients, pregabalin, SSRI/SNRI

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Análisis comparativo de costes del inicio de terapia con pregabalina o ISRS/ISRN en pacientes resistentes a las benzodiazepinas con trastorno de ansiedad generalizada en España

Objetivo: Comparar los costes sanitarios relativos, desde la perspectiva del Sistema Nacional de Salud (SNS), de iniciar tratamiento con pregabalina o ISRS/ISRN como terapias añadidas, en pacientes con trastorno de ansiedad generalizada (TAG), resistentes a la terapia basada en benzodiazepinas (RB).

Método: Se seleccionaron para este análisis económico post-hoc pacientes ambulatorios con TAG (DSM-IV) y RB que habían sido incluidos en un estudio de cohortes de 6 meses, prospectivo, multicéntrico y observacional. La resistencia a las benzodiazepinas se definió como respuesta insuficiente, con persistencia de síntomas de ansiedad (escala de ansiedad HAM-A≥16), después de 6 meses de tratamiento con benzodiazepinas. Los pacientes no habían sido expuestos previamente a pregabalina ni a ISRS/ISRN. Los datos relativos al uso de recursos sanitarios (fármacos, visitas médicas, hospitalizaciones, etc.) asociadas con el TAG se recogieron en la consulta de inicio y en la final del ensayo. Los costes relacionados se estimaron en cada consulta y se compararon los cambios ajustados utilizando ANCOVA.

Resultados: Se trató un total de 128 pacientes con TAG refractario con pregabalina y a 126 con ISRS/ISRN. Al compararla con los ISRS/ISRN, la pregabalina estuvo asociada significativamente con un menor porcentaje de usuarios de benzodiazepinas; 57,0% vs 87,3%, p<0,001, y una reducción mayor de las consultas médicas; -15,1 vs -13,0, p=0,029. La media total de los costes sanitarios decreció significativamente sólo en la cohorte de pregabalina; -289€ (p=0,003), aunque a los seis meses los costes no fueron significativamente diferentes entre los grupos; 977 € vs 822 €, respectivamente.

Conclusión: Iniciar tratamiento con pregabalina está asociado con una reducción significativa de las consultas médicas y de los costes totales del TAG en los recursos de salud al compararlos con los ISRS/IRSN, en pacientes resistentes a benzodiazepinas en el sistema español de salud. En comparación con los ISRS/ISRN, la terapia con pregabalina mostró un porcentaje significativamente menor de pacientes en tratamiento concomitante con benzodiazepinas.

Palabras claves: Análisis de coste comparativo, Trastorno de ansiedad generalizada, Pacientes resistentes a las benzodiazepinas, pregabalina, ISRS/ISRN

INTRODUCTION

Anxiety disorders are among the most common psychiatric disorders, with generalized anxiety disorder (GAD) being one of the most frequent and the most common mental disorders in primary care[1-3]. Lifetime prevalence of GAD has been estimated to be 2.8% in Europe and 5.7% in the United States and, according to a large epidemiological study, 2% in Spain[1,4,5]. Health policy decision makers should not only be aware of the available clinical evidence to support the effectiveness of a drug, but also consider the financial aspects that will allow them to determine the efficiency of new treatments and thus make optimal use of the existing limited economic resources. Economic evaluations that taken into account total health care resource utilization costs in addition to drug acquisition costs are an appropriate method to estimate the economic consequences associated with the management of anxiety disorders[6].

Given its chronic evolution of symptoms, co morbidity and related disability, patients with GAD experience loss of work productivity and high medical resource use. Consequentially, the estimates of human and economic burden associated with GAD are considerable[7,8]. Estimated gross direct cost of GAD in Spain has been reported recently[9]. In a total population of 3,014 patients with GAD, the gross annual direct costs amounted to €2 million, which included prescription drugs, physician services, laboratory tests and fixed costs. Pharmaceutical costs represented more than half of the total direct costs[9]. However, the overall economic burden associated with this disease in Spain has not been yet estimated.

The pharmacological management of GAD is focused on anxiolytic drugs, either in monotherapy or in combination. Benzodiazepines are an efficacious and rapid treatment for many patients with GAD[10]. However, benzodiazepines have limited efficacy in relieving comorbid depressive symptoms and have unwanted effects such as sedation, disturbance of memory and psychomotor functions, development of tolerance, abuse or dependence, and distressing withdrawal symptoms[11-15]. Due to these potential effects, general guidance is that benzodiazepines should be restricted to short term use[14,15].

