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ORIGINAL ARTICLE

# Cost of treatment of peripheral neuropathic pain with pregabalin or gabapentin in routine clinical practice: impact of their loss of exclusivity

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## Abstract

To analyze the effect of loss of exclusivity of data on the cost of treatment of peripheral neuropathic pain (PNP) with pregabalin or gabapentin in routine clinical practice. A retrospective observational study, with electronic medical records for patients enrolled at primary care centers managed by the health care provider Badalona Serveis Assistencials, who initiated treatment of PNP with pregabalin or gabapentin. The analysis used drugs and resources prices for year 2015. The 1163 electronic medical records (pregabalin; N = 764, gabapentin; N = 399) for patients (62.2% women) with a mean (standard deviation) age of 59.2 (14.7) years were analyzed. Treatment duration was slightly shorter with pregabalin than with gabapentin (5.2 vs 5.5 months; $P = 0.124$), with mean doses of 227.4 (178.6) mg and 900.0 (443.4) mg, respectively. The average study drug cost per patient was higher for pregabalin than for gabapentin; €214.6 (206.3) vs €157.4 (181.9), $P < 0.001$, although the cost of concomitant analgesic medication was lower; €176.5 (271.8) vs €306.7 (529.2), $P < 0.001$. The adjusted average total cost per patient was lower in those treated with pregabalin than in those treated with gabapentin; €2,413 (2119-2708) vs €3201 (2806–3.597); $P = 0.002$, owing to significantly lower health care costs; €1307 (1247-1367) vs €1538 (1458-1618), $P < 0.001$, and also non-health care costs; €1106 (819-1393) vs €1663 (1279-2048), $P = 0.023$, that was caused by a significantly lower use of concomitant medication, fewer medical visits to primary care, and fewer days of sick leave. After loss of exclusivity of both drugs, pregabalin continued to show lower health care and non-health care costs than gabapentin in the treatment of PNP in routine clinical practice.

KEYWORDS

costs, gabapentin, loss of data exclusivity, neuropathic pain, pregabalin

## 1 | INTRODUCTION

Peripheral neuropathic pain (PNP) is a direct result of a lesion or disease that affects the peripheral somatosensory system.[1] According to the International Association for the Study of Pain, neuropathic pain is defined as pain initiated or due to a primary lesion or dysfunction of the nervous system.[2] The most commonly used classification of PNP is based on aetiology, subdividing aetiologies according to location of the peripheral or central nervous system lesion.[1–3] The prevalence of PNP varies from 5% to 12% of the adult population.[4,5] This variability is, in part, due to a lack of uniform diagnostic criteria. In Spain, a population prevalence of 7.7% was obtained, associated with a high percentage of depression and impact on work productivity.[6,7] In studies conducted in neurology and primary care clinics, polyneuropathy is the most common cause of neuropathic pain.[6,7]

In some patients, PNP is difficult to treat.[1–3] Neuromodulators such as pregabalin and gabapentin are considered to be treatments of choice for PNP.[1,3,8–10] Both drugs seem to have a positive impact on the set of symptoms accompanying PNP and have similar efficacy and tolerability profiles.[8–12] The major difference between them lies in their pharmacokinetics, because pregabalin has a better pharmacokinetic profile, with linear absorption regardless of dose and receptor affinity 6 times greater than that of gabapentin. These aspects may explain why pregabalin is clinically more effective at a lower dose.[13–15] In addition, both medicines have now lost data exclusivity in the treatment of PNP, and their public and funding prices has therefore been substantially reduced.

PNP has a high impact, particularly on sufferers, and also on the society in general as well, becoming to be considered a public health problem.[1,3] Patients experience a worsening of their state of health and a greater degree of disability, and they often develop mood disorders associated with anxiety, depression, and sleep disorders.[16–18] These events translate to a loss of quality of life that affects their family and working lives.[1,3] As a consequence, PNP is associated with high costs both direct health care (treatment, visits, etc.) and indirect (work performance).[18,19] On the other hand, available evidence comparing pregabalin and gabapentin for resource use and cost is limited.[19–22] Moreover, new data are required adapted to the changing scenarios in health care policy in Spain, such as the following: (1) reductions in the reference prices of medicines following loss of data exclusivity (in this case for the treatment of PNP with gabapentin or pregabalin in routine clinical practice); (2) repercussions of the economic crisis in Spain for the prices associated with the different cost components; and/or (3) the growing need to conduct representative studies of the behavior of medicines in real life. Therefore, once loss of data exclusivity had occurred for gabapentin and pregabalin in the treatment of PNP, the objective of this study was to analyze its effect on the cost of treatment of PNP in a routine clinical practice setting, as well as to analyze the effect of sex, age, and type of neuropathic pain on that cost.

