Research Article

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Cost of treating peripheral neuropathic pain with pregabalin or gabapentin at therapeutic doses in routine practice

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Aim: To analyze the cost of peripheral neuropathic pain (PNP) treatment with pregabalin or gabapentin at therapeutic doses in routine clinical practice. **Methods:** Analysis of a retrospective, observational study of electronic medical records of patients treated for PNP with therapeutic doses of pregabalin or gabapentin, with 2 years' follow-up, considering PNP type, comorbidities, concomitant analgesia and resource use. **Results:** The weighted total average cost/patient was lower for pregabalin than gabapentin (€2464 [2197–2730] vs €3142 [2670–3614]; p = 0.014) due to significantly lower both healthcare and non-healthcare costs. This is explained by a significantly lower use of concomitant analgesia, fewer primary care visits and fewer days of sick leave. **Conclusion:** At therapeutic doses, pregabalin was found to have lower healthcare and non-healthcare costs than gabapentin in routine practice.

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Keywords: costs • gabapentin • peripheral neuropathic pain • pregabalin • therapeutic dose

Scientific associations define peripheral neuropathic pain (PNP) as pain initiated or caused by a primary lesion or dysfunction of the nervous system [1,2]. The prevalence of PNP varies between 5 and 12% in the adult population [3,4] and accounts for around 40% of all cases of chronic pain [1]. PNP tends to be a chronic condition with a high impact on sufferers (reduced quality of life) and on society in general (high medical costs); it is considered to be a public health problem [1–3].

Drug therapy is an essential part of the therapeutic arsenal in PNP patients. Neuromodulators such as pregabalin and gabapentin are considered to be treatments of first choice for PNP [1,2,5,6]. Although they differ in their pharmacokinetic properties and formulations, in clinical trials both drugs have demonstrated the capacity to reduce PNP, with similar tolerability profiles [7]. Nevertheless, under routine clinical practice conditions, significant differences have been noted between the two molecules in the treatment of chronic PNP depending on whether branded or generic versions of the same active substance are used [8], with loss of exclusivity of the drugs' reference prices [9], and even the effects of age and gender on clinical and economic consequences in the treatment of PNP [8,10]. Some patients do not receive the appropriate pharmacological treatment, or the doses prescribed are lower than recommended doses [1,2,5,6,11,12]. Some of the reasons for failing to meet the recommended doses may include difficulty taking the number of doses prescribed, where the regimen is particularly onerous, for example where patients are taking multiple medications, or due to limitations of the pharmaceutical formulation that make it especially difficult to achieve doses in the therapeutic range under routine clinical practice conditions [5,6,11,12]. For these reasons, there is little available evidence on the prescription of the recommended doses for the treatment of PNP in routine clinical practice (such evidence is only available from clinical trials), making this study particularly relevant [10].

Future Medicine

The objective of this study was to analyze the cost of PNP treated with pregabalin or gabapentin at therapeutic doses (doses between minimum effective dose and maximum permissible dose) in a routine clinical practice setting, as well as to analyze their effects based on gender, age and type of neuropathic pain.

Patients & methods

Design & study population

The database from a prior study was used to conduct this study [10]. A retrospective observational design was chosen, wherein the electronic medical records of patients of six primary care centers and their referral hospital were reviewed.

The patients seeking care and who started a new treatment with pregabalin or gabapentin in the therapeutic range (≥150 or ≥900 mg, respectively) from 2008 to 2012 (recruitment period, index date) were included in the study. Subjects had to fulfill the following criteria: age >18 years; be active patients in the database for at least 12 months before the start of the study; be in the repeat prescription programe for long-term medication (with record of the daily dose, time interval and duration of each treatment administered; ≥2 prescriptions during the follow-up period); guarantee of regular monitoring of patients during the study period (≥2 health records in the computer system); and diagnosed with PNP (previously or at the start of treatment). The study excluded: subjects who transferred to other centers, changed address or left the area; and permanently institutionalized patients. All records fulfilling inclusion and exclusion criteria were separated into two groups, and compared in the whole sample, according with pregabalin or gabapentin treatment. Additionally, four other comparisons were carried out based on age and gender: <65 years; ≥65 years; male; and female. The patient follow-up was for 2 years starting from the index date.

