

# Comparative effectiveness and costs of generic and brand-name gabapentin and venlafaxine in patients with neuropathic pain or generalized anxiety disorder in Spain

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**Objective:** To explore adherence/persistence with generic gabapentin/venlafaxine versus brand-name gabapentin/venlafaxine (Neurontin®/Vandral®) in peripheral neuropathic pain (pNP) or generalized anxiety disorder (GAD), respectively, and whether it is translated into different costs and patient outcomes in routine medical practice.

**Methods:** A retrospective, new-user cohort study was designed. Electronic medical records (EMR) of patients included in the health plan of Badalona Serveis Assistencials SA, Barcelona, Spain were exhaustively extracted for analysis. Participants were beneficiaries aged 18+ years, followed between 2008 and 2012, with a pNP/GAD International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code, who initiated treatment with generic or brand-name gabapentin or venlafaxine. Assessments included 1-year treatment persistence and adherence (medication possession ratio), health care costs, and reduction in severity of pain and anxiety symptoms.

**Results:** A total of 2,210 EMR were analyzed; 1,369 on gabapentin (brand 400; generic 969) and 841 on venlafaxine (brand 370 and generic 471). Brand-name gabapentin and venlafaxine were both significantly associated with longer persistence than generic: 7.3 versus 6.3 months,  $P < 0.001$ ; and 8.8 versus 8.1 months,  $P < 0.05$ , respectively. Brand-name was associated with higher adherence: 86.5% versus 81.3%,  $P < 0.001$ ; and 82.1% versus 79.0%,  $P < 0.05$ , respectively. Adjusted average costs were higher with generic compared with brand: €1,277 versus €1,057 (difference of €220 per patient;  $P < 0.001$ ) for gabapentin; and €1,110 versus €928 (difference of €182 per patient;  $P = 0.020$ ) for venlafaxine, both because of more use of medical visits and concomitant medication. Compared with generic, brand-name was associated with higher reduction in pain (7.8%;  $P < 0.001$ ) and anxiety (13.2%;  $P < 0.001$ ).

**Conclusion:** Patients initiating brand-name gabapentin or venlafaxine were more likely to adhere and persist on treatment of pNP or GAD, have lower health care costs, and show further reduction of pain and anxiety symptoms than with generic drugs in routine medical practice.

**Keywords:** brand medicinal products, generic medicinal products, adherence, persistence, use of resources, costs, outcomes

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## Introduction

Peripheral neuropathic pain (pNP), defined as pain initiated or caused by a primary lesion or nervous system dysfunction, is a common symptom.<sup>1,2</sup> The prevalence is estimated at 1%–8% in the adult population and represents around 40% of cases of chronic pain at primary care office visits.<sup>3,4</sup> Generalized anxiety disorder (GAD) is characterized by having symptoms of anxiety most days for at least several weeks,<sup>5,6</sup>

and it is the most common type of anxiety disorder seen in primary care,<sup>7</sup> with a prevalence of around 2%–5% in the general population, and also accounting for an important workload at the physician office.<sup>6,8</sup> These two medical conditions may have different pathophysiological mechanisms, but the reason of including both relates to their high prevalence in primary care, and related workload. Moreover, the chronic nature of the symptoms and the disability they often cause can produce considerable direct costs for health services and indirect costs resulting from absenteeism.<sup>9,10</sup> These circumstances affect all aspects of patient lives: family, social, and work. As such, many patients are not properly diagnosed, receive inadequate drug treatment, or are on lower doses than they should be.<sup>11,12</sup> For this reason, both conditions may be considered of relevance and pertinent to both clinicians and payers.

Drug therapy is one of the essential bases of treatment. It is known that generic medicinal products have the same efficacy, safety, and quality as the original brand-name, and are bioequivalent.<sup>13,14</sup> Motivation, the physician's awareness, and health intervention policies on generics are some of the factors influencing their use.<sup>14</sup> In general, patients are demanding better health care and want cost-effectiveness,<sup>13</sup> and this is a key component of the negotiation between payers, managers, and health professionals. In Spain, current policy regarding the restriction of the price of brand drugs compared with generics is no longer such a strong argument for requiring their use since they have, actually, the same financed price. Reviewing the available literature, some authors have found no pharmacological arguments against prescribing these products.<sup>15,16</sup> Others, however, disagree (brand vs generic) in the context of routine clinical practice for a number of reasons, one being treatment adherence, which can often lead to decreased effectiveness (confusing for patients, lack of therapeutic control, poor health outcomes) and a potential increase in associated health care costs.<sup>17–20</sup> Additionally, there is little evidence available on the relationship between these variables in routine clinical practice, and none on the impact on use of health care resources and their respective costs.

Thus, it is worthy to explore such controversy in health conditions that are relevant and pertinent to both clinicians and payers, and the health problems selected here seem to be aligned with such purpose and may be useful to illustrate the matter of this study. Our objective was, then, to estimate the treatment adherence and persistence in patients who initiated the therapy of either pNP or GAD with generic gabapentin/venlafaxine versus brand-name gabapentin/

venlafaxine (Neurontin®/Vandral®), and to compare whether it is translated into different costs and patient outcomes for pain and anxiety symptoms, in routine clinical practice in Spain.

## Patients and methods

### Study design and population

This was an observational, multicenter, retrospective study conducted by analyzing the electronic medical records (EMR) of patients included in the health plan of Badalona Serveis Assistencials (BSA) SA, a health provider in Badalona (Barcelona), Spain. Records from patients included in the study were followed at primary care level in any of the seven primary care (PC) health centers owned by BSA. Patients seeking care and who initiated a new treatment with gabapentin (Neurontin® or generic) or venlafaxine (Vandral® or generic) within years 2008–2012 (period of recruitment, index date) were included in the study. Patients had to fulfill the following inclusion criteria: age 18+ years; followed actively in BSA for at least 12 months before the start of the study; be in the refill prescription program for long-term medication (with record of the daily dose, time interval, and duration of each treatment administered;  $\geq 2$  prescriptions during the follow-up period); guarantee of regular monitoring of patients during the study period ( $\geq 2$  health records in the computer system); and diagnosed with pNP or GAD. Subjects transferred to other centers, displaced or outside area, patients permanently institutionalized, those who changed treatment (brand vs generic) in either direction, and patients who were prescribed the two active substances concomitantly (gabapentin and venlafaxine) were excluded from the analysis.