Effective treatments that may be used on a long-term basis include selective-serotonin reuptake inhibitors (SSRIs), and selective serotonin-norepinephrine reuptake inhibitors (SNRIs), with SSRIs recommended as the treatment of choice[16]. One of the major drawbacks of SSRI/SNRIs is the delayed onset of their therapeutic effect[16]. Additionally, SSRI/SNRIs are contraindicated as monotherapy in patients with co morbid bipolar disorder[17], a common coexisting morbidity in GAD patients[18,19]. Pregabalin is a calcium channel modulator that has been proven effective in the treatment of the psychic and somatic symptoms of GAD[20,21]. Pregabalin is well-tolerated in adult patients, has rapid onset of action (approximately one week), comparable efficacy to benzodiazepines and rates of discontinuation have generally been lower than those observed for both benzodiazepines and venlafaxine, a SNRI[20-23].

It is important to highlight that results from clinical trials could differ from daily clinical practice[24]. In clinical trials patients are selected according to restrictive criteria that usually exclude patients receiving several treatments, which is not necessarily the case for the many GAD patients treated in real clinical practice[22]. Healthcare resource utilization and related costs may differ depending on both the therapy and healthcare setting. The aim of this study was to compare healthcare costs of initiating treatment with pregabalin or SSRI/SNRIs in benzodiazepine-resistant outpatients with GAD treated according to current medical practice in Spain.

MATERIALS AND METHODS

Study design

The results of this economic analysis were based on data from a 6 month, multicentre, prospective observational study: the ADAN (Amplification of Definition of Anxiety) study[25]. In brief, the ADAN study was designed to elucidate the effect of broadening DSM-IV criteria for GAD and was approved by the local ethics committee of the Hospital

Clínico de San Carlos (Madrid). It was conducted according to the Helsinki declaration for research in the human being. The study was carried out between October 2007 and January 2009 in outpatient mental health centres in Spain. Due to the observational design of the study, only two visits (baseline and 6-months visit) were planned. In addition to its main objective, the ADAN study also assessed the use of healthcare resources and related costs, which were used for the present cost-analysis to compare the cost impact of initiating treatment with pregabalin versus SSRI/SNRIs.

Study population

In the ADAN study, trained psychiatrists, with at least 5 years experience in mental health diseases diagnosis were asked to select consecutive, newly-diagnosed GAD patients, according to DSM-IV criteria (APA 2000) and so-called broad criteria, until the predetermined sample size was obtained[25]. Patients of both sex, aged 18 or above, who had provided their written informed consent to participate in the study, were resistant to previous benzodiazepine therapy and had not previously received pregabalin nor SSRI/SNRIs therapy, were included in the present cost-analysis. In this analysis, only patients with a diagnosis of GAD according to DSM-IV criteria were considered eligible. Benzodiazapine resistance (BR) was defined as subjects with persistent symptoms/suboptimal response after a course of standard dose regimen with any benzodiazepine, alone or in combination, for at least 6 months prior to the baseline study visit. Persistent symptoms/suboptimal response was considered when patients showed a HAM-A scale[26,27] score > 16 and Clinic Global Impression score (CGI) (28) > 3 at baseline. To conduct this cost-analysis two groups of patients were identified for analysis from the ADAN trial. Patients were classified in the pregabalin group if they had not received pregabalin and/or SSRI/SNRIs previously and started therapy with pregabalin. Patients who started treatment with mirtazapine were included in the SSRI/SNRIs group because its anxiolytic effect is similar. Alternatively, patients were classified in the SSRI/SNRIs group if they had not received pregabalin and/or SSRI/SNRIs previously and started therapy with SSRI/SNRIs.

