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Clinical and Resource Utilization Patterns in Patients with Refractory Neuropathic Pain Prescribed Pregabalin for the First Time in Routine Medical Practice in Primary Care Settings in Spain

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Conflicts of interest: Javier Rejas and Maria Pérez are employees of Pfizer S.L.U. Xavier Masramón is an employee of European Biometric Institute (EBI), a paid contractor of Pfizer S.L.U. for the development of the statistical analysis application for this study. All other authors declare no conflicts of interest.

Contributors: This was a collaborative work, and the authors worked together closely. MTS, CP, AN, MP, and JR participated in the design of the original study and in the interpretation of data and drafting the manuscript. XM participated in the analysis and interpretation of data. All authors were responsible for literature review and extraction of references.

Abstract

Context and Objective. To describe clinical and resource utilization patterns in patients with refractory neuropathic pain (NeP) who were prescribed pregabalin for the first time in routine medical practice in primary care settings.

Methods. Post-hoc analysis of a 12-week prospective observational study including pregabalin naïve adult patients with refractory chronic NeP of at least 6-months duration. Self-reported pain intensity, disability, sleep disturbances, symptoms of anxiety and depression, disability, health-related quality of life (HRQoL), health care resource utilization, and corresponding costs were assessed in this post-hoc analysis.

Results. One thousand three hundred fifty-four patients were enrolled in the study, and three treatment groups were identified: 1) 598 patients replaced prior pain treatments with pregabalin as monotherapy; 2) 589 added pregabalin to their existing pain treatments; and 3) 167 other pain treatments were prescribed according with physician routine medical practice. Statistically significant differences were reported at baseline for intensity of pain, patient disability, severity of depressive symptoms, and HRQoL ($P < 0.01$ in all cases). No statistically significant differences were reported among the three treatment groups for anxiety

severity or sleep disturbances. Subjects who received add-on pregabalin had greater use of direct and indirect resources vs the other groups, resulting in significantly higher quarterly overall costs per patient: €2,397 (2,308), €2,470 (1,857), and €3,110 (2,496), respectively ($P < 0.001$).

Conclusion. These findings suggest that primary care physicians chose pregabalin as an option for treating refractory patients who tended to have much more severe NeP profiles, costing society more than when they chose other therapeutic strategies not including pregabalin.

Key Words. Pregabalin; Patient-Reported Outcomes; Pain; Health Care Resources; Productivity; Cost; Primary Care Settings

Introduction

Neuropathic pain (NeP) is induced by lesions or conditions that cause a primary injury or malfunction of the nervous system [1,2]. Prevalence of NeP has been estimated to range between 5% and 7.5% and is responsible for up to 25% of pain clinic visits [3,4]. NeP has an important individual and social impact [5–10]. Treatments are available for NeP, including antidepressant drugs, opioids, and several anticonvulsant drugs like pregabalin [11–13]. Many patients with NeP are often not properly diagnosed, do not receive suitable therapies, or are prescribed lower-than-recommended doses of an appropriate drug [10,14]. All of these influence the burden of disease [15–17], causing a substantial increase in health care and indirect costs [14,18–20].

The use of drugs in clinical trials differs from clinical practice settings, limiting the generalization of clinical trial results to a more heterogeneous population and real-world clinical practice conditions [21]. In randomized clinical trials, demographic and clinical baseline characteristics are balanced among treatment groups. However, these conditions do not reflect conditions in actual clinical practice. In this sense, observational studies are often used to evaluate the effectiveness of a product used and prescribed in routine medical practice, providing additional information on pre- and post-intervention settings, and also complements information from clinical trials [22]. This also happens in the field of NeP management, where a variety of factors at different levels can affect the therapeutic behavior of physicians, particularly, family physicians and general practitioners in particular. Understanding the medical profile and current treatment patterns in patients with NeP is crucial to the development of effective pain management strategies [23]. As a drug of first choice for the treatment of NeP [13], pregabalin may be affected by different medical considerations or criteria when determining the type of patients who should receive such treatment for the first time. Thus, the objective of this study was to describe clinical and resource utilization patterns in patients with NeP prescribed pregabalin for the first time in routine medical practice in primary care settings (PCS) in Spain. Findings in this research may help clinicians and decision makers to learn more about how pregabalin is used in the real world, thus allowing them to implement better therapeutic strategies for NeP.