## 2 | METHODS AND PATIENTS

### 2.1 | Study design and population

This study was conducted using the database from a previous study,[21] with a retrospective observational design, and based on the review of electronic medical records (EMRs) (electronic databases with dissociated data) for patients followed up on an outpatient or inpatient basis, from 6 primary care centers (managed by Badalona Serveis Assistencials) and their reference hospital (Hospital Municipal de Badalona). The population assigned to those centers was mostly urban, of medium-low socioeconomic standing and predominately working-class. The patients enrolled in the study had sought care with a diagnosis of PNP according to the ICPC-2 classification (described below) from January 01, 2006 to December 31, 2008 and met the following characteristics: (1) who is man or woman >18 years of age; (2) whose follow-up could be ensured (>2 records); (3) who were in the prescription program (record of the dose, etc.); and (4) who started treatment for the first time with gabapentin or pregabalin as a primary indication for the treatment of PNP (new users design).[23,24] The diagnosis of PNP was obtained based on the International Classification of Primary Care (ICPC-2; N92-N99),[25] and the emergency and hospital discharge coding of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Patients treated with pregabalin or gabapentin with any of the following PNP codes were enrolled: (1) painful focal neuropathy: (a) syndromes related to compression of peripheral nerves or roots (lumbar radiculopathy [353.1], thoracic radiculopathy [353.3], or cervical radiculopathy [353.0]; carpal tunnel syndrome [354.0] or tarsal tunnel syndrome [355.5]; and meralgia paraesthetica [355.1]); (b) syndromes related to inflammation of peripheral nerves (herpetic neuralgia, [053.13]); (c) syndromes associated with nerve trauma, with or without formation of neuroma (postoperative pain [338.28]); and (d) common syndromes of unknown aetiology (intercostal neuralgia, [353.8]); (2) painful polyneuropathy (polyneuropathy of acute or chronic onset: (a) associated with AIDS [357.4] or diabetic [357.2] and (b) small or large fiber polyneuropathy (vascular, toxic, inflammatory, and paraneoplastic [357.9]); (3) postherpetic neuralgia [053.13]; (4) trigeminal neuralgia [350.1] and other types of cranial neuralgia [352.9]; and (5) other common pain syndromes (tethered cord syndrome, multiple sclerosis, and syringomyelia [357.8×]). Patients who were transferred, moved, or outside of the area, as well as patients treated simultaneously with both medicines during the study period, were excluded from the study.

### 2.2 | Treatments administered

Information was obtained on the dose and duration of the main treatments studied—gabapentin and pregabalin—based on the information provided by the Catalan Health Service (CatSalut). Data were gathered on the number and format of the prescriptions received by the patients starting from the first prescription, within the abovementioned study period and for the 24 months following the start of treatment, and all EMRs that met selection criteria were extracted. Also for the 24-month follow-up period, information was obtained on the pharmacological prescriptions for specific and concomitant medicines for PNP provided by CatSalut according to the Anatomical Therapeutic Chemical Classification System[26]: non-steroidal anti-inflammatory drugs (M01), opioids (N02A), non-narcotic analgesics (N02B), and antidepressants (N06A).

### 2.3 | Socio-demographic and comorbidity variables

To control for the effect of potential confounding factors affecting the estimate of the main effects of the treatments evaluated, the following study variables were taken into account: age (continuous and by group), sex, occupational status (active worker or retiree), time from diagnosis of PNP to start of treatment with the drugs under study, as well as presence of comorbidities such as hypertension, type 2diabetes mellitus, dyslipidaemia, obesity, smoking habit, alcoholism, organ failure (heart, liver, or kidneys), ischaemic cardiomyopathy, cerebrovascular accident, obstructive pulmonary disease, bronchial asthma, dementia, psychosis, neurological diseases (Parkinson's disease, epilepsy, and multiple sclerosis), depressive syndrome, malignant

neoplasms, and substance abuse. In addition, the following were used for each patient cared for as a summary variable of general comorbidity: (1) the Charlson comorbidity index,[27] as an estimation of the seriousness of the patient's condition; and (2) the case-mix index, obtained based on adjusted clinical groups (ACGs), a system of classifying patients by iso-consumption of resources.[28] The ACG application provided resource use bands (RUBs), which were used to group each patient into 1 of 5 mutually exclusive categories depending on his or her morbidity: (1) healthy users with very low morbidity, (2) low morbidity, (3) moderate morbidity, (4) high morbidity, and (5) very high morbidity. Information on PNP severity was not collected, as this is not a routinely measured variable.

## 2.4 | Use of health care and non-health care resources and costs

Only health care costs related to PNP were taken into account, with respect to both health care activity (medical visits, days of hospitalization, emergencies, diagnostic and/or therapeutic requests, and rehabilitation/physiotherapy sessions) and indirect costs due to work productivity losses (number of days with complete occupational disability) because of PNP. No other potential indirect costs were taken into account. Total costs for any reason were not taken into account. The design of the cost system was identified, taking into account the characteristics of the organization and the degree of development of the available information systems. The cost was expressed as mean cost per patient (cost per unit) as was adjusted by covariates. Table 1 lists the different study items and their economic valuation for 2015, when loss of data exclusivity had already occurred for the medicines analyzed and their prices were current. The different prices were obtained based on the centers' analytical accounting, except medication and days of sick leave. The prescriptions were quantified according to public sale price in 2015. The indirect cost was quantified according to the average wage among professions (source: Spanish Statistical Office [INE]).[29] All costs were determined in the 24 months following the start of treatment with gabapentin or pregabalin. This study did not consider computing direct non-health care costs, ie, costs considered to be "out-of-pocket" expenses or paid by the patient/family, as they were not recorded in the database.

**TABLE 1** Details of costs per unit and of work productivity losses

| Health Care and Non-health Care Resources | Unit Costs (€) |
|---|---|
| Medical visits | |
| Medical visit to primary care | 23.5 |
| Medical visit to emergency department | 119.3 |
| Hospitalization (1 d) | 325.6 |
| Medical visit to specialized care | 105.9 |
| Complementary tests | |
| Laboratory tests | 22.6 |
| Conventional radiology | 18.8 |
| Diagnostic/therapeutic tests | 37.7 |
| Drug prescription | PSP |
| Work productivity—indirect costs | |
| Work-related cost per day not worked | 82.4 |

Abbbreviation: PSP, public selling price.

Source of health care resources: analytical accounting (year 2015).

Values are expressed in euros.

## 2.5 | Confidentiality of information and quality control

The confidentiality of the records established by the Spanish Organic Data Protection Law (15/1999, of 13 December) was respected, with dissociation of the data. The study was classified by the Spanish Agency for Medicines and Medical Devices as a post-authorization study—other design (EPA-OD) and subsequently approved by the Independent Ethics Committee of Hospital Universitari Germans Trias i Pujol in Badalona. The EMRs used in the study were managed by the body surface area provider, which ensured the confidentiality and anonymity (dissociation) of the data. The organization's computer system possessed a data warehouse with levels of data completeness. This ensured the quality of the study data.