Use of healthcare resources

Information regarding healthcare resource utilization associated with GAD in the previous 6 month period was retrospectively collected at baseline and at the 6-months study visit, by means of a case report form which was designed *ad hoc* for this economic analysis. Health care resource utilization included the following: Drug utilization, medical visits and hospitalizations (from patients´ medical records), and non-pharmacological treatments (recorded during face-to-face patient interviews). Diagnostic tests were not recorded since this variable was considered negligible in GAD. Health care resources utilization were classified in four categories: drug treatments, non-pharmacological therapies, medical visits (psychiatrists, psychologists, general practitioner or family physicians and emergency room visits) and days of hospitalisation in a psychiatry or internal medicine wards. Non-pharmacological therapies included all those treatments used in clinical practice as an alternative to drug treatments for GAD. This included psychosocial therapy, cognitive-conductive therapy, supportive groups and relaxation sessions. Medical visit included visits to primary care, emergency department, psychologist and psychiatrist.

Estimation of costs

The perspective of the Spanish National Health System was chosen for this analysis. Direct costs per patient were calculated only. Total costs per patient (in Euros year 2009) consisted of the sum of healthcare costs during a period of 6 months before (collected at baseline visit) and after patients entered the study (collected at the 6-month visit). The costs of drugs were estimated using retail price + taxes of the cheapest generic medication or reference price from the Spanish Pharmaceutical Drug Catalogue of 2009[29]. The cost of non-pharmacological treatments, medical visits, and hospitalisations was obtained from the eSALUD healthcare costs database for 2008[30] (Table 1) updated with the 2008 healthcare inflation rate[31]. Finally, some non-pharmacological resources were priced according to expert opinion and/or directly from the vendor/provider. The direct mean cost at baseline and at the 6-months visit and change from baseline was calculated by multiplying the number of resources used in each period by their respective prices.

Statistical analysis

For statistical analysis, only patients that fulfilled all inclusion criteria and none of the exclusion criteria were included. Descriptive statistics were extracted for the continuous variables in the study, including the assessment of central tendency and dispersion statistics with its 95% confidence interval when possible. The Kolmogorov-Smirnov test was applied to check adjustment of data to a Gaussian distribution. For categorical variables, absolute and relative frequencies were calculated. A descriptive statistical analysis with values for mean and standard deviation (SD) was performed. Mann-Whitney U-test was used to compare continuous variables between the two groups of patients at baseline, while the $\chi 2$-test or the Fisher's exact test were applied for categorical data. Differences in the use of healthcare resources and costs between the two treatment groups were tested using an analysis of covariance (ANCOVA), according to the recommendations of Thompson et al[32], with sex, age and number of psychiatric and medical

Table 1 Unit costs (€) of healthcare resources (Spain)

Resources	Unit cost (€)
Non-pharmacological treatment (per session)	
Psychosocial therapy[1]	45.0
Supportive groups[2]	23.0
Relaxation[1]	13.9
Yoga/Taichi[4]	35.0
Alternative therapies / Naturopathy[5]	35.0
Cognitive-behavioural therapy[6]	50.0
Psychoanalytical therapy[2]	50.0
Occupational therapy[1]	12.1
Drug addict rehabilitation therapy[3]	45.0
Therapy of couple[7]	110.0
Psychotherapy[2]	45.0
Supportive psychotherapy[2]	45.0
Therapeutic massages[2]	31.0
Physiotherapy/ rehabilitation[2]	30.0
Nursing home (per day)[1]	33.4
Acupuncture[1]	30.0
Medical visits (per unit)	
Primary care (or General Practitioner) [1]	10.2
Psychotherapist[1]	45.0
Psychiatrist[1]	67.3
Emergency room[1]	121.6
Hospitalisation	
Hospital stay in Psychiatric ward (one day)[1]	272.8

[1]Oblikue, 2008. eSALUD. SOIKOS (30) [2]Fremap, Mutua de Accidentes de Trabajo y Enfermedades Profesionales de la Seguridad Social número 61; 2008; [3]Hospital de la Santa Creu i San Pau, Barcelona, Spain; [4]Spanish National Federation of Yoga; [5]APTN, Spanish Federation of Natural Therapies and Unconventional Therapies; [6]AEPC, Spanish Association of Behavioral Psychology; [7]General Council of Colleges of Psychology of Spain

comorbidities as covariates. The change from baseline for quantitative variables was calculated as the final value minus baseline value and is presented as the mean value and its 95% CI.

A p-value of less than 0.05 was considered significant. Data analysis was performed using the Statistical Analysis System (SAS 9.1).