Patients and Methods

Study Design

This study describes a secondary post-hoc analysis of characteristics of pregabalin-naïve patients enrolled in a multicenter, observational, prospective 12-week study. The study objective was to analyze the cost of treatment and patient-reported health outcomes in patients with refractory NeP in real-life conditions in PCS: the LIDO study. Its design and main characteristic have been published elsewhere [24,25]. The study was approved by the Clinical Research Ethics Committee of Hospital de la Princesa (Madrid), and it was conducted in compliance with the principles of the Declaration of Helsinki for research in humans. In the LIDO study, patients could be prescribed pregabalin for the first time as monotherapy (replacing previous treatments), as add-on therapy to existing treatments, or no pregabalin at all. This last group was prescribed other existing marketed drugs for NeP according with physician own judgment. This article describes and compares the baseline patient characteristics in each group, to endeavor identify the patient circumstances that lead physicians to prescribe a given treatment.

Study Population

In brief, the original study included patients of both genders 18 years of age or older with NeP secondary to diabetic neuropathy, post-herpetic neuralgia, or trigeminal neuralgia according to International Classification of Diseases 10th revision codes. The subjects were refractory to previous analgesia and had been experiencing chronic pain for at least 6 months. The secondary analysis included only those patients who met the selection criteria and who had not received pregabalin treatment before study initiation. The sample size of the LIDO study was defined in accordance with its primary endpoint, i.e., to determine health care resource utilization and costs after a 12-week follow-up period, under usual medical practice conditions in PCS. Thus, no sample size was predetermined for the secondary analysis, whose patient characteristics at the baseline visit are presented in this article.

Clinical Assessments and Instruments of Measurement

During the baseline visit, selection criteria were verified, and socio-demographic, disease duration, and treatment duration data were collected.

Information regarding health care resources used in last 12 weeks (pharmacological and non-pharmacological

treatments, medical visits, hospitalizations, and diagnostic tests performed due to pain) were obtained from the patient by means of a face-to-face interview and medical records. Patients were also interviewed on the impact of pain on their self-perceived average work productivity (determined as 0–100% productivity) during the last 12 weeks, and information was collected about the number of work days lost due to pain. From these data, the number of lost workday equivalents (LWDE) was calculated using the following formula: LWDE = W1 + W2 (1-P); where W1 is the number of days unable to work or perform daily activities due to pain in the last 12 weeks; W2 the number of days working with pain in the same period; (1-P) the percentage of work disability; and P the percentage of effectiveness at work [26–28]. Patients were requested to complete the Spanish version of the Dolour Neuropathique 4 NeP diagnostic questionnaire, the Short Form McGill Pain Questionnaire (SF-MPQ), the Sheehan Disability Inventory (SDI), the Medical Outcomes Study Sleep Scale (MOS-Sleep), the Hospital Anxiety and Depression Scales (HADS), and the EuroQoL (EQ-5D) questionnaire [29–37].

The DN4 NeP diagnostic questionnaire is a 10-item questionnaire to distinguish between NeP and non-NeP. The SF-MPQ computes three pain scores: sensory, affective, and total, and also assesses patient pain intensity during the previous week on a 0–100 visual analog scale, and pain intensity at the time of assessment on an ordinal 6-point scale. The SDI assesses patient functional impairment in three different domains: work, social life, and family life/home responsibilities. The MOS-Sleep scale assesses key self-perceived aspects of sleep: sleep disturbances, snoring, and awakening short of breath or with a headache, sleep adequacy, daytime somnolence, and quantity of sleep. In addition, the MOS-Sleep scale provides a summary index of sleep disturbances; the higher the score, the worse the sleep. The HADS explores the presence of depression and anxiety symptoms. The EQ-5D is designed to describe patient health in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and also to assess the patient's current self-reported health status. Scores on those five items may also be used to calculate a utility index, ranging from –0.6 to 1.0, with highest scores representing better health status.

Estimation of Costs

Calculation of the total costs per patient included direct health care costs and indirect costs based on LWDE. Drugs costs were obtained from the Pharmacists Catalog for the year 2006 [38], by matching the retail prices + value added tax. Costs of non-pharmacological treatments, medical visits, hospitalizations, and diagnostic tests were obtained from the Soikos Health Care Costs database for the year 2005, updated for the year 2006 per the Consumer Prices Index of December 2005. Finally, the human capital method was applied to determine the cost of LWDE, and total national average wages per worker per month (first quarter 2006) divided by 30 days were obtained from the National Institute of Statistics.

Statistical Analysis

For statistical analyses, patients were classified into three groups, depending on the treatment initiated based on clinical judgment at the baseline visit: patients for whom switching to one or more drugs other than pregabalin was prescribed or for whom one or more drugs other than pregabalin were added to the previous treatment (other-treatments group); patients for whom monotherapy with pregabalin was prescribed as a substitute for the previous therapy (pregabalin-monotherapy group); and patients for whom pregabalin was added to the previous therapeutic regimen (pregabalin-add-on group).

