Cost comparison of adding pregabalin or gabapentin for the first time to the therapy of patients with painful axial radiculopathy treated in Spain

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Abstract

Objetives

This paper aims to compare the costs of initiating pregabalin or gabapentin in the therapeutic management of patients with painful axial radiculopathy in routine medical practice.

Methods

A retrospective claim database analysis was carried-out using medical records of patients of both gender aged >18 years with axial painful radiculopathy (ICD-9-CM codes: 353.0 [cervical], 353.3 [thoracic] or 353.1 [lumbar]) who initiated pregabalin or gabapentin therapy between 2006 and 2008. The economic evaluation included healthcare resource utilisation and corresponding costs from a third-payer perspective during 12 months post index date. Estimates of indirect costs due to sick leave were also computed.

Results

A total of 571 records were eligible for analysis: 375 (66%) treated with pregabalin and 193 (34%) gabapentin. Time since diagnosis, duration of treatment, prevalence of most co-morbidities and previous use of analgesics were comparable. However, concomitant use of analgesics was higher in the gabapentin cohort; 3.1 (1.7) vs. 2.8 (1.8); p<0.05, mainly due to greater use of opioids (31.1% vs. 21.2%; p<0.05) and non-narcotic drugs (63.7% vs. 52.1%; p<0.01). Adjusted total costs per patient were significantly lower in the pregabalin group; €2.472 (2.101–2.836) vs. €3.346 (2.866–3.825); p=0.005, due to lower absenteeism costs; €1.012 (658–1.365) vs. €1.595 (1.129–2.062); p=0.042, and lower adjusted healthcare costs; €1.460 (1.360–1.560) vs. €1.750 (1.618–1.882); p=0.001.

Conclusion

In a population setting, pregabalin-treated patients with painful radiculopathies were considerably less costly for the healthcare payer than those treated with gabapentin in routine clinical practice. Patients treated with pregabalin had significantly fewer days of sick leave than gabapentin-treated patients.

Key words

axial radiculopathy, healthcare resources, costs, absenteeism, gabapentin, pregabalin, routine medical care

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Authors' contributions
All authors had complete access to the data, participated in the analysis and/or interpretation of results, drafted and approved the content of the manuscript. ASM and JG participated in the design and idea of the original study and in the interpretation of data and drafting the manuscript. APC and RNA participated in data interpretation, review of manuscript and important contribution to several parts of the manuscript. All authors were responsible for literature review and extraction of references

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Introduction

Peripheral neuropathic pain (PNP), which is that induced by lesions or conditions affecting the somatosensory pathways within the peripheral or central nervous system, is a common symptom of various conditions (1, 2). The estimated adult prevalence of PNP ranges between 5 and 8%, and approximately 40% of cases have chronic pain (3-5). Chronic pain is a widespread problem, affecting 1 out of every 5 individuals, and there are some people who experience pain in one out of every three homes, with near 40% suffering from axial pain (3-5). Many frequently-presented diseases affect the neuromuscular system, of which some are chronic. The following classification is useful to systematise the study of neuromuscular pathology: neuropathy, radiculopathy, motor neuron diseases, diseases of the neuromuscular junction, and myopathies (1, 2, 6). Cervical, lumbar or thoracic radiculopathies (RAD) are defined by pain and functional impairment due to involvement of the spinal roots of the peripheral nerves (6-7). The prevalence of cases of RAD and myeloradiculopathy attended by neurology clinics ranges between 1 and 3% of patients (3).

Neuropathic pain in general and RAD in particular have a high social and individual impact, due to their high degree of severity, chronicity, morbidity and associated costs (8). Patients with these disorders have a worsened health status and more disability and often present mood disorders associated with depression, anxiety and worsened sleep (9, 10). As a consequence, their quality of life is worse, and this negatively affects the family and their occupational environments (11-13). PNP is difficult to treat, and many patients complain of untreatable severe pain (13, 17). In this sense, PNP does not respond to conventional analgesics (18). Several treatments for PNP are currently available, including antidepressants, tramadol, opiates, and a number of antiepileptics, of which gabapentin and pregabalin are considered to be first-choice therapies for PNP (19-24). The greatest difference between the two drugs seems to lie in their pharmacokinetics (25).

In randomised placebo-controlled trials, pregabalin has proven efficacy in relieving pain in patients with diabetic peripheral neuropathy and post-herpetic neuralgia, and also improving sleep and the quality of life (26-28). However, the use of drugs in clinical trials limits the generalisability of the results in more heterogeneous populations and in routine clinical practice. Therefore, naturalistic studies can provide valuable information on the effectiveness of a specific treatment in real clinical practice (29-32).

PNP and RAD are associated with high direct and indirect (work absenteeism or reduced work productivity) health costs (15, 33, 34). However, the available evidence comparing pregabalin and gabapentin in terms of resource use and costs is limited (35-38). Few studies have comprehensively evaluated these outcomes, and yet there is a growing need for studies representative of real clinical conditions, therefore, the importance of this research. The aim of this study was to describe the use and costs of health and non-healthcare resources in patients with cervical, thoracic or lumbar RAD initiating treatment with gabapentin or pregabalin in routine clinical practice.