RESULTS

A total of 254 subjects were included in this sub-analysis sample: 128 in the pregabalin group and 126 in the SSRI/SNRIs group. The two study groups were well balanced with respect to demographic characteristics at baseline (Table 2). Mean age was 45.6 years in the pregabalin group and 44.1 years in the SSRI/SNRIs group. Percentage of women (59% and 60.5%, respectively) and work active subjects (57.8% and 61.6%, respectively) were similar in both groups. Subjects in both groups showed similar mean baseline score in HAM-A scale: 25.5±7.4points in the SSRI/SNRI group versus 26.1±7.4 points in the pregabalin group (p=0.666). However, psychiatrists clinical impression (CGI) was slightly higher for the pregabalin group; 4.2±0.7 *vs* 3.9±0.7 (p=0.024).

Table 2 Demographic characteristics of patients

Characteristic	Pregabalin N= 128	SSRI/SNRI N= 126	p
Age (years), mean (SD)	45.6 (13.8)	44.1 (13.7)	0.301
Sex (female), n (%)	69 (53.9%)	69 (54.8%)	0.810
Body mass index (kg/m2), mean (SD)	25.1 (3.7)	24.4 (3.7)	0.145
Marital status, n (%)			0.151
Married or with couple	73 (57.5%)	82 (65.1%)	
Single	29 (22.8%)	33 (26.2%)	
Widow(er)	10 (7.8%)	3 (2.4%)	
Divorced / Separated	15 (11.8%)	8 (6.4%)	
Educational level, n (%)			0.852
No education	5 (3.9%)	3 (2.4%)	
Primary education	40 (31.3%)	36 (28.8%)	
Secondary education	27 (21.1%)	26 (20.1%)	
Intermediate educational level	25 (19.5%)	28 (22.4%)	
Higher education (university)	28 (21.9%)	31 (24.8%)	
Others	3 (2.3%)	1 (0.8%)	
Work status, n (%)			0.219
Active	74 (57.8%)	77 (61.6%)	
Housewife	22 (17.2%)	25 (20.0%)	
Sick leave	5 (3.9%)	4 (3.2%)	
Unemployed	12 (9.4%)	5 (4.0%)	
Retired	14 (10.9%)	9 (7.2%)	
Does not work (students)	1 (0.8%)	3 (2.4%)	
Others	0 (0.0%)	2 (1.6%)	

Values are expressed as mean (SD, standard deviation) unless otherwise stated. SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors

Health Care Resource Utilization

Pharmacological treatment

The use of pharmacological resources is shown in Table 3. The mean number of drugs used previously was significantly lower in the pregabalin group (1.4±0.8 *vs* 1.2±0.5, p=0.025). Both groups presented a similar utilization pattern of anxiolytic drugs at baseline, being alprazolam (32.8% in the pregabalin group and 27.0% in the SSRI/SNRIs group), diazepam (20.3% and 11.1%) and lorazepam (17.2% and 30.3%), the most commonly used benzodiazepines (Table 4). There were only differences between the two groups in the use of lorazepam (p=0.018), more commonly used in the SSRI/SNRIs group. During the 6 months period, patients in the pregabalin group were treated with flexible doses of pregabalin (mean dose was 183.8±91.8 mg/day) in monotherapy or as an add-on therapy to the existing treatment at the beginning of the study. In the SSRI/SNRI group, 5 patients (4.0%) were treated with citalopram (mean dose was 26.6±10.9 mg/day), 2 (1.6%) with duloxetine (90.0±42.4 mg/day), 43 (34.1%) with escitalopram (15.2±4.2 mg/day), 5 (4.0%) with fluoxetine (20.0 mg/day), 13 (10.3%) with mirtazapine (20.0±7.4 mg/day; 7 of them taking mirtazapine concomitantly with a SSRI/SNRI) , 36 (28.6%) with paroxetine (22.8±6.9 mg/day), 14 (11.1%) with sertraline (78.2±30.6 mg/day) and 15 (11.9%) with venlafaxine (144.5±58.3 mg/day). Some patients were also taking trazodone, concomitantly with a SSRI/SNRI (n=4, 3.2%).