### Study groups and calculation of sample size

There were two study groups: 1) patients initiating treatment with gabapentin for pNP for the first time; and 2) patients initiating treatment with venlafaxine for GAD for the first time. Each group had two subgroups: brand-name and generic. Generic prescription could be from different drug makers during the course of the study, even in the same patient, as it happens in routine medical practice in Spain. Patients were followed-up for 12 months after starting the medication. The calculation of sample size was established by finding a minimum difference of €60 (SD, 240) between brand and generic gabapentin and €40 (SD, 160) between brand and generic venlafaxine. With an error  $\alpha < 0.05$  and an error  $\beta < 0.1$ , these differences would enable detection of even the smallest differences according to Cohen's *d*-statistic with a minimal effect size of 0.25. With these parameters,

the study needed at least 340 sets of medical records in each of the four study groups. However, all available records that met the selection criteria in the study period from the start date were obtained (exhaustive sampling).

## Diagnosis and scales

The records of patients with pNP or GAD were obtained using the International Classification of Primary Care (ICPC-2),<sup>21</sup> codes N92–N94 or P74, and/or the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9th-CM, codes 350.1, 352.1, 352.9, 353.1, 352.2, 353.3, 353.6, 353.8, 354.0, 355.1, 355.5, 357.2, 357.4, 357.8, 357.9, 053.12, and 300.02). The criteria were always at discretion of the physician.

To estimate clinical effectiveness, we used the information recorded in the medical records on the Numeric Rating Scale (NRS) for pain,<sup>22</sup> for assessing the intensity of pNP in a range from 0 (no pain) to 10 (worst pain imaginable), and the Hamilton Anxiety Rating Scale (HARS, HAM-A) for GAD,<sup>23</sup> with 14 items ranging from 0 to 56 points (<7 points signifies no anxiety or in remission). The initial and final values were obtained (from first and last records available, respectively). Sociodemographic and comorbidity variables were also collected which included age (continuous and by range), time since diagnosis, and sex, in addition to previous medical history obtained using ICPC-2.<sup>21</sup> The following were used as general comorbidity summary variables: 1) the Charlson Comorbidity Index as an estimate of the patient's severity;<sup>24</sup> and 2) the individual case-mix index, obtained from the Adjusted Clinical Groups (ACG), a system for grouping patients according to resource consumption (iso-resource groups).<sup>25</sup> The ACG provides resource utilization bands (RUB) so that each patient, depending on his/her overall morbidity, is grouped into one of five mutually exclusive categories: 1) healthy users or very low morbidity, 2) low morbidity, 3) moderate morbidity, 4) high morbidity, and 5) very high morbidity.

## Medication, treatment adherence, and persistence

Medications prescribed for the treatment of pNP and GAD were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.<sup>26</sup> The information was obtained from the pharmacological dispensing records for drugs issued by the “CatSalut” (Catalan Health Service) application. The choice of drug for a particular patient was at the discretion of the doctor (clinical practice). Information was also obtained on treatment duration and the number of

treatments given (6 months) prior to starting gabapentin or venlafaxine. The “adherence rate” was defined according to the International Society for Pharmacoeconomics and Outcomes Research criteria and calculated from the medication utilization/medication possession ratio (MPR).<sup>27</sup> This was assessed from the first to the last prescription and represents the number of days of medication supplied divided by the number of days on treatment (counted from the index date to the last possible day with available medication).<sup>28</sup> “Persistence”, measured in months, was defined as the elapsed time between the index date (which corresponds to the first prescription of study drug) and the ending date (which corresponds to the date of last refill plus the number of pills/tablets prescribed) without discontinuing the initial treatment or without changing to another medication at least 30 days after the initial prescription. Treatment persistence was also assessed as the percentage of patients taking the initial treatment 3, 6, 9, and 12 months since the index date.

## Use of resources and cost analysis

“Health care costs” were considered to be those relating to health care activity (medical visits, days of hospitalization, hospital emergencies, and diagnostic or therapeutic referral requests) performed by health care professionals, and “non-health care costs” (indirect costs) were those relating to loss of labor productivity (days of temporary sick leave), all of them related with the health conditions studied here. Out-of-pocket costs were not collected in the study. The cost system design was defined considering the characteristics of the health provider and the degree of development of the available information systems. The product unit that served as the basis for the final calculation (during the study period) was the treated patient and the cost was expressed as average cost per patient (average cost/unit). The study's different concepts and their economic values are shown in Table 1 (corresponding to year 2013). Different fees were obtained from analytical accounting at the sites, except medication and days off work. Prescriptions were quantified by retail price per pack at the time of prescribing. Days off work or productivity losses were considered to be non-health care costs (indirect). The cost was quantified according to minimum wage.<sup>29</sup>

As happens in any retrospective study using existing recorded data, we dealt with the risk of not recording information properly or missing data. This problem was minimized, thanks to regular quality control of the database by the health provider, continuous training of physicians, and specific validation of the informatics system.

**Table I** Details of the unit costs and lost labor productivity (2013)

Health care and non-health care resources	Unit costs (€)
Doctors' visits	
Primary care doctors visit	23.7
Emergency room visits	119.9
Hospitalization (1 day)	327.3
Specialist doctors visit	68.9
Day hospital sessions	184.8
Investigations	
Laboratory tests	22.7
Conventional radiology	18.9
Diagnostic/therapeutic tests	37.9
Pharmaceutical prescription	Public selling price
Labor productivity – indirect costs	
Cost per day not worked	79.5

**Notes:** Source of health care resources: analytical accounting of Badalona Serveis Assistencials and by Instituto Nacional de Estadística (INE).<sup>29</sup> Values are expressed in euros (€).

## Ethics

The study followed the basic ethical principles contained in the Declaration of Helsinki for studies in the human being. The study protocol was first classified as a Post-Authorization Study – Other Designs (PAS-OD) by the Spanish Agency for Medicines and Medical Devices and, secondly, was reviewed and approved by the Independent Ethics Committee of Hospital Germans Trias i Pujol de Badalona, Barcelona. Data from subjects underwent a process of dissociation to preserve patient anonymity as set out in the Spanish Personal Data Protection Act 15/1999 of 13 December.

## Statistical analysis

Data were first carefully examined by exploratory analysis and specifically prepared, noting their frequency distribution and checking for possible data input or coding errors. A descriptive univariate statistical analysis was carried out after verifying normal distribution with the Kolmogorov–Smirnov test. The homogeneity of the data analyzed was checked according to geographical area of the participating sites. The analysis of geographical homogeneity showed no differences which were either statistically significant or of a relevant magnitude.

Persistence with the treatments being evaluated was initially analyzed descriptively, calculating the proportion of patients who remained on treatment at 3, 6, 9, and 12 months after the index date. Also, cumulative survival was estimated in the study of each cohort using the Kaplan–Meier method to calculate the unadjusted cumulative proportion of persistence at different times from the start of treatment. Statistical significance was analyzed with the Mantel–Cox (log-rank) test.