Diagnosis of PNP

The records of patients with PNP were obtained using the International Classification of Primary Care (ICPC-2) [13], codes N92-N99 and/or the International Classification of Diseases (ninth edition) Clinical Modification (ICD-9-CM, codes 350.1, 352.9, 353.1, 353.3, 353.8, 354.0, 355.1, 355.5, 357.2, 357.4, 357.8, 357.9, 053.13). The criteria were always at the discretion of the physician. To be considered as PNP, the pain had to be initiated or caused by a primary lesion or peripheral nervous system dysfunction, in other words, nerve roots, nerve plexus and nerves [1,2].

Sociodemographic & comorbidity variables

The following study variables were analyzed: age (continuous and by ranges), gender, employment status (active or retired), time between PNP diagnosis and start of treatment with the study drugs, and the presence of the comorbidities detailed in Table 1. In addition, the following were used for each patient treated as a co-variate of general comorbidity: the Charlson comorbidity index [14], as an estimation of the seriousness of the patient's condition; and the case-mix index, obtained based on adjusted clinical groups, a system of classifying patients by iso-consumption of resources [15]. The adjusted clinical groups application provided resource utilization bands (RUBs), which were used to group each patient into one of five 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.

Treatments administered

Information was obtained on the doses and duration of the main treatments studied, gabapentin and pregabalin, from the information provided by CatSalut (Catalan Health Service), as well as the number and presentation of the prescriptions received by the patients from the first prescription issued and for the 24 months following the start of treatment. Information was also obtained on pharmacological prescriptions for specific and concomitant medications for PNP, provided by CatSalut, based on the Anatomical Therapeutic Chemical Classification System [16].

Use of healthcare & non-healthcare resources & costs

Healthcare costs such as healthcare activity (medical visits, days of hospitalization, hospital emergencies and diagnostic or therapeutic referral requests) performed by healthcare professionals, and non-healthcare costs (productivity

Table 1. Baseline characteristics of the series studied and distribution of the different types of peripheral neuropathic pain by study group.

Study group	Pregabalin	Gabapentin	Total	p-value
Number of patients, %	*n = 711 (77.0%)*	*n = 212 (23.0%)*	*n = 923 (100%)*	
Sociodemographic characteristics				
Average age (years)	59.8 (14.6)	58.0 (14.5)	59.4 (14.6)	0.108
Gender (female)	64.1%	56.1%	62.3%	0.042
Retiree status	56.1%	58.0%	56.6%	0.624
Ranges:				
– 20–44 years	17.4%	19.8%	18.0%	
– 64 years	45.9%	48.6%	46.5%	
– 65–74 years	19.4%	17.9%	19.1%	
– >74 years	17.3%	13.7%	16.5%	0.520
General comorbidity				
Average Charlson index	0.5 (1.0)	0.6 (0.8)	0.6 (1.0)	0.177
Average RUB	3.1 (0.7)	3.2 (0.7)	3.1 (0.7)	0.321
RUB-1	2.4%	0.9%	2.1%	
RUB-2	10.5%	9.0%	10.2%	
RUB-3	64.1%	66.0%	64.6%	
RUB-4	18.7%	19.8%	19.0%	
RUB-5	4.2%	4.2%	4.2%	0.688
Associated comorbidities				
Hypertension	43.2%	37.8%	42.1%	0.199
Diabetes mellitus	19.7%	16.9%	19.1%	0.397
Dyslipidemia	48.1%	41.3%	46.8%	0.108
Obese	23.8%	16.9%	22.4%	0.051
Active smokers	23.3%	24.4%	23.6%	0.766
Alcoholism	1.5%	4.7%	2.2%	0.012
Coronary artery disease	6.6%	7.0%	6.7%	0.863
Stroke	3.1%	2.9%	3.1%	0.898
Bronchial asthma	7.9%	3.5%	7.0%	0.043
COPD	5.2%	6.4%	5.4%	0.536
Neuropathies	1.3%	4.7%	1.9%	0.004
Dementia (all types)	2.4%	2.9%	2.5%	0.697
Organic psychosis	1.4%	1.2%	1.4%	0.804
Depressive disorder	34.7%	30.2%	33.9%	0.262
Cancer	9.7%	5.2%	8.8%	0.064
Painful focal neuropathy				
Lumbar radiculopathy	27.7%	25.9%	27.3%	0.804
Cervical radiculopathy	17.2%	21.2%	18.1%	0.211
Meralgia paraesthetica	12.2%	10.8%	11.9%	0.777
Thoracic radiculopathy	5.1%	3.3%	4.7%	0.689
Carpal tunnel syndrome	1.4%	1.9%	1.5%	0.697
Painful neuropathy	1.0%	1.9%	1.2%	0.697
Intercostal neuralgia	1.1%	0.9%	1.1%	0.844
Postintervention neuroma	0.7%	0.0%	0.5%	0.957
All cases in the group (n = 612)	66.4%	66.0%	66.3%	0.224
Painful polyneuropathy				
Diabetic polyneuropathy	19.4%	21.7%	19.9%	0.857
Sensory polyneuropathy	1.0%	0.5%	0.9%	0.771