Methods

Study design and population

This was a retrospective longitudinal study based on information from the medical records of patients with chronic PNP. The study sample comprised patients from six primary care centres managed by Badalona Serveis Assistencials (BSA) SA (Apenins-Montigalà, Morera-Pomar, Montgat-Tiana, Nova Lloreda, La Riera y Martí-Julià), and two hospitals in Badalona. The study included all patients requiring care for axial radiculopathy from 01/01/2006 to 31/12/2008, who met the following criteria: a) male or female, b) age >18 years, c) diagnosis of painful axial radiculopathy (see below), d) patients covered by BSA health plan, and e) patients starting treatment with either gabapentin or pregabalin for the first time, with patient follow-up for 12 months post index date. The study excluded patients who were transferred to other primary care centres after index

date, incomplete data on healthcare resources utilisation, and patients treated simultaneously with gabapentin or pregabalin for the same health condition.
The study was classified by the Spanish Medicines Agency (AEMPS) as a Post-Authorisation Study – Other Designs (EPA-OD) trial type and subsequently approved by the Independent Ethics Committee of Hospital Universitario Germans Trías i Pujol of Badalona. Before the analysis, all data were carefully reviewed, checking the frequency distributions and searching for possible errors in recording or coding. Data confidentiality was respected at all times according to the Organic Law on Data Protection (15/1999 of the 13 December), and all data were decoupled to ensure anonymity.

Diagnosis of painful axial radiculopathy

The diagnosis of axial radiculopathy was obtained from the AP International Classification (CIAP-2), in component 7 of diseases (N92-N99) and health problems (39), and from hospital and emergency room discharge codes, according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Patients treated for the following painful focal neuropathies were included in the study: syndromes related to the compression of peripheral nerves or roots (lumbar [353.1], thoracic [353.3] or cervical radiculopathy [353.0]).

Treatments

Information on any concomitant analgesics was obtained (therapeutic group and active substance according to the Anatomical Therapeutic Chemical Classification System, [ATC]) (40) from computerised medical records (OMIAPWIN), as recommended by physicians for acute or chronic treatment, including non-steroidal anti-inflammatory drugs (NSAID, M01), opioids (N02A), analgesics (N02B) and antidepressants (N06A). Information on treatment duration and the number of treatments administered for PNP in the twelve months before initiating treatment with gabapentin or pregabalin was also obtained. However, the costs of treatment of associated co-morbidities were not included in the cost analysis. Patients were followed up for 12 months after the index date, which was considered the date the patients were treated with pregabalin or gabapentin for the first time. The searching of index date of such patients in the database elapsed three years, including years 2006 to 2008.

Socio-demographic and co-morbidity variables

The primary study variables were age, sex, occupational status, and time from diagnosis to initiation of treatment with gabapentin or pregabalin. The previous medical history, obtained from the CIAP-2 (39), included the family history, hypertension (K86, K87), diabetes mellitus (T89,T90), dyslipidaemia (T93), obesity (T82), smoking (P17), alcoholism (P15, P16), organ failure (heart, liver and kidneys), cerebrovascular accident (K90, K91, K93), chronic obstructive pulmonary disease (R95, chronic obstruction of the airways), bronchial asthma (R96), dementia or memory disorders (P70, P20), neurological diseases (Parkinson's disease [N87], epilepsy [N88], multiple sclerosis [N86]) and other neurological diseases (N99), depression (P76), malignancies (all types: A79, B72-75, D74-78, F75, H75, K72, L71, L97, N74-76, R84-86, T71-73, U75-79, W72-73, X75-81, Y77-79) and substance abuse (P1x).
The general co-morbidity summary variables used for each patient treated were the Charlson co-morbidity index (41), which is used as a proxy of the patient severity health status, and the individual causality index, obtained from the Adjusted Clinical Groups (ACG), which was used to ascertain the burden of co-morbidity. The ACG is a patient classification system based on iso-resource use (42, 43). The Grouper ACG® Case-mix System algorithm was used (42). The ACG application provides resource utilisation bands (RUB) with each patient, according to their general morbidity, being included in one of five mutually-exclusive categories: 1 (healthy or very low morbidity users), 2 (low morbidity), 3 (moderate morbidity), 4 (high morbidity), and 5 (very high morbidity).

Resource use and cost analysis

Direct healthcare costs considered were medical visits (primary and specialist care), days of hospitalisation, emergency room visits, diagnostic tests and referrals to rehabilitation and physiotherapy associated with the painful radiculopathies. The indirect costs considered were related to absenteeism (number of days of sick leave). Costs were calculated by multiplying the number of units of health resources used and days of sick leave by the corresponding cost. The cost was expressed as a mean cost per patient according to treatment with pregabalin or gabapentin during the 12-month follow-up period. The unit costs of the healthcare resources analysed were obtained from the centres' analytical accounts, except for medications and days of sick leave (Table I). Prescriptions were quantified according to the retail price per pack at the time of prescription, as published in the Catalogue of Pharmaceutical Products of the General Council of Spanish Pharmacists' Associations (44). Days of sick leave were classified as non-healthcare-related (indirect) costs, and were quantified according to the average inter-professional salary cost (source: National Institute of Statistics) (45). Antiepileptic and concomitant analgesic medication costs were obtained by multiplying the retail prices by the amount of the drug prescribed to the patient during the 12-month follow-up period according to the data recorded in the database. The study did not include non-healthcare-related direct costs (out-of-pocket costs covered by the patient/family) or drugs prescribed outside the healthcare provider system, as they were not contained in the database. Also, possible use of over the counter analgesic drugs, which are paid by the patient, were not computed.