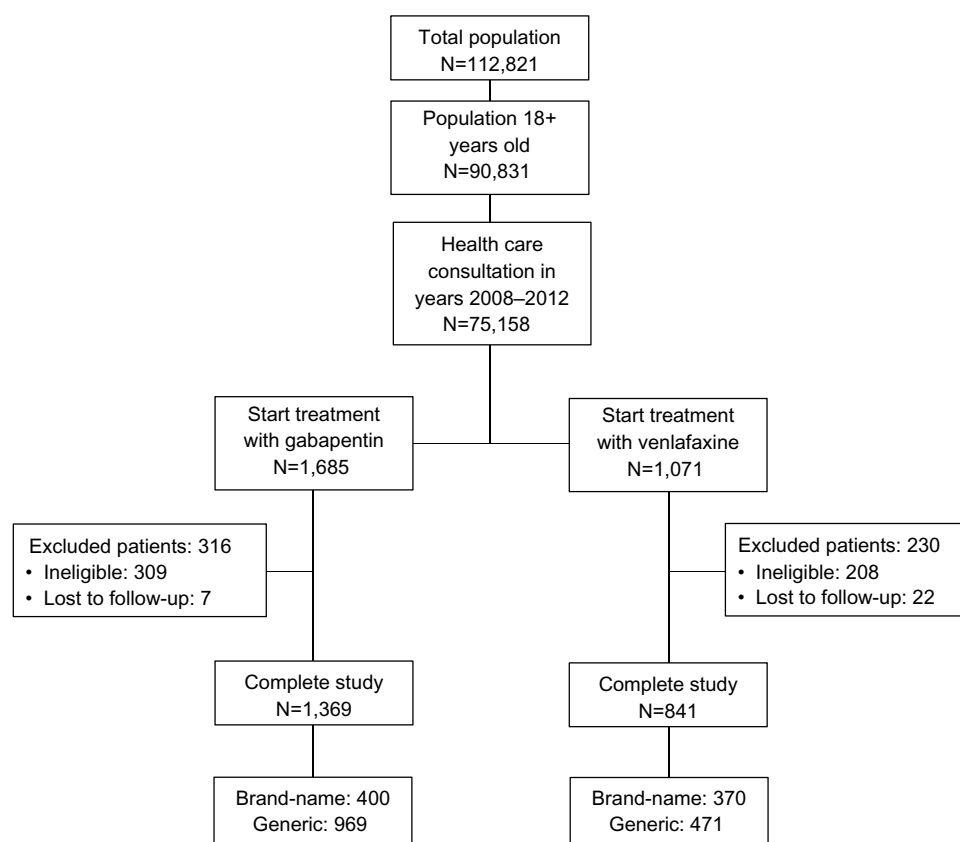
The analysis of resource utilization and associated costs included an initial bivariate analysis without controlling for potential confounding variables in which robust analysis of variance (ANOVA) (Welch and Brown–Forsythe test with subsequent pairwise comparisons using the Games–Howell test) and chi-tests were used according to data distribution. The use of resources and their associated costs were compared as recommended by Thompson and Barber using a general linear model (analysis of covariance [ANCOVA]) adjusted for the covariates sex, age, overall comorbidity (RUB, Charlson index), illness duration, the MPR, and treatment persistence.<sup>30</sup> Pairwise comparisons were adjusted to the procedure to estimate marginal means using the Bonferroni correction to estimate the *P*-value of statistical significance. Data were presented as adjusted mean differences between treatments with their respective 95% confidence interval calculated with re-sampling techniques (bootstrapping) corrected for bias, given the non-normal distributions of the resource utilization and cost variables.

Pain intensity and severity of anxiety symptoms were analyzed after performing a single imputation of missing values using a general linear model (ANCOVA) for absolute and relative variation between start and discontinuation of treatment of the pain and anxiety scores, respectively, and using a logistic regression model for the proportion of patients who were responders or in remission in terms of anxiety symptoms (score <7 points on the HAM-A scale), or had no pain/mild pain (score <4 on the NRS). The covariates used in the ANCOVA and logistic regression model were age, sex, and the score on the corresponding scale at the start of treatment. Missing values in the NRS were observed in 9.7% of patients receiving gabapentin, with no significant difference between brand (8.5%) and generic (10.2%), *P*=0.382. On the HAM-A scale, missing values were observed in 22.2% of patients receiving venlafaxine, also with no significant difference between brand (20.3%) and generic (23.8%), *P*=0.258. Imputation method was WOCF (worst available observation carried forward), which in this case was the score observed at the start-of-treatment visit. For both scales, we compared the scores at the first and final visits, absolute (points) and relative (%) variation of pain intensity and anxiety severity between visits, proportion of responders (reduction ≥50% from the initial score in pain intensity or anxiety severity at the final visit) and proportion of patients in remission in terms of anxiety symptoms (HAM-A <7 points), or having no pain/mild pain (visual analog scale [VAS] <4 points). The effect size (magnitude of changes) was calculated using Cohen's *d*-statistic.<sup>31</sup>

## Results

From an initial selection of 90,831 subjects aged over 18 years and assigned to the sites, 2,210 patients, who met the criteria for inclusion in the analysis, were recruited (29 [1.3%] patients were considered lost to follow-up). In the study group (Figure 1), 1,369 (61.9%) received treatment with gabapentin (brand: 400 [29.2%]; generic: 969 [70.8%]) and 841 with venlafaxine (brand: 370 [44.0%]; generic: 471 [56.0%]). Table 2 shows the demographic characteristics and associated comorbidities for the patients with pNP and GAD. By subgroup (brand, generic), the subjects on treatment with gabapentin had a different proportion of females (56.3% vs 63.2%;  $P=0.017$ ). With venlafaxine, there were no significant differences in any of the descriptive characteristics. There were no statistically significant differences in the distribution of ICPC/ICD-9 codes for pNP in the gabapentin groups between brand or generic ( $P=0.969$ ): axial radiculopathies, 56.8% in the brand group and 55.3% in the generic group; any type of neuralgias, 22.3% and 22.7%, respectively; neuropathies, 14.5% and 15.6%, respectively; and other pNP conditions, 6.5% and 6.4%, respectively.