Values expressed as percentage or mean (SD).
COPD: Chronic obstructive pulmonary disease; RUB: Resource utilization band; SD: Standard deviation.

Table 1. Baseline characteristics of the series studied and distribution of the different types of peripheral neuropathic pain by study group (cont.).

Study group	Pregabalin	Gabapentin	Total	p-value
Number of patients, %	*n = 711 (77.0%)*	*n = 212 (23.0%)*	*n = 923 (100%)*	
Demyelinating polyneuropathy	0.3%	0.9%	0.4%	0.985
AIDS polyneuropathy	0.3%	0.0%	0.2%	0.888
All cases in the group (n = 198)	21.0%	23.1%	21.5%	0.843
Other neuropathic pain				
Trigeminal neuralgia	6.9%	8.0%	7.2%	0.912
Postherpetic neuralgia	4.8%	2.8%	4.3%	0.847
Associated with multiple sclerosis	0.7%	0.0%	0.5%	0.843
All cases in the group (n = 111)	12.4%	10.8%	12.0%	0.887

Values expressed as percentage or mean (SD).
COPD: Chronic obstructive pulmonary disease; RUB: Resource utilization band; SD: Standard deviation.

losses) were taken into consideration. The cost was expressed as mean cost per patient (mean cost/unit). Unit costs for the year 2015 were obtained from an analysis of the centers' accounts, with the exception of medication, which was obtained from the Spanish General Council of Official Pharmacists' Associations' Bot Plus. Prescriptions were quantified by retail price per container at the time of prescribing. The costs calculation also included the following concomitant medications: non-steroidal anti-inflammatory drugs, opiates, analgesics, sedatives/hypnotic agents (anxiolytic agents) and antidepressants. The following tariffs were applied for healthcare resources: primary care visits (€23.50), emergency medical visits (€119.30), hospitalization (€325.60 per day), specialist medical visits (€105.90), outpatient visits (€184.80 per session), laboratory tests (€22.60 per conventional test), conventional radiology (€18.80) and diagnostic tests (€37.70). The indirect cost was quantified according to the average wage among professions provided by the National Institute on Statistics (€82.40 per day) [17]. All costs were determined in the 24 months following the start of treatment with gabapentin or pregabalin. This study did not consider calculating direct non-healthcare costs, in other words, costs considered to be "out-of-pocket" expenses or paid by the patient/family, as they were not recorded in the database.

Confidentiality of information & 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 of Medicines and Medical Devices (AEMPS) 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.

Statistical analysis

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 (IQ) ranges in non-parametric variables, once the Kolmogorov–Smirnov test had confirmed a normal distribution. In the bivariate analysis, the ANOVA, χ^2 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 comparison of resource use and its corresponding costs was performed according to the recommendations by Thompson and Barber using a general linear model with covariates [18]. The covariates were gender, age, time since diagnosis, Charlson index and RUB. The Bonferroni correction was applied for multiple comparisons. The software program used was SPSS version 17.0 for Windows, and statistical significance was established for $p < 0.05$.