## 2.6 | Statistical analysis

The sample size was not predetermined *a priori*, given that the study included comprehensive extraction of the EMRs that met selection criteria. Nonetheless, the statistical power of the study was calculated *a posteriori* based on the difference observed in the main effect of the treatments on the health care cost and total cost with the sample size eventually recruited. The power observed, with the sample size recruited and for the differences detected, was greater than 90% (type II error < 0.1) for a 95% confidence level (type I error < 0.05). A descriptive univariate statistical analysis was performed with values for mean, median, standard deviation, and 95% confidence interval (CI) in parametric variables, and median and interquartile ranges in nonparametric variables, once the Kolmogorov-Smirnov test had confirmed a normal distribution. In the bivariate analysis, the analysis of variance, chi-squared and Mann-Whitney-Wilcoxon nonparametric tests were used according to distribution of the data to analyze the homogeneity of the variables in the study groups. A logistic regression analysis was also performed with all the comorbidities associated with the use of pregabalin or gabapentin and the predetermined variables (age, sex, Charlson index, ACG, etc.) to determine their potential confounding effect on the estimate of the main effects of treatment with gabapentin or pregabalin. A comparison of resource use and its corresponding costs was performed according to the recommendations by Thompson and Barber using a general linear model (ANCOVA) with covariates deemed appropriate.[30] The covariates used in the model were sex, age, time since diagnosis, Charlson index, and RUB. The Bonferroni correction was applied for multiple comparisons when appropriate. The software program used was SPSS version 17.0 for Windows, and statistical significance was established for $P$ values < 0.05.

# 3 | RESULTS

From an initial selection of 86 206 patients more than 18 years of age assigned to the centers, 1160 patients were recruited who met the

**TABLE 2** Baseline characteristics and distribution of the different types of peripheral neuropathic pain by study group

| Study Group, Number of Patients (%) | Pregabalin, N = 764 (65.7%) | Gabapentin, N = 399 (34.3%) | Total, N = 1163 (100%) | *P* |
|---|---|---|---|---|
| **Socio-demographic characteristics** | | | | |
| Average age (y) | 59.8 (14.6) | 58.1 (14.8) | 59.2 (14.7) | 0.055 |
| Sex (female) | 64.5% | 57.6% | 62.2% | 0.051 |
| Retiree status | 56.0% | 55.4% | 56.8% | 0.654 |
| Range | | | | |
| 20 to 44 y | 17.1% | 19.5% | 18.0% | |
| 45 to 64 y | 45.5% | 45.6% | 45.6% | |
| 65 to 74 y | 20.2% | 20.6% | 20.3% | |
| >74 y | 17.1% | 14.3% | 16.2% | 0.534 |
| **General comorbidity** | | | | |
| Average Charlson index | 0.5 (1.1) | 0.6 (0.9) | 0.6 (1.0) | 0.147 |
| Average RUB | 3.1 (0.7) | 3.1 (0.7) | 3.1 (0.7) | 0.865 |
| RUB-1 | 2.2% | 1.8% | 2.1% | |
| RUB-2 | 10.5% | 9.8% | 10.2% | |
| RUB-3 | 64.7% | 66.4% | 65.3% | |
| RUB-4 | 18.6% | 18.3% | 18.5% | |
| RUB-5 | 4.1% | 3.8% | 4.0% | 0.963 |
| **Associated comorbidities**[1] | | | | |
| Hypertension | 43.6% | 41.1% | 42.7% | 0.416 |
| Type 2 diabetes mellitus | 19.8% | 17.3% | 18.9% | 0.307 |
| Dyslipidaemia | 49.0% | 41.9% | 46.5% | 0.021 |
| Obesity | 23.6% | 18.5% | 21.8% | 0.049 |
| Active smokers | 23.3% | 23.3% | 23.3% | 0.997 |
| Alcoholism | 3.3% | 5.5% | 4.0% | 0.092 |
| Ischaemic cardiomyopathy | 6.8% | 5.0% | 6.2% | 0.228 |
| Cerebrovascular accident | 3.3% | 3.5% | 3.4% | 0.832 |
| Bronchial asthma | 7.7% | 6.0% | 7.1% | 0.283 |
| COPD | 4.8% | 5.8% | 5.2% | 0.593 |
| Neuropathy | 1.3% | 3.3% | 2.0% | 0.023 |
| Dementia (all types) | 2.6% | 3.3% | 2.8% | 0.532 |
| Organic psychosis | 1.3% | 1.8% | 1.5% | 0.548 |
| Depressive syndrome | 34.7% | 28.6% | 32.6% | 0.035 |
| Malignant neoplasms | 9.4% | 6.8% | 8.5% | 0.123 |
| Substance abuse | 1.6% | 4.5% | 2.4% | 0.003 |
| **Painful focal neuropathy** | | | | |
| Lumbar radiculopathy | 27.1% | 24.8% | 26.3% | 0.268 |
| Cervical radiculopathy | 17.1% | 19.8% | 18.1% | 0.396 |
| Meralgia paraesthetica | 12.4% | 10.5% | 11.8% | 0.307 |
| Thoracic radiculopathy | 5.2% | 3.8% | 4.7% | 0.353 |
| Carpal tunnel syndrome | 1.4% | 2.5% | 1.8% | 0.178 |
| Painful neuropathy | 1.0% | 1.8% | 1.3% | 0.452 |
| Intercostal neuralgia | 1.0% | 1.3% | 1.1% | 0.567 |
| Postoperative neuroma | 0.7% | 0.8% | 0.7% | 0.535 |
| All cases in the group (N = 765) | 66.1% | 65.2% | 65.8% | 0.785 |
| **Painful polyneuropathy** | | | | |
| Diabetic polyneuropathy | 19.0% | 22.6% | 20.2% | 0.225 |
| Sensory polyneuropathy | 0.9% | 0.3% | 0.7% | 0.241 |
| Demyelinating polyneuropathy and AIDS | 0.7% | 0.5% | 0.6% | 0.427 |
| All cases in the group (N = 250) | 20.5% | 23.3% | 21.5% | 0.233 |
| **Other painful neuropathy** | | | | |
| Trigeminal neuralgia | 7.1% | 9.3% | 7.8% | 0.224 |