Table 3 Health resources utilization at baseline and 6-months visit and change from baseline

Recurso	Pregabalin N= 128			SSRI/SNRI N=126			P Entre grupos	
	Baseline	Final	Change (95%CI)	Baseline	Final	Change (95%CI)	Baseline	Final[1]
Number of drug treatments	1.4 (0.8)	1.9 (0.9)	0.55 (0.40. 0.71)ǂ	1.2 (0.5)	2.4 (0.9)	1.12 (0.96; 1.28) ǂ	0.025	< 0.001
Non-pharmacological treatment [2]								
Psychosocial therapy	0.1 (0.6)	0.2 (0.5)	0.01 (-0.05; 0.06)	0.1 (0.5)	0.1 (0.6)	0.04 (-0.02; 0.10)	0.077	0.457
Cognitive-behavioural therapies	0.2 (0.8)	0.4 (1.3)	0.29 (0.12; 0.46) ǂ	0.2 (0.7)	0.3 (0.7)	0.14 (-0.03; 0.32)	0.833	0.219
Supportive groups	0.1 (0.3)	0.1 (0.6)	0.07 (-0.04; 0.18)	0.1 (0.3)	0.1 (0.6)	0.08 (-0.04; 0.19)	0.734	0.909
Relaxation	0.3 (1.3)	0.6 (1.7)	0.31 (-0.02; 0.65)	0.3 (1.3)	0.9 (2.1)	0.52 (0.17. 0.87) †	0.657	0.400
Number of medical visits								
Primary care	13.2 (16.0)	1.7 (2.6)	-10.2 (-10.8; -9.5)ǂ	11.3 (8.9)	2.5 (4.3)	-9.3 (-10.0; -8.6) ǂ	0.955	0.084
Emergency department	4.2 (7.1)	0.2 (0.7)	-3.3 (-3.4; -3.2) ǂ	2.4 (5.2)	0.1 (0.4)	-3.4 (-3.5; -3.2) ǂ	0.007	0.380
Psychologist	2.9 (6.6)	1.6 (3.6)	-1.1 (-1.8; -0.23) †	1.8 (5.2)	2.4 (5.2)	0.2 (-0.6; 1.0)	0.082	0.027
Psychiatrist	5.2 (8.1)	3.3 (2.3)	-0.7 (-1.1; -0.3) ǂ	2.9 (5.2)	3.2 (2.1)	-0.5 (-0.9;0.0) ξ	0.002	0.319
Total medical visits	25.5 (24.8)	6.7 (5.7)	-15.1 (-16.4; -13.8) ǂ	18.3 (16.2)	8.3 (7.9)	-13.0 (-14.4; -11.6) ǂ	0.016	0.029
Number of hospitalisations	0.1 (1.2)	0.0 (0.1)	-0.23 (-0.24; -0.22) ǂ	0.3 (3.2)	0.0 (0.0)	-0.24 (-0.26; -0.23) ǂ	0.581	0.161

Values are expressed as mean (SD, standard deviation) or 95% confidence intervals (CI) unless otherwise stated. SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors. [1]Comparison of the change from baseline between the two groups adjusted by baseline values and sex, age and number of psychiatric and medical co-morbidities. [2]Number of sessions per month. ξ p < 0.05, † p < 0.01, ǂ p < 0.001.

At the end of the study, the mean adjusted change in the number of drugs used was statistically significant in both groups of patients: 0.55 (95%CI: 0.40, 0.71) in the pregabalin group and 1.12 (95%CI: 0.96, 1.28) in the SSRI/SNRIs group (Table 3). Patients receiving SSRI/SNRIs reported a significantly greater mean increase in the number of drugs used (p<0.001). Alprazolam, diazepam and lorazepam continued being the most commonly used benzodiazepines in both groups of patients (Table 4). As in the baseline visit, lorazepam was more frequently used in the SSRI/SNRIs group (27.0% *vs* 14.1% in the pregabalin group, p=0.013). Alprazolam was also more used in the SSRI/SNRIs group at the 6-months visit (27.0% *vs* 15.6%, p=0.032). The proportion of patients who received at least one benzodiazepine during the 6 months period was significantly lower in the pregabalin group (n=73, 57.0%) than in the SSRI/SNRIs group (n=110, 87.3%), p<0.001.