Results

Tha database used for this secondary analysis was formed by 86,206 electronic medical records of patients over 18 years of age. A total of 923 records of patients were recruited who met the inclusion/exclusion criteria described previously. There were 711 patients (77.0%) in the pregabalin study group and 212 patients (23.0%) in the gabapentin study group. Mean age was 59.4 (standard deviation: 14.6) years and 62.3% were female. Table 1 shows the baseline characteristics of patients analyzed according with the therapeutic group. Also, it shows the

Table 2. Characteristics of use of the main medication for peripheral neuropathic pain.

Study group	Pregabalin	Gabapentin	p-value
Number of patients,%	*n = 764 (65.7%)*	*n = 399 (34.3%)*	
Time since diagnosis (months)			
Mean (SD)	14.9 (13.3)	17.7 (10.0)	0.240
Median (P25–P75)	12.5 (3.6–21.0)	16.6 (9.1–20.3)	
Duration of treatment (months)			
Mean (SD)	5.4 (4.7)	5.8 (3.8)	0.423
Median (P25–P75)	3.0 (2.0–7.0)	5.5 (2.1–9.5)	
Daily dose of medicine			
Mean (SD)	238.8 (180.1)	1210.8 (409.6)	<0.001
Median (P25–P75)	150 (150–300)	900 (900–1200)	
Ranges:			
– 150 mg/day	488 (68.6%)	–	
– 300 mg/day	141 (19.8%)	–	
– ≤600 mg/day	69 (9.7%)	–	
– >600 mg/day	13 (1.8%)	–	
– 900 mg/day	–	87 (41.0%)	
– ≤1800 mg/day	–	113 (53.3%)	
– >1800 mg/day	–	12 (5.7%)	

Values expressed as percentage or mean.
P25–P75: 25th and 75th percentiles of the distribution; SD: Standard deviation.

distribution of the different types of PNP by study group. Numerical differences were observed between age and gender, although these were not statistically significant: a mean age of 59.8 years on pregabalin versus 58.0 years with gabapentin (p = 0.108); and a proportion of females of 64.1% versus 56.1% (p = 0.042). The proportion of associated comorbidities, RUB (3.1 vs 3.2; p = 0.321) and Charlson index (0.5 vs 0.6; p = 0.177) were similar for both groups studied. PNP was caused by some sort of painful focal neuropathy in near 65% of patients studies, with about 45% of them being of axial radiculopathy origen (cervical or lumbar). Polineuropathy was diagnosed in 21.5% of patients, with diabetic polyneuropathy being the most prevalent in the database. A total of 12% of cases were due to trigeminal/postherpetic neuralgia. The distribution of PNP showed no statistically significant differences regarding the use of pregabalin or gabapentin. Table 2 shows the characteristics of medication use. In general, mean duration of treatment with pregabalin was slightly lower than with gabapentin (5.4 vs 5.8 months), although without reaching statistical significance. Only 5.7% of patients in the gabapentin group were receiving doses above 1800 mg per day, while 11.5% of pregabalin subjects were treated with 600 or more mg per day.