(*Continues*)

**TABLE 2** (Continued)

| Study Group, Number of Patients (%) | Pregabalin, N = 764 (65.7%) | Gabapentin, N = 399 (34.3%) | Total, N = 1163 (100%) | *P* |
|---|---|---|---|---|
| Postherpetic neuralgia | 5.2% | 2.3% | 4.2% | 0.111 |
| Associated with multiple sclerosis | 0.8% | – | 0.5% | – |
| Associated with syringomyelia | 0.3% | – | 0.2% | – |
| All cases in the group (N = 148) | 13.4% | 11.5% | 12.7% | 0.626 |

Abbreviation: COPD: chronic obstructive pulmonary disease; RUB, resource use band.

Values are expressed as percentage or mean (standard deviation).

selection criteria for the study to be included in the statistical analysis. There were 764 patients (65.7%) in the pregabalin study group and 399 patients (34.3%) in the gabapentin study group. Their mean age was 59.2 (14.7) years and 62.2% were female. Among all patients, 46.5% had dyslipidaemia, 42.7% had hypertension, and 32.6% had depressive syndrome. Table 2 shows the baseline characteristics of the series studied and distribution of the different types of PNP by study group. Age and sex showed numerical differences that did not achieve statistical significance: a mean age of 59.8 years on pregabalin versus 58.1 years with gabapentin ($P$ = 0.055); and a proportion of women of 64.5% versus 57.6% ($P$ = 0.051). The proportion of associated comorbidities, RUB (3.1 versus 3.1; $P$ = 0.865) and Charlson index (0.5 versus 0.6; $P$ = 0.147) were not statistically different (Table 2). In the corrected logistic regression model, the use of pregabalin was associated with dyslipidaemia (odds ratio = 1.3; 95% CI: 1.1-1.7), while gabapentin was associated with the presence of neuropathy (odds ratio = 2.4; 95% CI: 1.1-5.7), $P$ < 0.033. In 65.8% (N = 765) of patients with PNP, it was due to some sort of radiculopathy (cervical or lumbar: 44.4%), in 21.5% (N = 250), it was due to polyneuropathy (diabetic: 20.2%), and in 12.0% (N = 140), it was due to trigeminal/postherpetic neuralgia. The distribution of PNP showed no statistically significant differences regarding the use of pregabalin or gabapentin.

Table 3 lists the characteristics of use of the medication. In general, mean duration of treatment with pregabalin was slightly lower than with gabapentin (5.2 versus 5.5 months), with ranges ≥8 months of 22.7% and 25.9%, respectively, although without reaching statistical significance. With pregabalin, 6.9% of the patients took doses lower than 150 mg/day (therapeutic range 150 to 600 mg/day), while with gabapentin, 46.9% of the patients took doses lower than 900 mg/day (therapeutic range 900 to 1800 mg/day).

In follow-up (2 years), the patients in the pregabalin group used fewer health care resources in medical visits in outpatient care (10.8

**TABLE 3** Characteristics of use of the main medication for peripheral neuropathic pain

| Study Group, Number of Patients (%) | Pregabalin, N = 764 (65.7%) | Gabapentin, N = 399 (34.3%) | *P* |
|---|---|---|---|
| Time since diagnosis (mo) | | | |
| Mean (SD) | 14.2 (13.1) | 15.4 (10.4) | 0.174 |
| Median (P25-P75) | 11.6 (2.8–20.3) | 12.6 (7.8–25.1) | |
| Duration of treatment (mo) | | | |
| Mean (SD) | 5.2 (4.6) | 5.5 (3.9) | 0.124 |
| Median (P25-P75) | 3.0 (2.0–7.0) | 4.4 (1.9–10.6) | |
| Ranges (N, %): | | | |
| 1 to 2 mo | 316 (41.4%) | 155 (38.8%) | 0.392 |
| 3–7 mo | 279 (35.9%) | 141 (35.3%) | 0.864 |
| ≥8 mo | 175 (22.7%) | 103 (25.9%) | 0.328 |
| Daily dose of medicine | | | |
| Mean (SD) | 227.4 (178.6) | 900.0 (443.4) | |
| Median (P25-P75) | 150 (150-300) | 800 (600-1200) | |
| Ranges (N, %): | | | |
| =75 mgr/d | 53 (6.9%) | – | |
| =150 mgr/d | 488 (63.9%) | – | |
| =300 mgr/d | 141 (18.5%) | – | |
| ≤600 mgr/d | 69 (9.0%) | – | |
| >600 mgr/d | 13 (1.7%) | – | |
| <900 mgr/d | – | 187 (46.9%) | |
| =900 mgr/d | – | 87 (21.8%) | |
| ≤1800 mgr/d | – | 113 (28.3%) | |
| >1800 mgr/d | – | 12 (3.0%) | |

Values are expressed as percentage or mean (SD: standard deviation); P25-P75 means 25th and 75th percentiles of the distribution; $P$ is the statistical significance.