Statistical analysis

Prior to analysis, data were thoroughly reviewed, in particular with reference to the computerised medical records, observing frequency distributions and searching for possible recording or encoding errors. Data confidentiality was respected pursuant to the Personal Data Protection Act (Law 15/1999, of 13 De-

cember), with decoupling of personal data. A descriptive univariate analysis was performed expressing parametric variables as the mean, median, standard deviation and 95% confidence intervals (CI) and non-parametric variables as the median and interquartile (IQ) range, once normal distribution was verified using the Kolmogorov-Smirnov test. In the bivariate analysis, the Student's *t*-test, ANOVA, chi-squared and the Mann-Whitney-Wilcoxon non-parametric test were used according to data distribution. A logistic regression analysis was performed to determine whether co-morbidities were associated with the use of pregabalin or gabapentin (dependent variable), with an enter procedure (statistic: Wald) and predetermined covariates (age, sex and Charlson index).

Healthcare resource utilisation and days of sick leave due to pain and their associated costs were compared according to the recommendations of Thompson and Barber (46) by using a general linear model with sex, age, Charlson index as treatment duration, as covariates to estimate marginal means with Bonferroni adjustment for multiple comparisons, when needed. The data were presented as mean differences per patient adjusted by covariates between treatments, with their 95% confidence intervals calculated using bootstrapping techniques. The paired comparisons in the proportion of use of concomitant analgesic drugs, before and during the study, in each group were performed using the McNemar related samples test, with the chi-squared statistic calculated between groups. The SPSSWIN statistical package, version 17.0, was used, with statistical significance established as $p<0.05$.

Table I. Unit costs and lost productivity.

Health and non-health resources	Unit costs (€), year 2010
Medical visits	
Medical visit – primary health care	22.74
Medical visit – emergency department	115.23
Hospitalisation (one day)	314.61
Medical visit – specialist	102.36
Investigations	
Laboratory tests	21.86
Conventional radiography	18.14
Diagnostic/therapeutic tests	36.45
Drug prescriptions	CGCOF Pharmaceutical catalogue (ref. 45)
Work productivity – indirect costs	
Cost of day not worked	79.61

Source of health care resources: authors' cost accounting. Amounts in euros. PVP: retail price.

Table II. Baseline characteristics of the series studied.

Study groups Number of patients, %	Pregabalin n=378 (66.2%)	Gabapentin n=193 (33.8%)	Total n=571 (100%)	*p*-value
Sociodemographic characteristics				
Mean age, years	60.1 (14.3)	58.6 (14.5)	59.6 (14.4)	0.231
Sex (female)	67.2%	54.4%	62.9%	0.008
Pensioner	53.4%	58.5%	55.2%	0.245
Ranges: 20–44 years	16.1%	18.7%	17.0%	
45–64 years	45.5%	45.6%	45.5%	
65–74 years	20.9%	22.3%	21.4%	
>74 years	17.5%	13.5%	16.1%	0.604
General co-morbidity				
Mean episodes	8.7 (4.0)	8.1 (4.4)	8.5 (4.1)	0.096
Mean Charlson index	0.5 (1.1)	0.7 (0.9)	0.6 (1.1)	0.047
Mean RUB	3.1 (0.7)	3.1 (0.7)	3.1 (0.7)	0.474
RUB-1	2.1%	1.6%	1.9%	
RUB-2	12.4%	11.4%	12.1%	
RUB-3	65.6%	64.8%	65.3%	
RUB-4	16.1%	18.7%	17.0%	
RUB-5	3.7%	3.6%	3.7%	0.937
Associated comorbidities[1]				
Hypertension	43.1%	46.1%	44.1%	0.469
Diabetes mellitus	20.9%	23.9%	21.9%	0.422
Dyslipidaemia	48.1%	46.6%	47.6%	0.732
Obesity	23.5%	19.2%	22.1%	0.233
Active smoker	24.3%	23.8%	24.2%	0.894
Alcoholism	2.6%	5.7%	3.7%	0.067
Ischaemic heart disease	7.4%	6.7%	7.2%	0.769
Cerebrovascular accident	4.0%	3.6%	3.9%	0.841
Bronchial asthma	7.7%	5.7%	7.0%	0.382
COPD	4.2%	6.7%	5.1%	0.198
Neuropathies	1.3%	4.1%	2.3%	0.032
Dementia (all types)	2.6%	3.1%	2.8%	0.752
Organic psychosis	2.1%	1.1%	1.8%	0.352
Depressive syndrome	39.2%	28.5%	35.6%	0.012
Malignant neoplasias	10.6%	6.2%	8.8%	0.051
Substance abuse	2.9%	5.2%	3.7%	0.173

RUB: resource utilisation bands; COPD: chronic obstructive pulmonary disease; values expressed as percentage or mean with standard deviation in parentheses, [1]*p*-values calculated with binary logistic regression adjusted for age and sex.