Table 3 shows the gross and adjusted costs (24-month follow-up) associated with PNP according to study group. Healthcare costs accounted by 53.7% of the total costs, while 46.3% corresponded to productivity losses due to days of sick leaves. The average per patient cost was €2653.40. Of the total costs, 40.2% were incurred in primary care and 13.5% were located in specialized care. Of the latter, 17.3% were incurred in drug prescription. The average cost/patient for antiepileptic medication was similar; €229.20 for pregabalin versus €224.20 for gabapentin (p = 0.762), although the cost of concomitant analgesic medication was significantly lower for pregabalin; €184.10 versus €386.20 (p < 0.001). By group, the total costs (healthcare and non-healthcare) for the patients on treatment with pregabalin were lower than with gabapentin (€2479.00 vs €3238.20; p = 0.006, Table 3). These differences remained after adjusting for co-variates. The mean adjusted total cost per patient was significantly lower with pregabalin than with gabapentin; €2463.60 for pregabalin versus €3142.10 for gabapentin (p = 0.014), with a mean adjusted difference of €678.50 in total costs (p = 0.014). The component of cost causing this significant difference was the one located at the primary care level (€298.80 on average per subjects; p < 0.001). The majority of the cost components were lower with pregabalin, except for those observed in specialized care, that were not statistically different. Table 4 lists the distribution of the main cost components according to gender, age and main diagnoses by study group. It should be noted that these differences were maintained in all subgroups, such that the patients on treatment with pregabalin were associated with a lower total cost. In all these subgroups, total costs were lower with pregabalin and the component explaining the main difference was again the one located at the

Table 3. Healthcare and non-healthcare costs per patient according to study group.

Study group	Pregabalin	Gabapentin	Total	p-value
Number of patients, %	*n = 711 (77.0%)*	*n = 212 (23.0%)*	*n = 923 (100%)*	
Uncorrected cost model				
Healthcare costs	1361.9 (703.3)	1635.1 (1017.9)	1424.6 (794.5)	<0.001
Costs in outpatient care	1002.2 (507.5)	1283.2 (798.5)	1066.7 (598.6)	<0.001
Medical visits	254.9 (163.1)	323.2 (212.0)	270.6 (177.7)	<0.001
Laboratory tests	44.4 (37.0)	43.2 (38.5)	44.1 (37.4)	0.682
Conventional radiology	28 (27.9)	25.6 (28.6)	27.4 (28.1)	0.277
Additional tests	19.5 (38.7)	14.4 (29.6)	18.4 (36.8)	0.076
Physiotherapy/rehabilitation	242 (187.3)	266.4 (251.7)	247.6 (204.0)	0.126
Antiepileptic medicines	229.2 (206.6)	224.2 (219.1)	228.1 (209.4)	0.762
Other medicines	184.1 (279.0)	386.2 (603.9)	230.5 (388.1)	<0.001
Costs in secondary care	359.7 (383.6)	351.9 (561.7)	357.9 (430.8)	0.817
Days of hospitalization	18.8 (105.6)	46.1 (442.6)	25.0 (231.4)	0.132
Medical visits	271.5 (299.4)	252.4 (306.0)	267.1 (300.8)	0.417
A&E	69.4 (130.6)	53.4 (99.4)	65.8 (124.2)	0.100
Non-healthcare costs (productivity)	1117.2 (3046.8)	1603.2 (4454.1)	1228.8 (3425)	0.070
Total costs (healthcare/non-healthcare)	2479.0 (3126.9)	3238.3 (4612.2)	2653.4 (3535.4)	0.006
Corrected cost model[†]			**Difference**	
Healthcare costs	1333.2	1635.6	-302.4	<0.001
95% CI	1273.6–1392.7	1530.1–1741.2		
Costs in primary care	985.1	1283.9	-298.8	<0.001
95% CI	940.8–1029.3	1205.5–1362.3		
Costs in secondary care	348.1	351.7	-3.6	0.916
95% CI	315.1–381.1	293.1–410.3		
Non-healthcare costs (productivity)	1130.4	1506.5	-376.1	0.159
95% CI	873.5–1387.3	1051.2–1961.7		
Total costs (healthcare/non-healthcare)	2463.6	3142.1	-678.5	0.014
95% CI	2197.3–2729.9	2670.1–3614.1		

[†]General Linear Model: the contrasts are based on the comparisons by linearly independent pairs between the estimated marginal means.
Values expressed as percentage or mean (SD). Co-variates: age, gender, time since diagnosis, Charlson index and RUB. Use: percentage of resource use among all patients.
RUB: Resources utilization bands; SD: Standard deviation.

primary healthcare level. The differences in postherpetic/trigeminal neuralgia and diabetic painful polineuropathy subgroups were not statistically different because of the small size of such groups.