Non-pharmacological treatment

At baseline, there were no differences between the two groups in the use of any of the considered non-pharmacological treatments (Table 3). During the study period, the mean adjusted number of monthly cognitive-behavioural sessions increased significantly in the pregabalin group, but not in the SSRI/SNRI group (p<0.001). Meanwhile, the number of relaxation sessions per month increased significantly in the SSRI/SNRI group (p<0.01), but not in the pregabalin group. After adjustment by baseline covariates, the changes in frequency of use of non-pharmacological treatments (psychosocial therapy, cognitive-behavioural therapies, supportive group sessions, relaxation sessions and other type of session) were similar between the two groups of patients (p>0.05).

Medical visits and hospitalizations

Mean number and type of medical visits as well as the mean number of hospitalizations are summarized in Table 3. At baseline, the mean number of medical visits was significantly higher in the group of patients that initiated therapy with pregabalin (25.5±24.8 *vs* 18.3±16.2, p=0.016). More specifically, the mean number of visits to the emergency department and to the psychiatrist was

Table 4 Benzodiazepine therapy at baseline and after 6 months with pregabalin or SSRI/SNRI therapy

	Pregabalin N=128		ISRS/ISRN N=126		p between groups
	N	%	n	%	
Previous benzodiazepines					
Alprazolam	42	32.8%	34	27.0%	0.339
Diazepam	26	20.3%	14	11.1%	0.058
Lorazepam	22	17.2%	38	30.2%	0.018
Bromazepam	20	15.6%	19	15.1%	1.000
Clonazepam	18	14.1%	12	9.5%	0.332
Others	12	9.4%	21	16.7%	0.095
Benzodiazepines at the 6-months visit					
Alprazolam	20	15.6%	34	27.0%	0.032
Diazepam	19	14.8%	24	19.1%	0.406
Lorazepam	18	14.1%	34	27.0%	0.013
Bromazepam	8	6.3%	8	6.4%	1.000
Clorazepate dipotassium	8	6.3%	15	11.9%	0.131
Others	12	9.4%	25	19.8%	0.021
Patients who received at least one benzodiazepine at the 6-months visit	73	57.0%	110	87.3%	< 0.001

SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors

significantly higher in the pregabalin group (p=0.007 and p=0.002, respectively). There was a significant reduction in the mean number of medical visits in both groups after 6 months of treatment, p<0.001. After adjustment by baseline covariates, this reduction was significantly higher in the pregabalin group: -15.1 (95%CI: -16.4, -13.8) *vs* -13.0 (95%CI: -14.4, -11.6) in the SSRI/SNRIs group (p=0.029). Also, initiating therapy with any type of these drugs led to a decrease in the mean number of hospitalizations in both groups of patients (p<0.001, Table 3).

Direct costs

Direct costs were obtained multiplying the unit costs presented in Table 1 by the total health resources used in each treatment group (Table 5). The mean direct total cost at the initiation of therapy was significantly different between the two groups of patients (p=0.001): €1,366.6 ± 1483.0 in the pregabalin group and €917.4±1372.1 in the SSRI/SNRIs group. This, mainly, because of a higher baseline mean cost of medical visits in the pregabalin group (€1,130.7±1,282.3 *vs* €676.7±963.2, p=0.001) which was the main component of the total cost representing 83% of the total cost in the pregabalin group and 74% in the SSRI/SNRIs group. However, six months after initiating therapy with pregabalin or SSRI/SNRIs, the mean direct costs were €977.0±713.4 and €822.5±610.7, respectively (p>0.05). The mean adjusted direct costs in the group of patients initiating therapy with pregabalin is significantly reduced by €289.2 (95%CI: 478.7, 99.8, p = 0.003), in contrast to the €193.9 (95%CI: 389.6, 1.8, p=0.052) reduction in the SSRI/SNRIs group. However, such reduction in the mean adjusted direct costs from baseline was not significantly different between the two groups of patients (p=0.488).

Medical visits were responsible for most of the costs, but in a lower total percentage, representing now only the 38% and 46% of the total cost, respectively. The previously described reduction in the number of medical visits in both groups resulted in a significant reduction in the costs associated to this health resource (€565.7 in the pregabalin group and €485 in the SSRI/SNRIs group, p<0.001 in both groups), although mean adjusted pharmacologic cost increased significantly in both groups of patients: €305.4 in the pregabalin group and €186.6 in the SSRI/SNRIs group (p<0.001).