Results

From the initial review of 86.206 patients aged >18 years assigned to the study centres, 571 patients who met the study criteria for inclusion were recruited for the statistical analysis, of which 378 (66%) were receiving pregabalin and 193 (34%) gabapentin. The mean age was 59.6 (14.4) years and 62.9% were female. Of all patients, 47.6% had dyslipidaemia, 44.1% hypertension and 35.6% depressive syndrome. A total of 53.6% (n=306) patients had lumbar radiculopathy, 36.8% (n=210) cervical radiculopathy, and 9.6% (n=55) thoracic radiculopathy. There were no differences in the distribution of RAD according to type of antiepileptic administered. Table II shows

general patient characteristics and associated co-morbidities according to the two study groups (pregabalin *versus* gabapentin). There were no significant differences in the mean age (60.1 *vs*. 58.6 years, *p*=0.231), proportion of females (67.2% *vs*. 54.4%, *p*=0.008), or co-morbidities: RUB (3.1 *vs*. 3.1, *p*=0.474) and Charlson index (0.5 *vs*. 0.7, *p*=0.047), respectively. Table III shows the characteristics of antiepileptic use. The mean treatment duration was slightly lower with pregabalin than with gabapentin (5.2 *vs*. 5.4 months); *p*=0.237. Of patients receiving pregabalin (approved dose in the range 150–600mg/day), 72.2% were taking doses <300 mg/day, while 68.4% of patients receiving gabapentin (approved dose 900–3600mg/day) were taking doses ≤900 mg/day. Only 9 patients (2.4%) received doses of pregabalin >600 mg/day, and no patient on gabapentin received a daily dose >3.600 mg.

Patients receiving pregabalin used fewer health resources in primary health care visits (10.8 *vs*. 15.0, *p*=0.001), days of hospital stay (0.1 *vs*. 0.3, *p*=0.012) and days of temporary sick leave (12.5 *vs*. 20.8, *p*=0.009, Table IV). There were significant differences in the use of concomitant medication (Table V). Although the number of analgesic drugs received by patients before initiation of study medication did not differ significantly (mean of 2.6 *vs*. 2.7 drugs), patients receiving pregabalin had frequently received an NSAID compared with patients receiving gabapentin (72.8% *vs*. 60.1%, *p*<0.01). Regarding non-narcotic analgesics use, patients in pregabalin group were prescribed less frequently (53.4% *vs*. 60.1%, *p*<0.05) this type of drugs, mainly due to lower use of acetaminophen (39.2% *vs*. 42.9%, *p*<0.05). The use of opioids and antidepressants before initiation with pregabalin or gabapentin was similar. However, concomitant use of analgesics differed significantly after the initiation of study medication. While there was a significant reduction in the concomitant use of NSAIDs (72.8% to 68.8%, *p*=0.039) and opioids (26.2% to 21.2%, *p*=0.041) in patients receiving pregabalin, there were no significant changes between pre- and post-initiation administration of these drugs in patients receiving gabapentin (Table V). Therefore, during the study, the proportion of patients receiving pregabalin, who also received opioids, was significantly lower than the proportion in patients receiving gabapentin (21.2% *vs*. 31.1%, *p*<0.05), mainly due to less administration of tramadol, alone or in combination. Likewise, patients receiving gabapentin took more non-narcotic analgesics (mainly paracetamol) throughout the study period (50.8% *vs*. 38.9%, *p*<0.01) (Table V).

Table VI shows the gross and adjusted cost analysis of RAD therapy according to the study groups. The total cost of patients included in the study was €1.6 million, of which 56.4% were direct health costs and 43.6% non-health costs (lost productivity), with a mean total unit cost of €2.803€. Of the total costs, 42.7% occurred in primary health care (including 9.9%

Table III. Characteristics of antiepileptic medication use.

Study groups Number of patients, %	Pregabalin n=378 (66.2%)	Gabapentin n=193 (33.8%)	*p*-value
Time since diagnosis, months			
Mean (SD)	14.1 (12.9)	15.7 (10.7)	0.344
Median (P25-P75)	11.5 (3.3–19.9)	12.5 (8.6–24.8)	
Treatment duration, months			
Mean (SD)	5.2 (4.6)	5.4 (3.9)	0.237
Median (P25-P75)	3.0 (2.0–7.0)	4.5 (2.1–10.4)	
Ranges (n, %):			
1–2 months	160 (42.3%)	78 (40.4%)	0.663
3–7 months	138 (36.5%)	68 (35.2%)	0.759
≥8 months	80 (21.2%)	47 (24.4%)	0.385
Daily dose of medication			
Mean (SD)	224.7 (186.5)	920.2 (437.4)	
Median (P25-P75)	150 (150–300)	800 (600–1200)	
Ranges (n, %):			
=75 mg/day	23 (6.1%)	---	
=150 mg/day	250 (66.1%)	---	
=300 mg/day	71 (18.8%)	---	
≤600 mg/day	25 (6.6%)	---	
>600 mg/day	9 (2.4%)	---	
<900 mg/day	---	104 (53.9%)	
=900 mg/day	---	28 (14.5%)	
≤1.800 mg/day	---	51 (26.4%)	
>1.800 mg/day	---	10 (5.2%)	

Values expressed as percentage or mean (with standard deviation in parentheses), P25-P75: 25 and 75 percentiles of the distribution, *p*-value: statistical significance.