Table 3 shows the characteristics of medication use. With gabapentin, mean treatment duration was longer for brand than generic (7.3 vs 6.3 months;  $P<0.001$ ); adherence expressed as MPR (86.5% vs 81.3%;  $P<0.001$ ) and mean daily dose of medication (1,322.5 vs 1,153.5 mg;  $P=0.008$ ) were higher; and treatment persistence was significantly longer (Figure 2A). With venlafaxine, mean treatment duration (8.8 vs 8.1 months;  $P=0.002$ ), MPR (82.1% vs 79.0%;  $P=0.045$ ), and treatment persistence time (Figure 2B) were all slightly longer with brand than with generic drug, but statistically significant. The medication prescribed to the patients in the pre-treatment (6 previous months) and treatment (12-month follow-up) periods are shown in Table 4. In the gabapentin group, the average number of concomitant medications administered to patients before receiving the initial brand medication (pre-treatment vs treatment period) decreased significantly in the case of brand (2.3 vs 1.9 drugs;  $P<0.001$ ), whereas there was no reduction in the case of generic (2.6 vs 2.5 drugs;  $P=0.261$ ), meaning that during the study, patients taking brand gabapentin used fewer drugs concomitantly for the neuropathic pain (1.9 vs 2.5;  $P<0.001$ ) (Table 4). In the venlafaxine group, the average



**Figure 1** General outline of the study.

**Note:** An observational retrospective design involving the review of existing medical records (computerized databases with existing data dissociated) of patients under primary care and hospital follow-up who started treatment with gabapentin or venlafaxine (brand-name vs generic).



**Table 2** Baseline characteristics of study series

Study groups	Gabapentin				Venlafaxine			
Subgroups	Brand	Generic	Total	P	Brand	Generic	Total	P
Number of patients, %	N=400 (29.2%)	N=969 (70.8%)	N=1,369 (100%)		N=370 (44.0%)	N=471 (56.0%)	N=841 (100%)	
<b>Demographic characteristics</b>								
Average age, years	64.2 (16.4)	64.8 (15.6)	64.6 (15.9)	0.525	61.0 (17.1)	60.5 (16.9)	60.7 (17.0)	0.656
Sex (female)	56.3%	63.2%	61.1%	0.017	61.4%	66.7%	64.3%	0.110
Pension regime, SS	67.5%	66.4%	66.7%	0.683	57.3%	55.8%	56.5%	0.672
Range: 19–44 years	13.8%	11.9%	12.4%		18.1%	19.7%	19.0%	
45–64 years	33.0%	36.1%	35.2%		38.9%	38.4%	38.6%	
65–74 years	22.8%	19.5%	20.5%		17.3%	16.6%	16.9%	
>74 years	30.5%	32.5%	31.9%	0.333	25.7%	25.3%	25.4%	0.943
<b>General comorbidity</b>								
Average number of diagnoses	7.0 (3.8)	7.1 (3.5)	7.1 (3.6)	0.643	7.0 (3.8)	7.1 (4.0)	7.1 (3.9)	0.816
Average Charlson index	0.7 (1.1)	0.7 (1.0)	0.7 (1.0)	0.930	0.6 (0.9)	0.6 (0.8)	0.6 (0.9)	0.864
Average RUB	2.9 (0.6)	2.9 (0.6)	2.9 (0.6)	0.777	2.9 (0.6)	2.9 (0.6)	2.9 (0.6)	0.527
RUB-1	3.3%	4.4%	4.1%		3.2%	3.8%	3.6%	
RUB-2	12.5%	10.2%	10.9%		13.8%	12.3%	13.0%	
RUB-3	73.5%	76.4%	75.5%		73.8%	73.2%	73.5%	
RUB-4	10.0%	7.4%	8.2%		8.9%	9.3%	9.2%	
RUB-5	0.8%	1.5%	1.3%	0.178	0.3%	1.3%	0.8%	0.542
<b>Associated comorbidities</b>								
Hypertension	40.3%	44.2%	43.0%	0.183	35.6%	37.6%	36.7%	0.555
Diabetes mellitus	18.8%	21.4%	20.6%	0.277	16.0%	15.1%	15.5%	0.703
Dyslipidemia	43.5%	48.2%	41.2%	0.172	44.0%	48.6%	46.6%	0.185
Obesity	17.5%	20.1%	20.5%	0.214	14.1%	17.4%	16.0%	0.198
Active smokers	22.0%	21.4%	21.5%	0.794	19.3%	21.9%	20.7%	0.361
Alcoholism	3.5%	3.2%	3.3%	0.776	5.7%	3.2%	4.3%	0.074
Ischemic heart disease	7.3%	7.8%	7.7%	0.708	5.7%	6.6%	6.2%	0.602
CVA	12.5%	12.6%	12.6%	0.963	11.4%	11.0%	11.2%	0.865
Cardiovascular event	17.5%	17.9%	17.8%	0.876	14.9%	14.9%	14.9%	0.973
Organ failure	14.0%	16.6%	15.9%	0.228	12.8%	12.7%	12.8%	0.989
Asthma	6.0%	7.2%	6.9%	0.415	6.8%	5.2%	5.8%	0.149
COPD	6.3%	5.8%	5.9%	0.737	3.5%	4.7%	4.2%	0.413
Neuropathies	2.8%	1.3%	1.8%	0.071	2.4%	1.3%	1.8%	0.204
Dementia (all types)	4.5%	2.8%	3.3%	0.106	4.3%	5.5%	5.0%	0.440
Organic psychosis	1.0%	0.7%	0.8%	0.601	4.1%	5.5%	4.9%	0.336
Malignant neoplasms	15.0%	12.2%	13.0%	0.158	7.1%	9.6%	8.5%	0.199

**Note:** Values are expressed as percentage or mean ( $\pm$  standard deviation).

**Abbreviations:** SS, social security; RUB, resource utilization bands; CVA, cerebrovascular accident.

number of concomitant medications was also higher in the generic group (2.5 vs 2.0 drugs;  $P<0.001$ ), with a significant reduction in use of concomitant medication in the case of brand venlafaxine ( $-0.25$  drugs;  $P=0.001$ ) which was not observed in the generic group. This was due, particularly, to a reduction in the use of anxiolytics (sedatives/hypnotics; 64.3% vs 51.6%;  $P<0.001$ ). Once again, these differences were not found in the generic subgroup (2.6 vs 2.5 drugs;  $P=0.117$ ); however, a reduction was found in the use of anxiolytics (74.9% vs 67.5%;  $P<0.001$ ), although smaller in magnitude than with brand (Table 5).