**TABLE 4** Average per unit of resource use according to study group

| Study Group, Number of Patients (%) | Pregabalin, N = 764 (65.7%) | Gabapentin, N = 399 (34.3%) | Total, N = 1163 (100%) | *P* |
|---|---|---|---|---|
| **Outpatient care** | | | | |
| Medical visits | 10.8 (7.1) | 14.2 (9.0) | 12.0 (7.9) | 0.002 |
| Laboratory tests | 2.0 (1.6) | 1.9 (2.6) | 2.0 (1.6) | 0.566 |
| Conventional radiology | 1.4 (1.4) | 1.3 (1.4) | 1.4 (1.4) | 0.290 |
| Complementary tests | 0.5 (1.1) | 0.5 (1.1) | 0.5 (1.1) | 0.563 |
| Physiotherapy/rehabilitation sessions | 2.2 (1.7) | 2.5 (2.3) | 2.3 (1.9) | 0.026 |
| **Specialized care** | | | | |
| Days of hospitalization | 0.1 (0.3) | 0.2 (1.5) | 0.1 (0.9) | 0.023 |
| Specialist medical visits | 2.6 (3.8) | 2.4 (2.7) | 2.5 (2.8) | 0.314 |
| Emergency department visits | 0.6 (1.1) | 0.5 (1.2) | 0.6 (1.1) | 0.463 |
| Days of occupational disability | 13.2 (36.2) | 20.8 (64.5) | 15.8 (47.9) | 0.009 |

Values are expressed as mean (standard deviation).

**TABLE 5** Health care and non-health care costs per patient according to study group

| | Pregabalin | | Gabapentin | | Total | | |
|---|---|---|---|---|---|---|---|
| **Study Group** | **Use** | **Average/Unit** | **Use** | **Average/Unit** | **Use** | **Average/Unit** | ***P*** |
| **Uncorrected Costs (€)** | | | | | | | |
| Health care costs | | 1339.8 (698.1) | | 1537.2 (1011.5) | | 1407.5 (824.1) | < 0.001 |
| Costs in primary care | | 981.1 (503.7) | | 1161.4 (728.7) | | 1043 (596.5) | < 0.001 |
| Medical visits | 100.0% | 255.3 (165.8) | 100.0% | 336.2 (211.8) | 100.0% | 283.1 (186.8) | < 0.001 |
| Laboratory tests | 78.5% | 44.8 (37.3) | 78.4% | 43.1 (37.3) | 78.7% | 44.2 (37.3) | 0.466 |
| Conventional radiology | 67.1% | 27.8 (27.7) | 61.7% | 25.9 (27.9) | 65.3% | 27.1 (27.8) | 0.290 |
| Complementary tests | 33.6% | 19.1 (37.9) | 31.3% | 17.8 (36.1) | 32.8% | 18.7 (37.3) | 0.563 |
| Physiotherapy/rehabilitation | 82.6% | 243.0 (186.1) | 82.1% | 274.3 (248.0) | 82.4% | 253.7 (209.8) | 0.016 |
| Antiepileptic medicines | 100.0% | 214.6 (206.3) | 100.0% | 157.4 (181.9) | 100.0% | 195.0 (200.1) | < 0.001 |
| Other medicines | 90.1% | 176.5 (271.8) | 93.8% | 306.7 (529.2) | 90.8% | 221.2 (385.0) | < 0.001 |
| Costs in specialized care | | 358.7 (379.0) | | 375.8 (600.7) | | 364.6 (466.9) | 0.553 |
| Days of hospitalization | 2.5% | 18.3 (104.5) | 3.4% | 61.2 (500.7) | 3.1% | 33.0 (305.7) | 0.023 |
| Medical visits | 67.9% | 271.5 (296.6) | 66.4% | 253.3 (284.6) | 67.4% | 265.3 (292.6) | 0.314 |
| A&E | 35.2% | 68.8 (129.4) | 32.9% | 61.3 (143.7) | 33.6% | 66.2 (134.5) | 0.363 |
| Non-health care costs (productivity) | 20.7% | 1088.0 (2979.9) | 23.1% | 1716.9 (5315.8) | 21.8% | 1303.7 (3949.5) | 0.010 |
| Total uncorrected costs | | 2427.8 (3066.9) | | 3254.1 (5398) | | 2711.3 (4038.6) | 0.001 |
| **Corrected Costs (€)**[a] | | | | | | **Difference** | |
| Health care costs | | 1307.0 | | 1538.0 | | −231.0 | < 0.001 |
| 95% CI | | 1247.1–1367.1 | | 1457.6–1618.4 | | −130.3; −330.9 | |
| Costs in primary care | | 961.7 | | 1163.2 | | −201.5 | < 0.001 |
| 95% CI | | 918.7–1004.7 | | 1105.6–1220.9 | | −128.7; −272.3 | |
| Costs in specialized care | | 345.3 | | 374.8 | | −29.5 | 0.320 |
| 95% CI | | 310.6–380.0 | | 328.3–421.3 | | −17.8 ; −58.1 | |
| Non-health care costs (productivity) | | 1106.2 | | 1663.4 | | −557.2 | 0.023 |
| 95% CI | | 819.3–1393.1 | | 1278.6–2048.1 | | −81.0; −1041.5 | |
| Total corrected costs | | 2413.2 | | 3201.4 | | −788.2 | 0.002 |
| 95% CI | | 2118.6–2707.8 | | 2806.3–3596.5 | | −298.7;−1285.0 | |

Abbreviation: CI, confidence interval.

[a]ANCOVA model is the contrasts are based on the comparisons by linearly independent pairs between the estimated marginal means. Variables are age, sex, time since diagnosis, Charlson index, and resource use band. Use as percentage of resource use among all patients.