Table IV. Mean unit cost of resources according to study groups.

Study groups Number of patients, %	Pregabalin n=378 (66.2%)	Gabapentin n=193 (33.8%)	Total n=571 (100%)	*p*-value
Outpatient care				
Medical visits	10.8 (7.1)	15.0 (9.2)	12.2 (8.1)	0.001
Laboratory tests	2.0 (1.7)	2.0 (1.7)	2.0 (1.7)	0.669
Conventional radiology	1.5 (1.4)	1.4 (1.4)	1.4 (1.4)	0.301
Complementary tests	0.6 (1.2)	0.5 (0.9)	0.6 (1.1)	0.212
Physiotherapy/rehabilitation	2.3 (1.7)	2.4 (2.1)	2.4 (1.8)	0.652
Specialised care				
Days of hospitalisation	0.1 (0.3)	0.3 (2.1)	0.2 (1.2)	0.012
Medical visits	2.7 (2.9)	2.6 (2.7)	2.7 (2.8)	0.531
Emergency department	0.6 (0.9)	0.5 (0.9)	0.5 (0.9)	0.419
Days of sick leave	12.5 (34.3)	20.8 (54.2)	15.3 (42.2)	0.026

Values expressed as mean (with standard deviation in parentheses), *p*-value: statistical significance adjusted by age, sex and Charlson index.

Table V. Medication prescribed to patients concomitantly during a 12-month period before and after receiving pregabalin or gabapentin.

Study group		Pregabalin						Gabapentin					
Study period		Pre-treatment		Treatment				Pre-treatment		Treatment			
Patients, %		n	%	n	%	Diff.	*p*-value	n	%	n	%	Diff.	*p*-value
Mean number of drugs (SD)		2.6 (1.7)		2.8 (1.8)		0.2	0.452	2.7 (1.8)		3.1 (1.7)		0.4	0.024
Therapeutic group: NSAIDs		275	72.8	260	68.8	-4.0	0.039	116	60.1†	122	63.2†	3.1	0.218
M01AB01	Indomethacin	6	1.6	11	2.9	1.3	0.732	5	2.6	9	4.7	2.1	0.388
M01AB05	Diclofenac	87	23.0	70	18.5	-4.5	0.178	31	16.1	44	22.8	6.7	0.254
M01AB16	Aceclofenac	39	10.3	40	10.6	0.3	0.798	12	6.2	24	12.4	6.2	0.282
M01AC01	Piroxicam	10	2.6	10	2.6	0.0	0.956	5	2.6	5	2.6	0.0	0.968
M01AC05	Lornoxicam	7	1.9	5	1.3	-0.5	0.759	2	1.0	2	1.0	0.0	0.955
M01AC06	Meloxicam	15	4.0	14	3.7	-0.3	0.881	7	3.6	13	6.7	3.1	0.426
M01AE01	Ibuprofen	165	43.7	136	36.0	-7.7	0.048	65	33.7*	70	36.3	2.6	0.378
M01AE02	Naproxen	22	5.8	28	7.4	1.6	0.833	12	6.2	14	7.3	1.0	0.822
M01AE14	Dexibuprofen	7	1.9	5	1.3	-0.5	0.727	4	2.1	5	2.6	0.5	0.859
M01AE17	Dexketoprofen	50	13.2	48	12.7	-0.5	0.782	18	9.3	25	13.0	3.6	0.327
M01AH01	Celecoxib	8	2.1	18	4.8	2.6	0.261	1	0.5	10	5.2	4.7	0.657
Therapeutic group: opioids		99	26.2	80	21.2	-5.0	0.041	55	28.5	60	31.1*	2.6	0.347
N02AA01	Morphine	1	0.3	0	0.0	-0.3	0.753	1	0.5	5	2.6	2.1	0.525
N02AA05	Oxicodone	1	0.3	1	0.3	0.0	0.951	1	0.5	2	1.0	0.5	0.853
N02AA59	Codeine	12	3.2	15	4.0	0.8	0.855	10	5.2	4	2.1	-3.1	0.458
N02AB03	Fentanyl	14	3.7	8	2.1	-1.6	0.723	5	2.6	8	4.1	1.6	0.698
N02AX	Tramadol (alone or in association)	81	21.4	48	12.7	-8.7	0.013	64	33.2	57	29.5	-3.6	0.213
Therapeutic group: analgesics		202	53.4	197	52.1	-1.3	0.652	116	60.1*	123	63.7†	3.6	0.183
N02BB02	Metamizol sodium	79	20.9	81	21.4	0.5	0.728	40	20.7	46	23.8	3.1	0.257
N02BE01	Paracetamol	148	39.2	147	38.9	-0.3	0.713	95	49.2*	98	50.8†	1.6	0.367
N02BE51	Paracetamol (association)	6	1.6	23	6.1	4.5	0.527	14	7.3	17	8.8	1.6	0.579
Therapeutic group: antidepressants		123	32.5	125	33.1	0.5	0.751	70	36.3	75	38.9	2.6	0.222
N06AA09	Amitriptyline	39	10.3	37	9.8	-0.5	0.692	12	6.2	20	10.4	4.1	0.615
N06AB03	Fluoxetine	21	5.6	17	4.5	-1.1	0.576	14	7.3	20	10.4	3.1	0.577
N06AB04	Citalopram	10	2.6	20	5.3	2.6	0.456	9	4.7	16	8.3	3.6	0.486
N06AB05	Paroxetine	31	8.2	30	7.9	-0.3	0.651	23	11.9	22	11.4	-0.5	0.873
N06AB06	Sertraline	13	3.4	11	2.9	-0.5	0.584	7	3.6	5	2.6	-1.0	0.867
N06AB10	Escitalopram	14	3.7	9	2.4	-1.3	0.547	7	3.6	14	7.3	3.6	0.568
N06AX05	Trazodone	5	1.3	5	1.3	0.0	0.911	1	0.5	5	2.6	2.1	0.657
N06AX11	Mirtazapine	9	2.4	19	5.0	2.6	0.484	3	1.6	8	4.1	2.6	0.781
N06AX16	Venlafaxine	2	0.5	1	0.3	-0.3	0.622	8	4.1	15	7.8	3.6	0.555
N06AX21	Duloxetine	4	1.1	13	3.4	2.4	0.589	2	1.0	11	5.7	4.7	0.519