The use of health care resources was lower in patients treated with brand gabapentin with, in particular, fewer

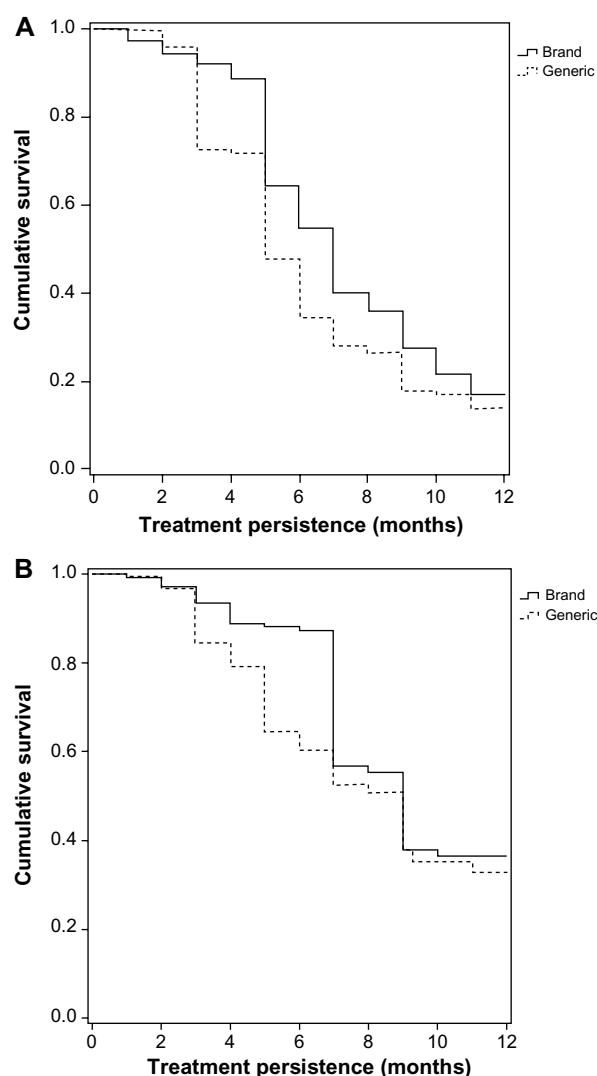
primary care medical visits (12.5 vs 15.5;  $P=0.001$ ), hospital emergencies (0.4 vs 0.7;  $P<0.001$ ), and investigations than those who received generic gabapentin (Table 6). In the venlafaxine group, the main differences in favor of the use of brand over generic were seen in primary care medical visits (11.1 vs 13.9;  $P<0.001$ ), hospital emergencies (0.4 vs 0.6;  $P=0.006$ ), and laboratory tests (0.7 vs 1.0;  $P=0.002$ ). There were no significant differences in lost labor productivity (Table 5). With gabapentin, the average/total unit cost was greater with the administration of generic than with brand (€1,665.60 vs €1,461.40;  $P=0.048$ , Table 6). Similar results were found with venlafaxine (€1,510.10 vs €1,308.80;  $P=0.040$ ), respectively. With gabapentin, the average/total

**Table 3** Characteristics of medication use: treatment adherence/compliance and persistence

Study groups	Gabapentin		Venlafaxine		P	Total	Generic	Brand	P-value
	Brand	Generic	Brand	Generic					
Subgroups	N=400 (29.2%)	N=969 (70.8%)	N=370 (44.0%)	N=471 (56.0%)		N=1,369 (100%)		N=841 (100%)	
Number of patients, %									
Time since diagnosis (years)									
Mean (SD)	1.5 (1.2)	1.6 (1.2)	2.6 (2.5)	2.7 (2.7)	0.529	1.6 (1.2)		2.7 (2.6)	0.712
Median (P25–P75)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (2.0–4.0)	1.0 (2.0–5.0)		1.0 (1.0–2.0)		1.0 (2.0–5.0)	
Possession of treatment (months)									
Mean (SD)	6.4 (3)	5.5 (3.5)	7.4 (3.2)	6.9 (3.9)	<0.001	5.7 (3.4)		7.1 (3.6)	0.047
Median (P25–P75)	6.0 (4.0–8.0)	4.0 (4.0–8.0)	7.0 (5.0–11.0)	7.0 (4.0–11.0)		5.0 (4.0–8.0)		7.0 (4.0–11.0)	
Duration of treatment (months)									
Mean (SD)	7.3 (3.0)	6.3 (3.1)	8.8 (2.9)	8.1 (3.6)	<0.001	6.6 (3.1)		8.4 (3.3)	0.002
Median (P25–P75)	7.0 (5.0–10.0)	5.0 (3.0–9.0)	9.0 (5.0–12.0)	9.0 (5.0–12.0)		6.0 (5.0–9.0)		9.0 (5.5–12.0)	
Medication possession ratio									
Mean (SD)	86.5%	81.3%	82.1%	78.2%	<0.001	82.8%		79.0%	0.045
Median (P25–P75)	85.7 (80.0–88.9)	80.0 (66.7–88.9)	77.7 (71.4–91.7)	83.3 (71.5–91.7)		83.3 (80.0–88.9)		80.0 (72.5–91.7)	
Daily dose of medication									
Mean (SD)	1,322.5 (524.2)	1,153.5 (451.2)	102.8 (38.4)	100.9 (35.5)	0.008	1,202.9 (479.7)		101.2 (36.8)	0.449
Median (P25–P75)	900 (900–1,800)	900 (900–1,200)	75 (75–150)	75 (75–150)		900 (900–1,800)		75 (75–150)	
Range (N, %)									
<900 mg/day	11 (2.8)	38 (3.9)	–	–		49 (3.6)		–	
=900 mg/day	195 (48.8)	597 (61.6)	–	–		792 (57.9)		–	
≤1,800 mg/day	151 (37.8)	256 (26.4)	–	–		407 (29.7)		–	
>1,800 mg/day	43 (10.8)	78 (8.0)	–	–	0.003	121 (8.8)		–	0.112
<75 mg/day	–	–	3 (0.8)	14 (3.0)		–		17 (2.0)	
=75 mg/day	–	–	226 (61.1)	262 (55.6)		–		488 (58.0)	
≤150 mg/day	–	–	13 (3.5)	43 (9.1)		–		56 (6.7)	
>150 mg/day	–	–	128 (34.6)	152 (32.3)		–		280 (33.3)	
Treatment persistence (months) <sup>a</sup>									
3 months	92.0%	72.3%	93.5%	84.7%	<0.001	78.1%		88.6%	<0.001
6 months	54.8%	34.5%	87.6%	60.5%	<0.001	40.4%		72.4%	<0.001
9 months	27.5%	17.8%	55.4%	44.4%	<0.001	20.6%		49.2%	0.001
12 months	18.3%	13.9%	37.8%	31.4%	0.039	15.8%		33.5%	0.052

**Notes:** Values are expressed as mean (± standard deviation) or percentage. <sup>a</sup>Persistence was defined as time, measured in months, without discontinuing the initial treatment or without changing to another medication at least 30 days after the initial prescription.

**Abbreviations:** SD, standard deviation; P, percentile.



**Figure 2** Persistence curve for initial treatment (gabapentin, venlafaxine): comparison of the brand medication with the generic.