Values are expressed as percentage or mean (standard deviation).

versus 14.2; $P$ = 0.002), days of hospitalization (0.1 versus 0.2; $P$ = 0.023) and days of transitory occupational disability (13.2 versus 20.8; $P$ = 0.009); see Table 4. Table 5 shows the gross and corrected costs associated with PNP according to study group. The total cost for the patients enrolled in the study amounted to €3.3 million, 51.9% of which was for direct health care costs, and 48.1% of which

was for non-health care costs (productivity losses), with a total average per unit of €2,711.3. Of the total costs, 38.5% were incurred in primary care, 13.4% were incurred in specialized care, and, of the latter, 15.4% were incurred in drug prescription. By group, the total costs (health care and non-health care) for the patients on treatment with pregabalin were lower in comparison with gabapentin (€2,427.8 versus €3,254.1; $P = 0.001$). These differences were maintained after adjusting for covariates (Table 5). The adjusted average total costs per patient was €2413.2 for pregabalin versus €3,201.4 with gabapentin (mean difference of €788 per patient per treatment, $P = 0.002$), owing to significantly lower health care costs; €1 307 (1 247-1367) vs €1538 (1458-1618), $P < 0.001$, and also non-health care costs; €1106 (819-1393) vs €1663 (1279-2048), $P = 0.023$. By components of costs, the average study drug cost per patient was higher for pregabalin than for gabapentin; €214.6 (206.3) vs €157.4 (181.9), $P < 0.001$, although the cost of concomitant analgesic medication was significantly lower; €176.5 (271.8) vs €306.7 (529.2), $P < 0.001$, yielding that the total cost in analgesic medication was significantly lower in the pregabalin group; €391 vs €464, $P < 0.05$ (Figure 1). Most cost components were lower with pregabalin, except for those observed in specialized care. Table 6 lists the distribution of the main cost components according to sex, age, and main diagnoses by study group. It should be noted that differences in average costs per patient observed in the whole sample were maintained in all subgroups, such that the patients on treatment with pregabalin were associated with lower both total and health care costs, except for subgroups of painful diabetic neuropathy and painful mononeuropathies whose differences did not reach statistical significance because of the small sample size of these subgroups (Table 6).

## 4 | DISCUSSION

This study analyzed the effect of loss of data exclusivity for pregabalin and gabapentin on the cost of PNP with these medicines, given that this is important information for decision-making in health under routine medical practice conditions in the Spanish health care setting, and owing to the extensive use made of these drugs. There have been very few economic studies conducted in Spain or other countries comparing the cost of treatment of PNP with pregabalin and gabapentin, and we are not aware of any with our study's objective. Before loss of data exclusivity, the total cost of PNP per patient was around €728 lower in those treated with pregabalin than in those receiving gabapentin during the 2 years of follow-up of the patients, €162 of which was for the health care cost component.[21] This difference (statistically significant, $P = 0.003$) was explained by lower use of health care resources (mainly medical visits and concomitant analgesic

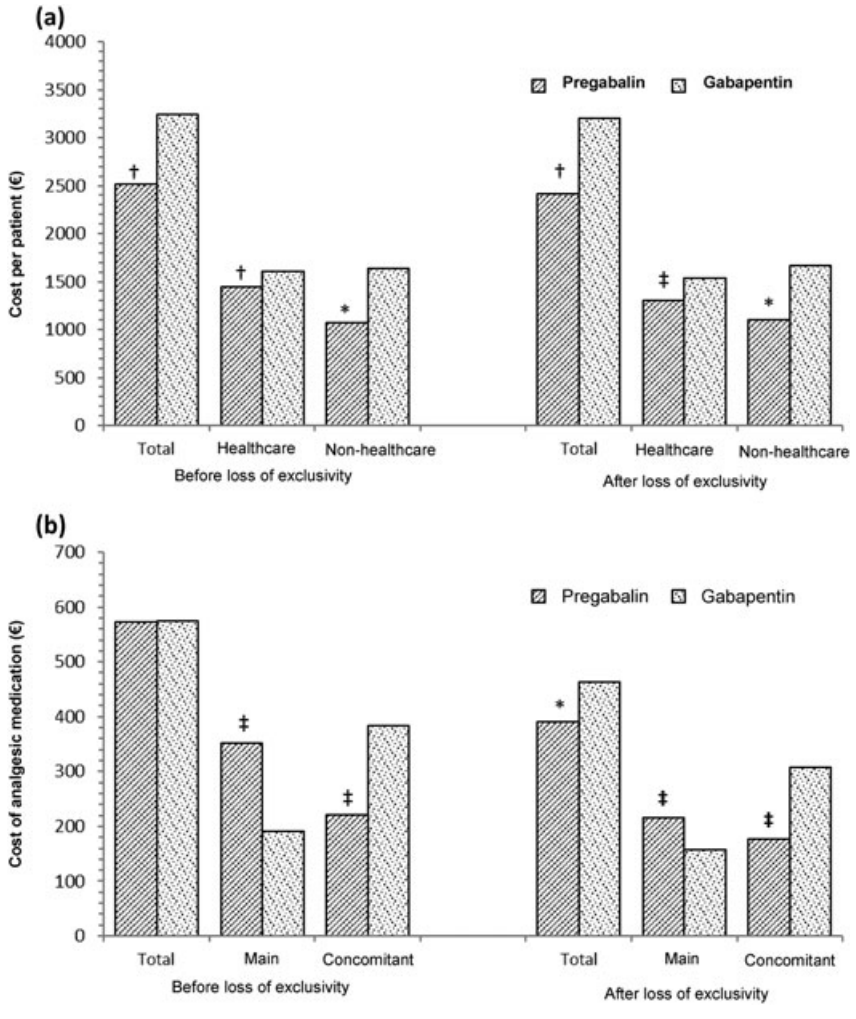


**FIGURE 1** (a) Effect of loss of exclusivity of data on the total cost per patient and (b) cost of analgesic medication (Graph B) of the treatment of peripheral neuropathic pain with gabapentin or pregabalin.
Costs (year €2015) are medical costs per patient and treatment. The main analgesic medication is pregabalin or gabapentin.
*p < 0.05; †p < 0.01; ‡p < 0.001 vs gabapentin.