DISCUSSION

In this study, healthcare resource utilization and costs

Table 5 Direct cost by treatment group at baseline, at 6-months visit and change from baseline

Costs (€)	Pregabalin N=128			ISRS/ ISRN N=126			P between groups	
	Baseline	Final	Change (CI95%)	Baseline	Final	Change (CI95%)	Baseline	Final*
Total costs	1366.6 (1483.0)	977.0 (713.4)	-289.2 (-478.7; -99.8)†	917.4 (1372.1)	822.5 (610.7)	-193.9 (-389.6; 1.8)	0.001	0.488
Drugs	61.2 (175.3)	353.8 (241.8)	305.4 (276.0; 334.7)‡	33.1 (68.1)	212.7 (139.5)	186.6 (156.3; 216.9)‡	0.071	<0.001
Non-pharmacological treatment	136.4 (287.0)	246.8 (404.9)	132.1 (71.7; 192.6)‡	129.6 (314.6)	230.5 (324.1)	93.9 (31.4; 1564)†	0.342	0.384
Medical visits	1130.7 (1282.3)	374.2 (516.1)	-565.7 (-628.6; -502.7)‡	676.7 (963.2)	379.3 (370.8)	-485.0 (-550.0; -420.1)‡	0.001	0.080
Hospitalisation	38.4 (322.5)	2.13 (24.1)	-63.5 (-66.7; -60.3)‡	77.9 (874.9)	0.00 (0.00)	-66.8 (-70.1; -63.5)‡	0.581	0.161

* Comparison of the change from baseline between the two groups adjusted by baseline values and sex, age and number of psychiatric and medical co-morbidities. Values are expressed as mean (SD, standard deviation) unless otherwise stated. SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin–Norepinephrine Reuptake Inhibitors
ξ $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$

related to initiating treatment with pregabalin or SSRI/SNRIs in benzodiazepine-resistant out-patients with GAD was computed in the context of regular clinical practice in Spain. The study design used allowed us to estimate the total mean cost per patient in both cohorts using data directly from every day clinical practice. The main finding from this economic analysis was that initiating therapy with pregabalin is related to a significant reduction in direct costs. Such a decrease was not seen in the group of patients initiating therapy with SSRI/SNRIs. The component of costs related to pharmacological treatment (acquisition costs) increased significantly in both groups of patients, but was, as expected, greater in the pregabalin group, due to its higher acquisition cost than in the comparator group. These increases in costs related to pharmacological treatment were offset by significant reductions in the costs related to medical visits, which were the main component of the total cost in the treatment of these GAD patients. Accordingly, the mean utilization of medical visits was significantly reduced in both groups of patients, although this reduction was more marked in the group of patients initiating therapy with pregabalin. Interestingly, the reduction in the number of medical visits in both groups of patients was attributable to a reduction in the number of visits made to primary care. This observation could be of relevance taking into account the increasing waiting list times for specialist psychiatric referrals in the Spanish National Health System.

When comparing the results from this study with two costs analysis published in Spain[9,33], we found that in the most recently published study, the annual cost of GAD in primary care was estimated at €817, which included the pharmaceutical prescription, the visit to the specialist and monitoring. Unlike in our study, in this study GAD was diagnosed with ICD-10 criteria, costs and resources were estimated for a time horizon of 1 year and only the primary care setting was considered. Such differences do not allow direct comparisons between this study and ours. In a previous study, the same author analyzed the healthcare use and the economical impact of effective treatments in GAD patients in a primary care setting[33]. In this study a diagnosis of GAD was confirmed using DSM-IV criteria. The mean direct cost/year adjusted by age, gender and morbidity burden was estimated at €686, from which pharmaceutical cost represented 59% of the total cost. This cost is proportionally higher than our estimate where the pharmaceutical costs represents 36% of the total cost in the pregabalin group, and 27%, in the SSRI/SNRI group. In that study, healthcare resource utilization was obtained retrospectively from medical records, while in our study the pharmacological resource data were obtained prospectively. In a previous cost-effectiveness analysis, Vera-Llonch et al. estimated that the total costs over 1 year were €3,871 for pregabalin and €3,234 for venlafaxine (Euros 2007)[34,35]. The total costs consisted of mean costs of pharmacotherapy over 1 year (€1,664 for pregabalin and €780 for venlafaxine) and

mean costs of medical-care services (including primary care physicians, mental health-care providers, laboratory tests, and inpatient days). The latter were estimated to be €2,207 for patients receiving pregabalin and €2,454 for venlafaxine. That cost-effectiveness analysis was based in a formal clinical trial study was carried out in the Spanish primary care setting; therefore, its results are not directly comparable with the results presented here given that the ADAN study was carried out in Spanish outpatient psychiatric clinics under routine medical practice.