**Notes:** (A) Kaplan–Meier curve for estimation of the median duration of initial treatment with gabapentin. Comparisons between subgroups (brand vs generic): Mantel–Cox log-rank test: 19.541;  $P < 0.001$ . (B) Kaplan–Meier curve for estimation of the median duration of initial treatment with venlafaxine. Comparisons between subgroups (brand vs generic): Mantel–Cox log-rank test: 6.071;  $P = 0.014$ .

unit cost adjusted for covariates was €1,720 versus €1,398, respectively ( $P = 0.008$ ). The costs incurred in primary care were responsible for a portion of this difference in cost between brand and generic (€855 vs €722;  $P < 0.001$ ), while the differences observed in specialist care did not reach statistical significance ( $P = 0.075$ ). Again, the results for venlafaxine were similar (Table 6). The average/total unit cost adjusted for covariates was higher with generic (€1,549 vs €1,290;  $P = 0.035$ ); also due to the primary care component (€796 vs €670;  $P = 0.001$ ) respectively. Comparing generic with brand, for gabapentin, the adjusted average total health care costs per patient were €1,277 versus €1,057 (difference €220,  $P < 0.001$ ), and for venlafaxine, €1,110 versus €928

(difference €182,  $P < 0.020$ ). In both cases, the higher costs with generic were due to greater use of visits and concomitant medication (Tables 5 and 6).

Although no statistically significant differences were found in scores on the pain and anxiety scales at baseline between groups, patients treated with brand gabapentin showed a greater adjusted relative reduction in pain at the end of the study compared with generic: on average 51% with brand compared to 43% with generic ( $P < 0.001$ ,  $d = 0.36$ ), leading to a proportion of responders 3.1 times higher (64% vs 39%;  $P < 0.001$ ) and 2.7 times higher in terms of patients with no pain/mild pain (58% vs 38%,  $P < 0.001$ ) (Table 7). Patients on treatment with venlafaxine had similar results in the reduction of anxiety (HAM-A), with an adjusted relative reduction in anxiety symptoms at the end of the study of 62% on average with brand versus 48% with generic ( $P < 0.001$ ;  $d = 0.51$ ), leading to a proportion of responders 5.5 times higher (67% vs 39%;  $P < 0.001$ ), and patients in remission, 10.7 times higher (16% vs 2%;  $P < 0.001$ ) (Table 7).

## Discussion

The two health conditions studied here are relevant and pertinent because of their elevated prevalence at primary care level and burden for medical care. Also, we selected two types of drugs to consistently illustrate the differences between brand-name drugs and generic drugs. The results of the study show that when comparing generic and brand gabapentin and venlafaxine in patients with pNP and GAD, respectively, generic was shown to have lower adherence and a shorter treatment persistence, which was associated with incremental use of resources producing additional health care costs for the Spanish National Health System. This increment might be considered substantial due to the frequency of these health problems in routine medical practice. There is little evidence available evaluating such measurements in a single study, and this makes our work conceptually attractive and gives it a more comprehensive approach than anything published to date. Moreover, these are patients who did not have their medication changed, but took the medication initially prescribed (although the appearance of generic drugs could vary from one manufacturer to another), and this enhances the measure of effect in our study. However, it has to be said that without adequate standardization of methods in terms of patient characteristics, and the number and extent of the variables studied, the results should be interpreted with caution and we must be conservative about the external validity of the results as the study was carried out in a local population setting only. Furthermore, although previously reported in the



**Table 4** Medication prescribed to the patients in pre-treatment (6 previous months) and treatment (12-month follow-up)

<b>Gabapentin</b>		<b>Brand</b>		<b>Generic</b>		<b>Difference<sup>a</sup></b>	<b>P-value</b>
<b>Therapeutic class</b>	<b>Period</b>	<b>N</b>	<b>Mean (SD) or %</b>	<b>N</b>	<b>Mean (SD) or %</b>		
Average number of drugs	Pre-treatment	400	2.3 (1.2)	969	2.6 (1.3)	0.3	<0.001
	Treatment	400	1.9 (1.1)	969	2.5 (1.4)	0.5	<0.001
	Difference		-0.34		-0.04		
	P-value		<0.001		0.261		
NSAIDs	Pre-treatment	244	61.0%	703	72.5%	11.5%	0.001
	Treatment	192	48.0%	674	69.6%	21.6%	<0.001
	Difference		-13.0%		-3.0%		
	P-value		<0.001		0.085		
Analgesics (non-narcotic)	Pre-treatment	240	60.0%	674	69.6%	9.6%	0.011
	Treatment	186	46.5%	643	66.4%	19.9%	<0.001
	Difference		-13.5%		-3.2%		
	P-value		<0.001		0.076		
Opiates	Pre-treatment	119	29.8%	309	31.9%	2.1%	0.689
	Treatment	110	27.5%	289	29.8%	2.3%	0.695
	Difference		-2.3%		-2.1%		
	P-value		0.335		0.189		
Anxiolytics	Pre-treatment	166	41.5%	455	47.0%	5.5%	0.268
	Treatment	149	37.3%	448	46.2%	9.0%	0.055
	Difference		-4.3%		-0.7%		
	P-value		0.056		0.635		
Antidepressants	Pre-treatment	110	27.5%	285	29.4%	1.9%	0.557
	Treatment	115	28.8%	321	33.1%	4.4%	0.429
	Difference		1.3%		3.7%		
	P-value		0.559		0.005		
<b>Venlafaxine</b>		<b>Brand</b>		<b>Generic</b>		<b>Difference<sup>a</sup></b>	<b>P-value</b>
<b>Therapeutic class</b>	<b>Period</b>	<b>N</b>	<b>Mean (SD) or %</b>	<b>N</b>	<b>Mean (SD) or %</b>		
Average number of drugs	Pre-treatment	371	2.3 (1.5)	471	2.6 (1.6)	0.3	0.002
	Treatment	371	2.0 (1.4)	471	2.5 (1.5)	0.4	<0.001
	Difference		-0.25		-0.10		
	P-value		0.001		0.117		
NSAIDs	Pre-treatment	168	45.4%	257	54.6%	9.2%	0.044
	Treatment	143	38.6%	259	55.0%	16.4%	0.002
	Difference		-6.8%		0.4%		
	P-value		0.017		0.870		
Analgesics (non-narcotic)	Pre-treatment	161	43.5%	216	45.9%	2.3%	0.699
	Treatment	160	43.2%	221	46.9%	3.7%	0.607
	Difference		-0.3%		1.1%		
	P-value		0.924		0.676		
Opiates	Pre-treatment	56	15.1%	74	15.7%	0.6%	0.887
	Treatment	65	17.6%	73	15.5%	-2.1%	0.748
	Difference		2.4%		-0.2%		
	P-value		0.217		0.901		
Anxiolytics	Pre-treatment	238	64.3%	353	74.9%	10.6%	0.009
	Treatment	191	51.6%	318	67.5%	15.9%	0.006
	Difference		-12.7%		-7.4%		
	P-value		<0.001		<0.001		
Antidepressants	Pre-treatment	56	15.1%	75	15.9%	0.8%	0.787
	Treatment	49	13.2%	70	14.9%	1.7%	0.667
	Difference		-1.9%		-1.0%		
	P-value		0.734		0.876		
Antipsychotic agents	Pre-treatment	54	14.6%	89	18.9%	4.3%	0.427
	Treatment	48	13.0%	88	18.7%	5.7%	0.358
	Difference		-1.6%		-0.2%		
	P-value		0.343		0.889		