**TABLE 6** Distribution of the main cost components according to sex, age and main diagnoses by study group

| Cost Distribution | Pregabalin | Gabapentin | Total | *P* |
|---|---|---|---|---|
| **Male** | **N = 270** | **N = 169** | **N = 439** | |
| Primary care | 895.4 (449.8) | 1145.3 (755.6) | 991.6 (598.4) | < 0.001 |
| Specialized care | 303.1 (366.6) | 352.7 (690.1) | 322.2 (515.6) | 0.327 |
| Health care costs | 1198.5 (653.7) | 1498.0 (1074.0) | 1313.8 (852.1) | < 0.001 |
| Non-health care costs | 1086.1 (2757.9) | 1836.1 (6130.1) | 1374.8 (4383.9) | 0.081 |
| Total cost | 2284.6 (2830.5) | 3334.1 (6185.2) | 2688.6 (4456) | 0.016 |
| **Female** | **N = 494** | **N = 230** | **N = 724** | |
| Primary care | 1028 (525.4) | 1173.3 (709.7) | 1074.2 (593.5) | 0.002 |
| Specialized care | 389.1 (382.6) | 392.8 (526.4) | 390.2 (433.1) | 0.915 |
| Health care costs | 1417.1 (710.0) | 1566.1 (964.3) | 1464.4 (801.9) | 0.020 |
| Non-health care costs | 1089.0 (3097.1) | 1629.3 (4639.5) | 1260.6 (3663.6) | 0.065 |
| Total cost | 2506.1 (3188.7) | 3195.4 (4750.6) | 2725 (3766.3) | 0.022 |
| **Age < 65 y** | **N = 462** | **N = 260** | **N = 722** | |
| Primary care | 951.6 (510.4) | 1091.1 (744.4) | 1001.9 (608.4) | 0.003 |
| Specialized care | 368.5 (371.2) | 347.0 (534.3) | 360.7 (436.8) | 0.526 |
| Health care costs | 1320.1 (696.5) | 1438.1 (987.8) | 1362.6 (814.8) | 0.062 |
| Non-health care costs | 1737.3 (3638.1) | 2619.9 (6404.3) | 2055.1 (4834.9) | 0.018 |
| Total cost | 3057.4 (3724.6) | 4057.9 (6505.2) | 3417.7 (4929.8) | 0.009 |
| **Age ≥ 65 y** | **N = 302** | **N = 139** | **N = 441** | |
| Primary care | 1026.2 (490.5) | 1292.9 (681.6) | 1110.3 (570.7) | < 0.001 |
| Specialized care | 343.7 (390.9) | 429.7 (707.4) | 370.8 (512.9) | 0.102 |
| Health care costs | 1370.0 (700.5) | 1722.7 (1032.7) | 1481.1 (834.9) | < 0.001 |
| Non-health care costs | 94.7 (774.3) | 27.9 (328.5) | 73.6 (667.1) | 0.329 |
| Total cost | 1464.7 (1027.7) | 1750.5 (1058.2) | 1554.8 (1044.7) | 0.007 |
| **Radiculopathy (cervical/thoracic/lumbar)** | **N = 378** | **N = 193** | **N = 571** | |
| Primary care | 987.5 (518.9) | 1226.1 (729.4) | 1068.2 (608.3) | < 0.001 |
| Specialized care | 377.7 (379.0) | 442.9 (748.1) | 399.7 (533.3) | 0.167 |
| Health care costs | 1365.2 (705.3) | 1669 (1103.2) | 1467.9 (871.6) | < 0.001 |
| Non-health care costs | 1031.7 (2823.9) | 1717.9 (4465.0) | 1263.7 (3477.8) | 0.026 |
| Total cost | 2396.9 (2895.7) | 3386.9 (4511.9) | 2731.5 (3552.8) | 0.002 |
| **Postherpetic/trigeminal neuralgia** | **N = 94** | **N = 46** | **N = 140** | |
| Primary care | 988.2 (523.2) | 1077.4 (820.3) | 1017.5 (634.6) | 0.436 |
| Specialized care | 343.8 (356.5) | 317.0 (356.7) | 335.0 (355.5) | 0.678 |
| Health care costs | 1331.9 (714.5) | 1352.5 (800.8) | 1299.9 (3375.8) | 0.666 |
| Non-health care costs | 535.6 (2303.4) | 1394.5 (960.8) | 1048.8 (3077.7) | 0.168 |
| Total cost | 1867.9 (3450.4) | 2747 (2364.2) | 2401.3 (3143.9) | 0.061 |
| **Diabetic neuropathy** | **N = 145** | **N = 90** | **N = 235** | |
| Primary care | 977.3 (480.7) | 1137.2 (762.2) | 1038.5 (607.7) | 0.049 |
| Specialized care | 353.9 (378.8) | 304.0 (450.8) | 334.8 (407.6) | 0.363 |
| Health care costs | 1331.2 (691.2) | 1441.3 (919.3) | 1373.3 (786.3) | 0.298 |
| Non-health care costs | 913.2 (2705.5) | 2013.2 (7245.5) | 1334.5 (4975.8) | 0.100 |
| Total cost | 2244.3 (2776.4) | 3454.5 (7278.4) | 2707.8 (5023.9) | 0.048 |

Values expressed as mean (standard deviation). Costs are corrected for the variables age, sex, time since diagnosis, Charlson index, and resource use band.