Discussion

This study sets out the cost of PNP treatment with either pregabalin or gabapentin within the range of therapeutic doses, given that this is relevant information for healthcare decision-making in routine clinical practice in our healthcare setting. There have been very few economic studies conducted in Spain or other countries comparing the cost of PNP treatment with pregabalin and gabapentin and we are not aware of any with our study's objective. 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 must be interpreted with caution, and care should be taken in the external validation of the results.

Without taking into account the therapeutic range of the drug (pregabalin/gabapentin) [10], the total cost of PNP per patient was around €728 lower in those treated with pregabalin than in those treated with gabapentin during the 2 years of patient follow-up, €162 of which was for the healthcare cost component [10]. This difference was explained by lower use of healthcare resources (mainly medical visits and concomitant analgesic medication) in the patients who received pregabalin in comparison with gabapentin, which clearly offset the greater cost of

Table 4. Distribution of the main cost components according to gender, age and main diagnoses by study group.

Study group	Pregabalin	Gabapentin	Total	p-value
Male	n = 255	n = 93	n = 348	
Primary care	916 (447.5)	1244.8 (831.9)	1003.9 (592.7)	<0.001
Secondary care	310.4 (373.7)	336.1 (735.4)	317.2 (495.7)	0.669
Healthcare costs	1226.4 (653.6)	1580.9 (1120.2)	1321.1 (818.6)	<0.001
Non-healthcare costs	1125.4 (2822.5)	1431.7 (3959.6)	1207.3 (3163.3)	0.425
Total cost	2351.8 (2885.5)	3012.6 (4183.2)	2528.4 (3289.4)	0.042
Female	n = 456	n = 119	n = 575	
Primary care	1050.3 (532.6)	1313.3 (773.7)	1104.7 (599.4)	<0.001
Secondary care	387.3 (386.7)	364.2 (377.2)	382.5 (384.6)	0.560
Healthcare costs	1437.6 (719.3)	1677.5 (932.9)	1487.3 (773.6)	0.003
Non-healthcare costs	1112.5 (3168.3)	1737.2 (4817.7)	1241.8 (3576.7)	0.090
Total cost	2550.2 (3254.9)	3414.7 (4931.8)	2729.1 (3677.1)	0.022
Age <65 years	n = 433	n = 145	n = 578	
Primary care	969 (514.9)	1219.6 (824.5)	1031.9 (616.4)	<0.001
Secondary care	366.9 (374.5)	329.4 (495.8)	357.5 (408.2)	0.338
Healthcare costs	1335.9 (701.8)	1548.9 (1007.9)	1389.4 (794.2)	0.005
Non-healthcare costs	1768.4 (3708.4)	2344 (5227)	1912.8 (4144.5)	0.148
Total cost	3104.3 (3789.3)	3892.9 (5415.3)	3302.2 (4264.5)	0.044
Age ≤65 years	n = 278	n = 67	n = 345	
Primary care	1053.8 (492.3)	1421 (725.9)	1125.1 (563.4)	<0.001
Secondary care	348.5 (397.8)	400.7 (684.8)	358.6 (466.7)	0.412
Healthcare costs	1402.3 (705.1)	1821.7 (1022)	1483.7 (792.7)	<0.001
Non-healthcare costs	102.8 (806.7)	0 (0)	82.9 (725)	0.298
Total cost	1505.1 (1050.7)	1821.7 (1022)	1566.6 (1051.2)	0.027
Radiculopathy (cervical, thoracic and lumbar)	n = 355	n = 107	n = 462	
Primary care	1007.5 (520)	1348.9 (800.1)	1086.5 (612.9)	<0.001
Secondary care	374.2 (378.8)	407.8 (706.2)	382 (474.4)	0.522
Healthcare costs	1381.7 (705.2)	1756.7 (1080.3)	1468.5 (821.7)	0.000
Non-healthcare costs	1090 (2902.9)	1477 (3797.5)	1179.6 (3132.6)	0.263
Total cost	2471.6 (2966)	3233.6 (3906)	2648.1 (3219.8)	0.032
Postherpetic/trigeminal neuralgia	n = 83	n = 23	n = 106	
Primary care	1019 (540.4)	1145.8 (779.5)	1046.5 (598.4)	0.371
Secondary care	348 (368.3)	203.9 (197.8)	316.7 (343)	0.074
Healthcare costs	1367 (737.6)	1349.6 (791.3)	1363.2 (745.7)	0.922
Non-healthcare costs	553.5 (3391.5)	1313.5 (3159.5)	601.5 (3329.3)	0.222
Total cost	1920.6 (3455.6)	2663.2 (3070.4)	2064.7 (3363.4)	0.098
Diabetic neuropathy	n = 138	n = 46	n = 184	
Primary care	993.2 (481.8)	1256.7 (897)	1059.1 (620.3)	0.012
Secondary care	360.1 (382.9)	281.6 (312.9)	340.4 (367.4)	0.211
Healthcare costs	1353.2 (691.3)	1538.3 (1007.5)	1399.5 (783.5)	0.166
Non-healthcare costs	909.3 (2740.7)	1650.6 (3206.9)	1219.7 (2861.6)	0.367
Total cost	2262.6 (2809.7)	3188.9 (3290.4)	2419.1 (2940.4)	0.083