Patient baseline characteristics were described by means and standard deviations for quantitative variables, and by distributions of absolute and relative frequencies for qualitative variables. The Kolmogorov–Smirnov test was used to verify the normal distribution of quantitative variables, and analyses of variance (ANOVA), Kruskal–Wallis tests, and chi-square tests were used to ensure the homogeneity of baseline variables in the three assessment groups. Absolute values were obtained to quantify the use of health care resources, LWDEs, and overall costs in the 12 weeks before the baseline visit. The statistical significance of between-group comparisons was adjusted using the Tukey test for multiple comparisons. The between-group comparisons were performed in each pregabalin group vs the other-treatments group only when the ANOVA was statistically significant, solely to protect the study from an excess of pair comparisons. All statistical tests were two-sided and were considered significant when $P < 0.05$. The SAS statistical package version 8.2 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Patient Distribution

A total of 1,845 patients were included in the LIDO study, 1,354 of whom had not been previously exposed to pregabalin. The secondary analysis was performed with patients distributed into three groups according to the treatment prescribed: other-treatments 167 (12.3%), pregabalin-monotherapy 598 (44.2%), and pregabalin-add-on 589 (43.5%). The three treatment groups were similar in terms of socio-demographic characteristics. The recruited population was between 59 and 60 years of age on average in the study groups, with 55–60% women and 65–69% not currently working (Table 1). On average, patients had NeP for 2 years. The most frequent cause of NeP was diabetic neuropathy (54.4%), followed by post-herpetic neuralgia (33.8%), and trigeminal neuralgia (11.8%), with no differences between the treatment groups (Table 1).

Table 1 Demographics and clinical characteristics

Characteristic	Other Treatments (N = 167)*	Pregabalin Monotherapy (N = 598)*	Pregabalin Add-on (N = 589)*	*P*
Gender (female), N (%)	83 (55.3)	309 (60.4)	282 (57.8)	0.4874
Age, mean (SD)	60.4 (12.4)	58.6 (12.5)	59.7 (13.0)	0.1486
Body mass index, (Kg/m^2)	26.9 (3,5)	27.3 (3,8)	27.3 (3,9)	0.4673
Civil status (married or with partner), N (%)	107 (69.0%)	378 (66.4%)	386 (67.6%)	0.6041
Working status, N (%)				
Active	54 (32.5)	204 (34.6)	181 (31.0)	0.3835
Housewife	31 (18.7)	75 (12.7)	87 (14.9)	
Off sick	10 (6.0)	45 (7.6)	62 (10.6)	
Unemployed	3 (1.8)	15 (2.6)	11 (1.9)	
Retired	59 (35.5)	208 (35.3)	216 (37.0)	
Does not practice	9 (5.4)	42 (7.1)	27 (4.6)	
Time of progress (years), mean (SD)	2.1 (3.1)	1.9 (3.4)	2.0 (3.4)	0.7130
Diagnosis, (%)				
Diabetic neuropathy	47.9	58.2	53.0	0.2852
Post-herpetic neuralgia	37.2	31.2	36.9	
Trigeminal neuralgia	14.9	10.7	10.1	

* Some patients did not report all data (<5%).
SD = standard deviation.

Patient-Reported Outcomes

The total score on the DN4 questionnaire was close to 7 in all groups, although slightly lower in the other treatments group compared with the pregabalin groups ($P < 0.05$; Table 2). Baseline pain intensity was moderate to severe according to SF-MPQ and significantly lower in subjects who received other treatments ($P = 0.002$; Table 2). Likewise, when comparing with patients who received pregabalin, other treatments patients also had significantly lower pain scores at the time of the interview according to SF-MPQ PPI or during the previous week according to the SF-MPQ VAS (Table 2).

Overall, patients experienced from moderate sleep problems due to NeP (Sleep-MOS summary index score of nearly 50; Table 2). Scores on the six dimensions of the MOS-Sleep questionnaire followed a similar pattern, and only the "sleep disturbance" and "adequacy of sleep" dimensions were significantly better in the group not exposed to pregabalin (Table 2). The patients in the pregabalin-add-on group presented poorer psychiatric conditions. Depression levels were significantly higher in the pregabalin-add-on group than in the other two groups (Table 2). This group also had a significantly higher percentage of patients with severe depression (16 [10.5%] other-treatments; 92 [16.4%] pregabalin-monotherapy; and 112 [20.3%] pregabalin-polytherapy; $P < 0.005$) as well as severe anxiety (16 [10.5%] other-treatment; 77 [13.7%] pregabalin-monotherapy; 99 [18.0%] pregabalin-polytherapy; $P < 0.05$).