During the study period, patients consumed multiple medications simultaneously, *$p<0.05$, † $p<0.01$ for comparisons between pretreatment and treatment groups; Diff: difference in percentages (treatment and pretreatment); SD: standard deviation.

Table VI. Model of gross and adjusted mean costs per patient according to study groups.

Study groups	Pregabalin		Gabapentin		Total		
	Users (%)	Unit cost	Users (%)	Unit cost	Users (%)	Unit cost	*p*-value[§]
Health costs, in euros		1.499 (793)		1.745 (1,160)		1.582 (940)	0.003
Outpatient costs		1.134 (644)		1.317 (841)		1.196 (722)	0.004
Medical visits	100.0%	245 (161)	100.0%	341 (209)	100.0%	278 (184)	<0.001
Laboratory tests	81.0%	45 (37)	80.8%	43 (37)	80.9%	44 (37)	0.609
Conventional radiography	69.1%	27 (26)	62.2%	25 (26)	66.7%	26 (26)	0.320
Complementary tests	36.8%	22 (44)	33.7%	18 (31)	35.7%	20 (40)	0.212
Physiotherapy/rehabilitation	84.7%	238 (174)	82.4%	246 (215)	83.9%	241 (189)	0.652
Anticonvulsive drugs	100.0%	343 (330)	100.0%	222 (245)	100.0%	302 (309)	<0.001
Other drugs	92.3%	214 (371)	95.9%	423 (645)	92.1%	284 (491)	<0.001
Specialised care costs		365 (366)		428 (723)		386 (515)	0.167
Days of hospitalisation	4.1%	19 (99)	4.7%	106 (655)	4.2%	48 (391)	0.012
Medical visits	70.6%	281 (296)	67.9%	265 (280)	69.7%	275 (291)	0.530
Emergency department	35.4%	65 (105)	32.1%	57 (109)	34.3%	62 (106)	0.419
Non-health costs (days off-work), in euros	21.4%	997 (2.728)	23.3%	1.660 (4.314)	22.1%	1.221 (3.360)	0.026
Total costs, unadjusted		2.496 (2,815)		3.405 (4.368)		2.803 (3.443)	0.003
						Difference	
Health costs		1.460 (1.360–1.560)		1.750 (1.618–1.882)		-290	0.001
Costs, primary health care		1.109 (1.032–1.186)		1.320 (1.219–1.422)		-211	0.001
Costs, specialised care		351 (296–407)		430 (357–504)		-79	0.092
Non-health costs (days off-work)		1.012 (658–1.365)		1.595 (1.129–2.062)		-583	0.042
Total costs, adjusted[*]		2.472 (2.109–2.836)		3.346 (2.866–3.825)		-873	0.005

Values expressed as percentage or mean (with standard deviation in parentheses), *p*-value [§]: statistical significance between the cost of the two study groups ([*]) Values expressed as means and mean differences with 95%CI adjusted for the covariates age, sex, Charlson index and treatment duration.