Values expressed as mean. Costs corrected for the co-variates age, gender, time since diagnosis, Charlson index and resources utilization bands.

procuring pregabalin versus gabapentin [10]. When the effect on patients who received doses in the therapeutic range is analyzed, in whom the difference between pregabalin and gabapentin in the cost of antiepileptic medication is also no longer apparent, the differences between the two drugs persist. In other words, there is a notable saving with pregabalin in comparison to gabapentin (difference: €679/patient), again due to the lower use of concomitant

analgesic medication and fewer medical visits. These results continue to be consistent when analyzed separately by gender, age group and different types of aetiology causing PNP, except for some neuralgias in which the differences did not reach statistical significance owing to the small number of patients. One of the reasons that may explain such findings is that titration until therapeutic dosage is faster (or more ease) with pregabalin in comparison with gabapentin. Thus, subjects receiving gabapentin need more time to reach a dose within the range of its recommended therapeutic dosage, and also due to its particular formulation and pharmacodynamics (need be taken three-times a day) many patients have difficulties in receiving the appropriate dosage under routine medical care, that differs from what occurred in traditional randomized clinical trials. As a consequence, these patients use more visits to physicians and more concomitant analgesics than with pregabalin, and also days of sick leave although this component was not statistically different between drugs. Also, we cannot rule out completely that patients who are treated with gabapentin under routine medical practice are difficult to be treated to higher dosages such as the one observed in randomized clinical trial with such drug.

The results observed in our retrospective study are consistent with other series published in the scientific literature either in Spain [19,20], and elsewhere as well [21–24]. All of such references, irrespectively of the economic type of study (cohort observational trial, economic modeling or clinical trial) have shown that in different types of PNP, pregabalin therapy is normally associated with lower healthcare resources utilization and fewer days of sick leave in comparison with gabapentin leading to a lower economic impact to the National Health System budgets, which is relevant when health decision is taken on a routine basis. As commented previously, physicians in their routine practice should be aware that titration with gabapentin is more difficult than with a more novel drug such as pregabalin, abiliting patient to reach the therapeutic analgesic dosage no only faster, but an effective doses. Two more recent publications, from Wang *et al.* [25] and from Schaefer and coworkers [26], concludes that pregabalin is an effective treatment for postherpetic neuralgia and PNP in general, the higher cost of the drug being offset by lower pain scores and more pain-free days, and corroborates the reduction of work-related costs in patients treated with pregabalin. Despite variations in methodology, these studies are consistent with our results. Part of the difference in costs between pregabalin and gabapentin was attributed to the costs deriving from primary care, while the differences observed in secondary care did not reach statistical significance. Again, findings that primary care physicians should be awarded of difficulties when titration with gabapentin in the real word. Thus, the information that this study provides may be important not only for physicians but also for healthcare decision-makers, particularly those interested in the area of PNP.