medication) in the patients who received pregabalin in comparison with gabapentin, which clearly offset the greater cost of acquiring pregabalin versus gabapentin (see Figure 1).[21] Although loss of data exclusivity has caused a considerable reduction of funded and public prices for both pregabalin and gabapentin since then, there is still a relevant gap in their cost when used to treat PNP in routine medical practice in Spain. However, because of the reduction observed in the price of concomitant analgesic medication between the 2 analyses, the combined cost for all analgesic medication, which before was practically equal (€572 with pregabalin vs €575 with gabapentin), has been considerably reduced at present, especially in the pregabalin group; €391 vs €464, $P < 0.05$ (Figure 1). Nonetheless, and despite the aforementioned reduction in the cost of acquisition of analgesic medication, owing a significant reduction in the primary care component of costs, such reduction was partially offset by the increase in the cost of the other treatment components. As a consequence, the total costs per

patient varied only within a range of €40 to€100 and there remained a substantial saving of €788 per patient for pregabalin in comparison with gabapentin following loss of data exclusivity (€231 in the health care component funded by the Spanish National Health System). These results were consistent when analyzed separately by sex, age group, and different types of aetiology causing PNP, except for painful mononeuropathy (postherpetic and trigeminal neuralgia), in which the differences did not reach statistical significance as a consequence of the small number of patients.

This study determined disease cost based on the longitudinal follow-up of patients cared for at different health care levels in a routine clinical practice setting and from a population perspective. It is one of the series with the highest number of subjects studied, which should be interpreted as a study strength.[31–36] However, it should be noted that without appropriate standardization of patient characteristics, as well as in the number and extent of the variables studied, the results obtained should be interpreted with caution, and care should be taken in the external validation of the results. The results observed in our retrospective study are consistent with those of other series published in the Spanish health care setting, although before loss of data exclusivity occurred for both medicines.[31,32] A study by Perez *et al*[31] with a prospective observational design conducted in a health care setting similar to ours reported similar results (lower resource use and costs associated with treatment with pregabalin). Such results were also observed by Navarro *et al*[32] in patients refractory to gabapentin who switched their treatment to pregabalin. In other health care settings, Gore *et al*[33] conducted a retrospective analysis with these 2 medicines in patients with postherpetic neuralgia and observed that the patients treated with pregabalin had lower use of concomitant medication. This result was also observed in our study, together with a lower health care burden and lower occupational disability with pregabalin. Recently, Igarashi *et al*,[34] in a cost-effectiveness study conducted in Japan, reported that patients on treatment with pregabalin for chronic low back pain with a neuropathic component showed costs of health care and work productivity loss that were significantly lower in comparison with the routine medical practice model; this is consistent with our findings. Athanasakis *et al*[20] reported that the mean cost of medication with pregabalin was greater than that of gabapentin (€134.40); however, this higher cost was partially offset by lower direct costs (specialist visits and diagnostic tests). These researchers concluded that treatment of PNP with pregabalin in comparison with gabapentin is a cost-effective intervention for the National Health System in Greece. Similarly, Chevalier *et al*,[35] in a modeling study, concluded that from the perspective of the payer in Belgium pregabalin offers a slight increase in quality of life in the populations studied in comparison with standard care. Other studies have corroborated the reduction of work-related costs in patients treated with pregabalin.[36] These findings are consistent with ours. Part of the difference in costs between pregabalin and gabapentin was observed in the costs deriving from primary care, while the differences observed in specialized care did not reach statistical significance.

There are many studies in the scientific literature on the impact of patent protection and loss of data exclusivity on the prices of medicines and their potential impact on pharmaceutical spending.[37–43] However, we did not find any studies similar to ours in the Spanish scientific literature analyzing the effect of the reduction in the cost of acquisition of medicines due to loss of data exclusivity on disease cost under real-life conditions such as those conducted in other settings with other types of drug.[44–46] Nonetheless, the information that this study provides may be important for health care decision-makers, particularly those interested in the area of pain. Our study, as expected, showed a substantial lowering of the analgesic component of the pharmaceutical cost of treatment of PNP with gabapentin and mainly pregabalin, which could be important for health care decision-makers when planning their health care resources. On the other hand, our study also showed that part of the potential savings in pharmaceutical spending may be reduced by the increase in other health care cost components.

This study was not free of potential limitations, including errors in disease categorization (type of PNP), potential patient classification bias, and choice of therapeutic groups selected by the prescribing physician. However, no important differences were observed in the comparability of the groups when starting treatment in the study, at least in the variables analyzed, such as demographic characteristics and associated comorbidities. Therefore, the study showed the limitations inherent in retrospective studies, such as under-recording of the disease or the potential variability of professionals and patients, as the study had an observational design. Other limitations of the study consisted of a lack of measurement of pain severity and treatment adherence, although presumably their distribution should have been similar in the 2 study groups. Also, information regarding the tool, if any, used to support the neuropathic diagnostic of pain was not analyzed as it is not recorded regularly. Future research must involve studies of cost-effectiveness and diagnostic and treatment delay, in addition to replicating the study in other health care organizations (generalization of the results). Given the design of the study, it cannot be known whether pregabalin has a better safety profile or better pharmacokinetic properties; randomized clinical trials should be conducted that compare the results obtained in this study. In conclusion, despite the limitations indicated, on a population level and in a routine clinical practice setting, pregabalin in comparison with gabapentin after loss of data exclusivity for these medicines was still associated with lower health care costs, particularly costs of analgesic drugs and medical visits, and non-health care costs for fewer days of occupational disability in patients with PNP. This resulted in cost-savings for the Spanish National Health System and the society.

## CONFLICT OF INTEREST

Antoni Sicras-Mainar was a paid consultant to Pfizer GEP SLU in connection with the development of this manuscript. Javier Rejas-Gutiérrez and María Pérez-Páramo are employees of Pfizer SLU and Pfizer GEP SLU, respectively. Ruth Navarro-Artieda declares that she has no conflicts of interest related to this study.

## AUTHOR CONTRIBUTION

This research was conceived and designed by A.S.M., J.R.G., and M.P.P.; all authors contributed to the data interpretation, drafting, revision, and approval of the submitted manuscript.

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