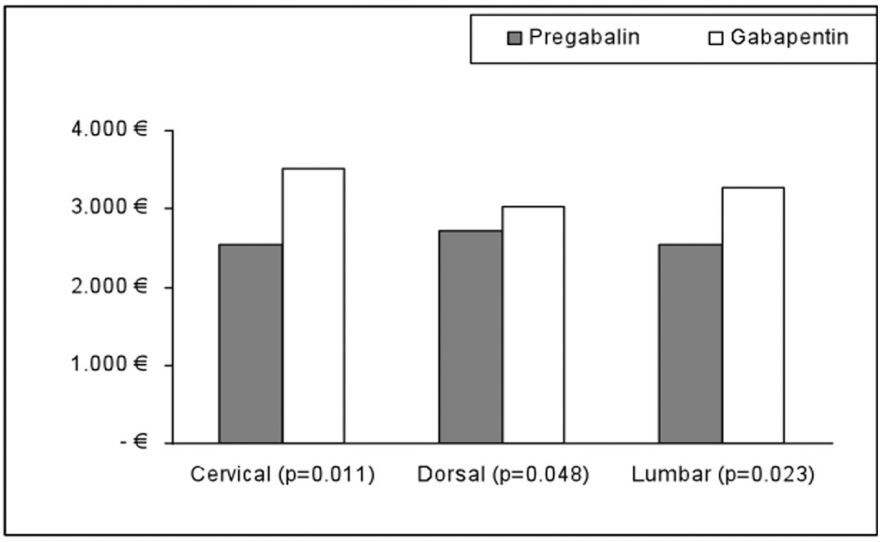
in primary care visits) and 13.8% in hospitals: drug prescriptions accounted for 23.9% of the total cost. The mean total cost per patient adjusted for covariates was €2.472 for patients receiving pregabalin and €3.346 in patients receiving gabapentin (p=0.005). Specifically, costs were lower in patients receiving pregabalin with respect to lost productivity (€1.012 *vs*. €1.595, p=0.042), which was responsible for most of the additional cost of gabapentin over pregabalin; € 583 (66.8%) of a total of €873. However, the adjusted differences in the health component of the cost also contributed substantially to the marginal difference (€290, p=0.001). A large part of the difference in costs was due to the costs occurring in primary care (€1.109 *vs*. €1.320, p=0.001): differences in hospital-incurred costs did not differ significantly (p=0.092). According to type of RAD, there was a lower mean total unit cost in patients receiving pregabalin who had lumbar radiculopathy (€2.552 *vs*. €3.264, p=0.023), cervical radiculopathy (€2.550 *vs*. €3.513, p=0.011), and thoracic radiculopathy (€2.728 *vs*. €3.021, p=0.048), respectively (Fig. 1).

Discussion

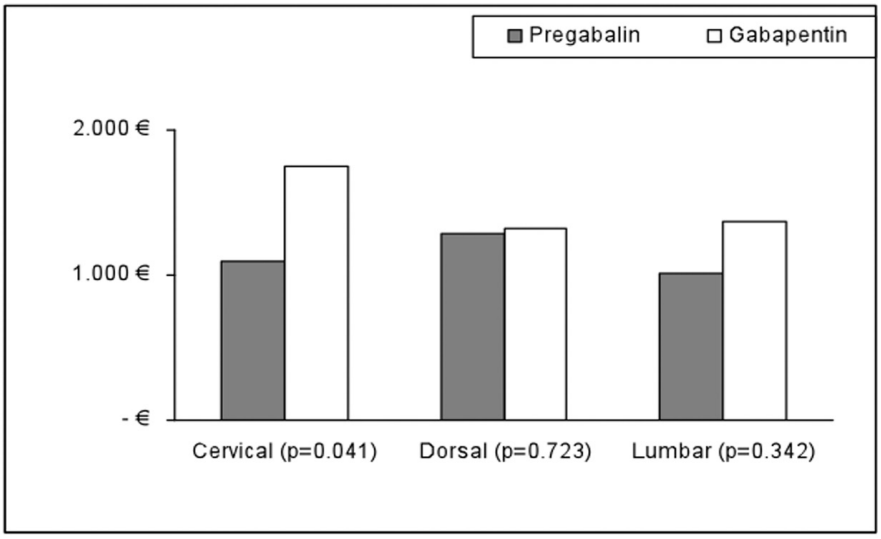
Of the available evidence on the clinical aspects of RAD, there is little data on the use of resources and total health costs in routine clinical practice (8). This may provide our study with conceptual appeal and homogeneity in the variables used. However, without adequate standardisation of methodologies in terms of patient characteristics and the number and size of the variables studied, the results and their external validity should be interpreted with caution. This study details the different types of RAD, the cost of the disease, and longitudinal follow-up of patients at different levels of care in routine clinical practice.

The results observed in our retrospective study are consistent with other published series with a prospective observational design carried out in the Spanish National Healthcare system, but with a smaller patient sample (8, 38). In addition, our findings are consistent with the only reported study with a similar design, which focused on patients with post-herpetic neuralgia. Gore *et al*. (36) made a retrospective analysis of the doses of gabapentin and pregabalin prescribed and the concomitant use of other analgesics in patients with post-herpetic neuralgia, and found that treatment initiation with gabapentin was associated with increased use of opiates, which was reduced with pregabalin, findings clearly similar to ours.