As this study was designed as a retrospective one using existing data, we certanly have to deal with potential limitations, that could include errors in disease categorization (type of PNP), under-recording of the disease, potential variability of professionals and patients and classification bias and choice of therapeutic groups selected by the prescribing physician, the so called selection bias. In the statistical analysis, no important differences were observed in the comparability of the groups when starting treatment with the drugs assessed in the study, at least in the variables analyzed, such as demographic characteristics and associated comorbidities. Nonetheless, the analysis tried to control for confounding co-variates, such as gender, age, time since diagnosis, Charlson index and the resources utilization band (RUB), that were considered to have a potential role on the main end points of the study. Also, to gain in comparability, the study extracted records with exposition to the drugs analyzed for the first time. Finally, but not less important, the study was not able to obtain measurement of pain severity and treatment adherence. Likewise, the tolerability profile (adverse event) of the drugs. The last because in the database, potential side effects of drugs are captured in a narrative way in free open fields in the database, being difficult the statistical analtysis of such data.

Future research must involve studies of cost–effectiveness and diagnostic and treatment delay, in addition to replicating the study in other healthcare organizations (generalization of the results). Given that, owing to the study design, 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.

Conclusion

Despite the limitations indicated, on a population level and in a routine clinical practice setting, when prescribed at doses in the therapeutic range recommended for the treatment of PNP, pregabalin was associated with lower healthcare and non-healthcare costs in comparison with gabapentin, particularly those costs relating to analgesic drugs and medical visits. This results in a lower total cost for the Spanish National Health System.

Future Perspective

This article has shown that treating peripheral neuropathic pain with pregabalin was associated with lower costs to the National Health System in Spain in comparison with gabapentin. As a consequence, these findings may be of help to payers and health decision makers who are in charge of healthcare budgets. On the other hand, this research postulated that pharmacodynamics differences of pain medications evaluated here, could be one of the reasons explaining the findings of the study. Thus, utilization of pain drugs with easy-to-take formulations could be associated with less healthcare resources utilization and analgesics consumption.

Summary points

- The aim of the study was to analyze the cost of peripheral neuropathic pain (PNP) treatment with pregabalin or gabapentin at therapeutic doses in routine clinical practice.
- There is little available evidence on the prescription of doses in the therapeutic range for the treatment of PNP in routine clinical practice as patients are often not prescribed or have difficulty taking the recommended doses.
- This was a secondary analysis of a retrospective, observational study conducted using electronic medical records of patients of primary care centers who had received doses of pregabalin or gabapentin treatment within their therapeutic ranges for PNP.
- The analysis included comorbidity, number and seriousness, type of PNP, concomitant analgesic medication and use of healthcare and non-healthcare resources to assess the cost of treatment for the year 2015.
- 923 electronic medical records were analyzed (pregabalin; n = 711, gabapentin; n = 212), 62.3% of which were women, with a mean age of 59.4 years.
- The average cost/patient for antiepileptic medication was similar (€229.20 for pregabalin vs €224.20 for gabapentin [$p = 0.762$]), although the cost of concomitant analgesic medication was lower for pregabalin (€184.10 vs €386.20 [$p < 0.001$]).
- The weighted total average cost/patient in 2015 was lower in patients treated with pregabalin than with gabapentin; €2464 (2197–2730) versus €3142 (2670–3614), $p = 0.014$, due primarily to the significantly lower healthcare costs, and to a lesser extent non-healthcare costs.
- The reduction in cost is explained by a significantly lower use of concomitant analgesic medication, fewer primary care doctor's visits and fewer days of sick leave.
- The same differences are also apparent when subjects are grouped by type of PNP, age and gender.
- In doses in the therapeutic range recommended for the treatment of PNP, pregabalin was found to have lower healthcare and non-healthcare costs than gabapentin in routine clinical practice.

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Ethical conduct of research

The Authors state that the study has been classified by the Spanish Agency for Medicines and Medical Devices (AEMPS) 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. In addition, the confidentiality of the records established by the Spanish Organic Data Protection Law (15/1999, of 13 December) has been respected, with dissociation of the data.

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