**Notes:** <sup>a</sup>Percentage difference (treatment and pre-treatment; generic vs brand). During the study period, the patients were taking various medications at the same time.

**Abbreviations:** SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs.



**Table 6** Health care and non-health care costs (lost labor productivity) by study group

Study groups		Gabapentin			Venlafaxine					
Subgroups		Brand	Generic	Total	P-value	Brand	Generic	Total	P-value	
	Number of patients, %	N=400 (29.2%)	N=969 (70.8%)	N=1,369 (100%)		N=370 (44.0%)	N=471 (56.0%)	N=841 (100%)		
Health care costs		1,083.3 (844.5)	1,274.8 (1,051.4)	1,218.8 (998.9)	0.001	948.7 (805.9)	1,106.7 (1,302.5)	1,037.2 (1,113.9)	0.041	
	Primary care costs	751.7 (479.9)	850.6 (445.7)	821.7 (458)	<0.001	686.4 (517.9)	805.7 (545)	753.2 (536.2)	0.001	
Doctors' visits		296.5 (231.5)	367.0 (251.3)	346.4 (247.7)	<0.001	263.2 (231.2)	328.7 (251.7)	299.9 (244.9)	<0.001	
Laboratory tests		18.7 (25.9)	25.5 (27.4)	23.5 (27.1)	<0.001	16.6 (23.6)	21.9 (25.7)	19.6 (25.0)	0.002	
Conventional radiology		12.4 (18.3)	17.0 (19.7)	15.6 (19.4)	<0.001	9.1 (18.3)	10.0 (16.4)	9.6 (17.2)	0.458	
Investigations		5.7 (14.8)	8.7 (19.5)	7.8 (18.3)	0.006	5.6 (28.6)	3.9 (13.5)	4.7 (21.5)	0.259	
Main study medication		255.5 (109.8)	207.5 (67)	221.5 (84.7)	<0.001	205 (153.1)	166.6 (207.7)	183.5 (186.5)	0.003	
Concomitant medication <sup>a</sup>		163.0 (315.0)	224.9 (291.6)	206.8 (299.8)	<0.001	186.8 (332.7)	274.6 (351.3)	236.0 (345.8)	0.002	
Hospital care costs		331.6 (614.6)	424.2 (858.1)	397.1 (795.6)	0.050	262.3 (534.5)	301.0 (1,139.4)	284.0 (923.2)	0.546	
Days of hospitalization		81.8 (357.9)	110.5 (579.7)	102.1 (524.7)	0.359	67.2 (378.1)	102.8 (1,074.3)	87.2 (841.9)	0.543	
Hospital visits		166.6 (251.4)	178.5 (244.8)	175 (246.7)	0.414	130.0 (259.1)	118.2 (172.5)	123.4 (214.9)	0.430	
Day hospital sessions		39.7 (250.9)	53.0 (351.1)	49.1 (325)	0.492	15.5 (103.8)	11.0 (105.2)	13.0 (104.6)	0.536	
Hospital emergencies		43.5 (93.5)	82.2 (97.3)	70.9 (97.7)	<0.001	49.6 (104)	69.0 (99.7)	60.4 (102.0)	0.006	
Non-health care costs (productivity)		378 (1,592.8)	390.9 (1,688.9)	387.1 (1,660.9)	0.897	360.1 (1,708.7)	403.4 (1,779.3)	384.4 (1,747.7)	0.722	
Total costs, unadjusted		1,461.4 (1,835.8)	1,665.6 (2,053.7)	1,605.9 (1,994)	0.048	1,308.8 (1,920.8)	1,510.1 (2,197.1)	1,421.6 (2,081.3)	0.040	
Adjusted costs <sup>b</sup>				Difference				Difference		
Health care costs		1,057	1,277	-220	<0.001	928	1,110	-182	0.020	
95% CI		959-1,155	1,213-1,341			814-1,042	1,006-1,215			
Primary care costs		722	855	-133	<0.001	670	796	-126	0.001	
95% CI		678-766	826-884			616-724	747-845			
Specialist care costs		335	422	-87	0.075	257	314	-57	0.388	
95% CI		255-415	370-474			161-353	226-402			
Non-health care costs (productivity)		340	442	-102	0.307	362	438	-76	0.546	
95% CI		178-504	336-549			181-544	272-604			
Total adjusted costs		1,398	1,720	-322	0.008	1,290	1,549	-259	0.035	
95% CI		1,200-1,596	1,590-1,849			1,072-1,509	1,350-1,749			

**Notes:** Values are expressed as mean ( $\pm$  standard deviation). <sup>a</sup>Concomitant medication (antipsychotic agents, antidepressants, anxiolytics, opiates, analgesics, and non-steroidal anti-inflammatory drugs); <sup>b</sup>adjusted for covariates (age, sex, medication possession ratio, treatment persistence, time since diagnosis, resource utilization bands, and Charlson index). All cost values are expressed in €.