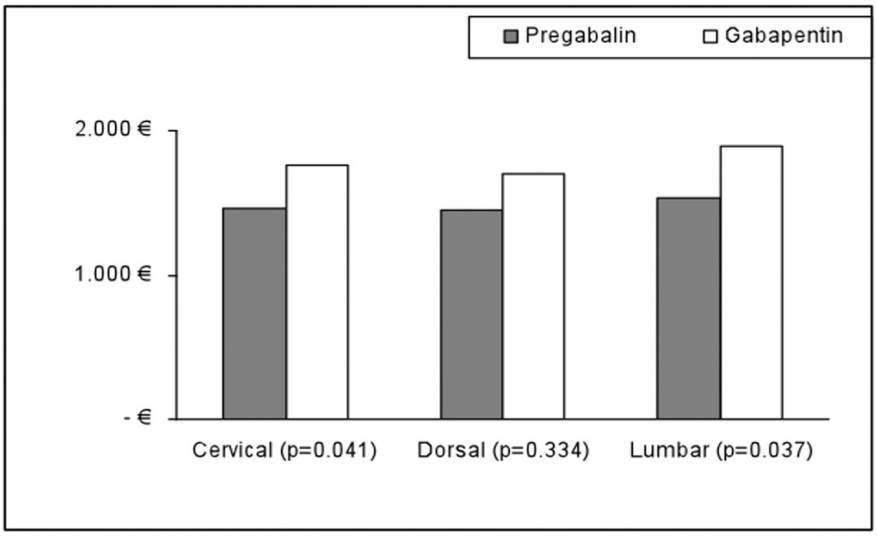
A sizable part, both statistically and numerically, of the cost difference between pregabalin and gabapentin was due to the unit costs incurred in primary care (€1.109 in the pregabalin group and €1.320 in the gabapentin group), while differences in hospital care were significant but negligible. The adjusted marginal cost difference in primary care is explained by the significantly lower cost of medical visits (-€96) and concomitant analgesia in patients receiving pregabalin, which offset the higher acquisition cost of the drug compared with gabapentin (+€120). The higher acquisition cost of pregabalin was compensated for not only by savings due to fewer primary care visits, but also by the substantially fewer days of occupational disability, a finding also observed in a recent Spanish study with a similar methodology (48). With respect to the magnitude and



A



B



C

Fig. 1. Distribution of costs according to type of radiculopathy.
A: total cost; **B**: cost of lost productivity; **C**: direct health cost.

effect of pregabalin in reducing health resource utilisation, sick leave and associated costs, our findings, obtained by analysing healthcare provider databases, are consistent with the results obtained in prospective observational studies conducted in Spanish primary healthcare settings in patients with pure neuropathic pain (painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia) and cervical or lumbar radiculopathy (8, 47, 48). While these differences may result from overestimation of treatment effects due to an observational and, frequently, uncontrolled design, this does not explain the differences between the two drugs found in the present analysis. A key factor that may probably explain these differences are the doses used. Approximately, 68% of patients in the study were treated with a dose of gabapentin below 1.200 mg, which is considered the lowest limit of the therapeutic range (the mean dose was 900 mg/day) (49). In contrast, the mean pregabalin dose of 227 mg/day was within its effective dose range (150–600 mg/day in more than 92% of subjects treated). While the use of lower-than-recommended doses for treating pain, including neuropathic pain, has frequently been reported (50, 51), this still does not explain the dose differences found in our study. Interestingly, a retrospective study comparing gabapentin and pregabalin in post-herpetic neuralgia patients yielded similar results in a different environment (36). The study found that a greater proportion of pregabalin-treated patients reached the therapeutic dose (*i.e.* at least 150 mg/day), while few gabapentin-treated patients did so (*i.e.* at least 1800 mg/day).

Our results suggest that patients with RAD are attended mainly in primary care (8, 29, 30). If the diagnosis is in doubt or if treatment fails, consultation with a specialist or a multidisciplinary pain unit is advised (52, 53). The possible limitations of this study might be due to the accuracy of the diagnosis, possible bias in the classification of patients, the choice of the therapeutic groups selected, and the attribution of costs according to the computerised system developed. However, we ob-

served no significant differences in the comparability of the groups at the initiation of treatment, at least in the variables analysed, including the number and type of pain medication received, type of neuropathic pain, demographic characteristics and co-morbidities, although small differences such as slightly older age, a higher proportion of women, greater co-morbidity and more use of NSAIDs not indicated for neuropathic pain in patients receiving pregabalin, may have favoured gabapentin. This observational study shows the limitations of retrospective studies, including under-reporting of the disease or possible patient- and professional variability. Other limitations include the lack of measurement of pain severity and treatment adherence, although their distribution may be presumed to be similar in the two groups. Future studies in other healthcare organisations should include data on the cost-effectiveness and delay in diagnosis and treatment. Successful care of patients with chronic diseases such as RAD should be based on multidisciplinary teams that promote effective intervention strategies in which patients are closely engaged in self-care (18, 19, 53).

In conclusion, despite the limitations mentioned, the analysis of this large sample of subjects with RAD suggests that, in routine clinical practice in Spain, pregabalin may be more effective than gabapentin in reducing healthcare and non-healthcare resource utilisation in patients with painful radiculopathy. In turn, these findings translated into less cost for the health payer, apparently because therapeutic doses of pregabalin were used more often than therapeutic doses of gabapentin. We cannot speculate the reasons for this. Thus, randomised clinical trials comparing these clinical results in populations highly-representative of routine medical practice should be conducted.

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