Benzodiazepines are still widely used and for a longer period than recommended. One of the main objectives of GAD therapies is to continue treatment for long enough periods of time, in order to lead to remission and, where possible, prevent relapse and avoid utilization of benzodiazepines in the long-term[36], particularly when there are available effective therapies that may administered during long periods of time[37]. Regarding the use of pharmacological treatments, this sub-analysis of the ADAN study found out that the mean number of drugs prescribed in the two groups increased. Despite many guidelines and authors recommending against the use of long-term therapy with benzodiazepines[36, 37], many patients in this study continued therapy with these drugs. However, the proportion of patients who received at least one benzodiazepine during the 6 months period was significantly lower in the pregabalin group than in the SSRI/SNRI group (57% *versus* 87%). As a results, physicians could fulfil the therapeutic goals recommended by guidelines related with use of benzodiazepines by initiating GAD therapy with pregabalin[37].

This cost-analysis presents some limitations that should be considered. One limitation is that the study was performed from the perspective of the National Health System, and therefore neither indirect costs associated to GAD treatment nor the so-called out-of pocket costs have been considered. Some studies show that the indirect costs, resulting mainly from employee absenteeism, represent an increase of more than twice as much of direct costs[39-41]. Another possible limitation is the observational design of the original source of data, the ADAN study, with its inherent limitations which are mainly that it was not a clinical trial. Nevertheless, rather than to consider this as a methodological weakness of our analysis, it should be considered as an advantage for payers or for the National Healthcare Service because the study was based on real world data which allows health decision makers to draw conclusions and estimate actual costs and resource utilization. As well as this, study sample size could be considered small, and the power was below 80% in effectiveness comparisons, meaning that the study may be limited to guarantee that differences in effectiveness could exists between the two groups of GAD therapies analyzed.

In conclusion, and despite the limitations mentioned, this study showed that the higher drug acquisition cost of pregabalin was counter-balanced by a great reduction in other health care resource use and costs. Therefore, suggesting that initiating therapy with pregabalin in benzodiazepine-resistant patients with GAD would result in a substantial and significant reduction of direct costs for the National Health System. The results of the study show that by treating GAD with pregabalin the cost does not necessarily increase when comparing with the treatment with SSRI/SNRI drugs in a routine clinical practice basis. However, it could be additionally observed that pregabalin reduces the use of benzodiazepines as concomitant anxiolytic therapy.

AUTHORS' DISCLOSURE AND CONFLICT OF INTERESTS

Dr. JL Carrasco is member of national and international advisory boards at Janssen-Cilag, Pfizer, Lilly, Servier, Astra-Zeneca, Lundbeck, and Abbot. Dr. E Álvarez has received consulting and educational honoraria from several pharmaceutical companies including Eli Lilly, Sanofi-Aventis, Lundbeck, Pfizer; and he has participated as main local investigator in clinical trials from Eli Lilly, Bristol-Myers and Sanofi-Aventis and also as national coordinator of clinical trials from Servier and Lundbeck. Dr JM. Olivares is member of regional, national, and international advisory boards for Janssen-Cilag, Lilly, Astra-Zeneca and Bristol-Myers and he has been involved in designing and/or participating in clinical trials for Janssen-Cilag, Lilly, Astra-Zeneca, Pfizer, Lundbeck, Glaxo and Bristol-Myers, and he has received educational grants for research, honoraria and travel support for activities as a consultant/advisor and lecturer/faculty member for Janssen-Cilag, Lilly, Astra-Zeneca, Pfizer, Lundbeck, Glaxo, Novartis and Bristol-Myers. Javier Rejas is employed in Pfizer, S.L.U. All other authors declare that they have no conflicts of interests as a consequence of this paper.

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