**Abbreviation:** CI, confidence interval.

**Table 7** Variation of pain intensity and anxiety symptoms between baseline and treatment discontinuation by study group

Variable	Brand	Generic	Difference/OR (95% CI) <sup>a</sup>	P-value
Pain intensity (VAS)				
Start of treatment	7.1 (1.5)	7.2 (1.4)	-0.1 (-0.1; 0.3)	0.340
Treatment discontinuation	3.6 (2.4)	4.1 (2.0)	-0.5 (-0.7; -0.2)	<0.001
Change start-discontinuation (pts)	-3.5 (2.0)	-3.1 (1.8)	-0.5 (-0.7; -0.2)	<0.001
Relative variation (%)	-51.0 (27.5)	-43.2 (22.5)	-7.8 (-10.7; -4.9)	<0.001
Responders ( $\downarrow \geq 50\%$ ), %	64.3	38.8	3.1 (2.4; 4.1) <sup>b</sup>	<0.001
Remission (<4 pts), %	58.3	37.6	2.7 (2.0; 3.5) <sup>b</sup>	<0.001
Anxiety symptoms (HAM-A)				
Start of treatment	24.8 (6.9)	25.6 (6.7)	-0.9 (-1.9; 0.2)	0.108
Treatment discontinuation	9.5 (2.6)	13.0 (5.1)	-3.4 (-4.0; -2.9)	<0.001
Change start-discontinuation (pts)	-15.7 (5.7)	-12.3 (5.5)	-3.4 (-4.0; -2.9)	<0.001
Relative variation (%)	-61.5 (10.1)	-48.2 (13.6)	-13.2 (-15.1; -11.4)	<0.001
Responders ( $\downarrow \geq 50\%$ ), %	67.0	39.1	5.5 (3.8; 8.1) <sup>b</sup>	<0.001
Remission (<7 pts), %	15.9	1.9	10.7 (5.1; 22.8) <sup>b</sup>	<0.001

**Notes:** Values are expressed as mean ( $\pm$  standard deviation) unless otherwise specified. VAS, range 0–10; HAM-A, range 0–56; <sup>a</sup>values adjusted for age, sex, and score at start of treatment; <sup>b</sup>OR.

**Abbreviations:** OR, odds ratio; CI, confidence interval; VAS, visual analog scale; pts, points; HAM-A, Hamilton Anxiety Rating Scale.

result of the placebo effect,<sup>42</sup> which might drive the patients to temporarily interrupt the treatment and/or discontinue definitively the therapy until his/her family physician makes a decision.

The results of our study are the first to show that the use of generics is associated with increased use of health care resources and costs, with a degree of clinical effectiveness somewhat inferior to the brand drug in the two drugs analyzed. The temporal relationship between lack of adherence, lower persistence, less clinical effectiveness, and more use of health resources is beyond doubt and very consistent in the literature.<sup>33,43,44</sup> However, one criticism may be raised by the fact that patients receiving generics were taken more drugs in the pretreatment period both with gabapentin and venlafaxine as well. Consequently, that could jeopardize the baseline comparability of groups since it could be interpreted as certain channeling effect toward including more refractory patients in the generic cohorts. Nevertheless, at least in the case of the gabapentin group, such differences accounted for medicines (nonsteroidal anti-inflammatory drugs [NSAIDs] and non-narcotic analgesics) with a limited use in neuropathic pain conditions making such criticism less plausible. Also, and although not pair-matched because of the sample size, brand-name and generic cohorts were fairly comparable at baseline in all but one variable (sex in the case of the gabapentin group), and the multivariate statistic methodology applied accounted for possible confounders that usually are a source of differential health resource use and costs.

On the other hand, Tran et al report that the use of generics is associated with a reduction in therapeutic control

objectives (clinical effectiveness: LDL cholesterol) in the treatment of dyslipidemia and, in a prospective study,<sup>45</sup> Gagne et al found that patients starting treatment with generic statins, compared with brand, had a higher non-compliance and higher rates of cardiovascular events.<sup>19</sup> The previously mentioned data cannot be generalized, but are consistent with other published studies.<sup>33</sup> The results also show that the cost of background drugs was higher in patients treated with brand gabapentin and venlafaxine. This could be due to three factors: 1) the study had a long patient inclusion period (5 years), in the early years of which the price of brand drugs was higher than generics (they were not at reference price); 2) treatment adherence and persistence among these patients was also higher; and 3) there was a greater proportion of patients (particularly in the gabapentin group) who had received higher doses of the drug. The most plausible explanation, however, may be the greater persistence with brand treatment. The higher cost of drugs mentioned earlier was offset by lower total costs, mainly due to a reduction in medical visits and concomitant medications for the health conditions assessed here. The estimated potential saving per patient/year using brand instead of generic was €322 with gabapentin and €259 with venlafaxine (€220 and €182 if health care costs alone are considered, respectively). It is our opinion that this reduction in unit costs (about 17% with an effect size according to Cohen's *d*-statistic of moderate magnitude)<sup>31</sup> is meaningful in terms of efficiency in the clinical management of this group of patients given the high prevalence of these disorders. The influence of the factors discussed earlier (factors associated with lack of adherence with generics) has probably affected all this.<sup>37–43</sup>

The results of this study point to some strategies for intervention, especially for policy-makers and health service governing bodies. Changes in the appearance of the drug can cause patients to lose confidence in the safety or effectiveness of the generic prescription, affecting non-adherence to treatment, especially in chronic diseases and patients on multiple medications.<sup>17,19,33</sup> Reducing the variability in appearance among drugs which are chemically identical could help promote adherence.<sup>37</sup> Initially, the governing bodies could make it a requirement of new applicants for generics that the shape and color of the pills are homogeneous and consistent with the brand medication. However, the most plausible and practical suggestion would be that having such a demanding policy on the use of generics is no longer necessary, since it has ceased to be an argument for reducing pharmaceutical expenditure.

## Limitations

The possible limitations of the study are those inherent to retrospective studies, such as under-registering of resources use, coding errors of disorders, or possible variability among the health care professionals and patients due to the observational design, or even the costing system used and the possibility of a classification bias. In this regard, any inaccuracy in diagnostic coding in the diagnosis of pNP or GAD, or the lack of some variable that could influence the final results (socioeconomic status of patients, changes in the drug doses prescribed, changes in form and presentation in the generics, etc), should be considered as a limitation of the study. Moreover, we were not able to obtain data for all patients on measurement of clinical effectiveness (health outcomes, assessment scales), especially in the final period; however, this omission was spread evenly between the study's two subgroups and the fact that the imputation was very conservative (worst available value) confers a certain degree of robustness to the results. However, we believe that the main drawbacks of this study, and where the results should be interpreted with caution, are: 1) selection bias by the physician when starting brand or generic treatment, since this was not done randomly as is usual in routine clinical practice which may jeopardize the comparability of groups; and 2) the external validity of the results (generalizability of the data), since the study was conducted in a single local health service-providing organization.

Future prospects offered by this study should focus on replication in other health care institutions and promoting intervention strategies designed to promote adherence to

medicines. In conclusion, patients who started treatment with brand-name gabapentin (pNP) and venlafaxine (GAD) showed greater adherence and persistence to treatment and better outcomes in the clinical variables compared with generics, resulting in lower costs for the Spanish National Health System.

## Authors' contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

J Rejas-Gutiérrez is an employee of Pfizer SLU. The other authors have no conflicts of interest in this work. No funding was received for this study.

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