Significant differences between groups were observed for impact of NeP on social and working activities (disability) and perceived stress as measured by the SDI. NeP symptoms interfered with work, social life, and family life more actively in subjects in the pregabalin-add-on group, who had a higher disability level than the other groups ($P < 0.0001$), while the other treatments subjects were the least disabled (Table 2). The general patient health status according to the EQ-5D questionnaire was significantly better in the other treatments group. The percentage of patients who reported having problems in all five dimensions of the EQ-5D was significantly higher in the pregabalin-treated groups, except in the "Pain or discomfort of any type" dimension, in which 97.4% of the patients reported being affected (Table 2). The majority of patients also reported having problems in their usual activities (81.4%) and presence of anxiety or depression (77.4%).

Direct Health Care and Indirect Resource Utilization and Associated Costs

The majority of the total patients (69.7%) were treated with more than one drug. The mean number of previous treatments was significantly lower in patients in the pregabalin-monotherapy group ($P < 0.001$; Table 3). Forty percent of the patients in the pregabalin-monotherapy group were already on previous monotherapy vs 28.7% of the other treatments and 21.6% of the pregabalin-add-on groups. Whereas 42.6% of patients in the other treatments group and 47.6% in the pregabalin-add-on vs 28.2% in the pregabalin-monotherapy groups received more than three drugs. The most frequent treatments were analgesics, particularly nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, which were used by at least 60% and nearly 40% of the subjects, respectively. Furthermore, significant between-group differences were found in the

Table 2 Health patient-reported outcomes

Health Outcomes	Other Treatments (N = 167)*	Pregabalin Monotherapy (N = 598)*	Pregabalin Add-on (N = 589)*	*P*
DN4 Questionnaire, mean (SD)	6.4 (1.7)	6.8 (1.8)	6.8 (1.7)	0.033
SF-MPQ, mean (SD)				
Sensory (0–33)	14.0 (5.5)	16.0 (6.1)	15.8 (5.9)	0.001
Affective (0–12)	4.4 (3.4)	5.0 (3.2)	5.2 (3.3)	0.017
Total (0–45)	18.5 (8.0)	21.0 (8.4)	21.1 (8.4)	0.002
PPI (0–5)	2.4 (0.9)	2.7 (0.8)	2.7 (0.9)	<0.001
VAS (0–100)	66.8 (17.6)	71.4 (15.2)	72.6 (15.7)	<0.001
Sleep-MOS, mean (SD)				
Summary index (0–100)	47.1 (17.2)	48.0 (19.0)	50.1 (17.3)	0.063
Sleep disturbance (0–100)	49.6 (19)	50.9 (21.4)	53.8 (20)	0.018
Snoring (0–100)	43 (30.3)	37.9 (29.3)	38.1 (27.9)	0.140
Shortness of breath (0–100)	32.3 (29)	32.3 (27.7)	31.3 (25.6)	0.785
Sleep quantity, hours	5.8 (1.2)	5.7 (1.5)	5.6 (1.4)	0.191
Adequacy of sleep (100–0)	43.9 (22.5)	41.4 (25.1)	36.8 (22.5)	0.001
Daytime somnolence (0–100)	42 (20.2)	41.1 (20.7)	40.9 (18.7)	0.840
HADS, mean (SD)				
Depression (0–21)	9.9 (4.9)	10.3 (4.3)	10.9 (4.5)	0.010
Anxiety (0–21)	10.2 (3.7)	10.5 (4.1)	10.9 (4.1)	0.087
SDI, mean (SD)				
Disability† (0–30)	16.5 (6.3)	18.0 (6.3)	19.4 (5.6)	<0.001
Perceived stress (0–10)	5.5 (2.1)	5.9 (2.1)	6.3 (2.0)	<0.001
Perceived social support (0–100)	56.5 (24.8)	55.6 (23.2)	58.7 (23.5)	<0.001
EQ-5D				
VAS, mean (SD)	49.6 (18.1)	42.2 (18.4)	40.5 (18.0)	<0.001
Mobility disturbances, N (%)	64 (41.8)	350 (61.6)	341 (60.7)	<0.001
Self-care problems, nN (%)	57 (37.3)	270 (47.7)	298 (53.0)	0.002
Problems of day life activities, N (%)	109 (71.7)	463 (81.8)	480 (85.6)	0.003
Pain or discomfort of any type, N (%)	145 (95.4)	553 (97.5)	554 (98.6)	0.059
Presence of anxiety/depression, N (%)	113 (73.9)	423 (74.7)	459 (82.0)	0.006

* Some patients did not report all data (<5%).
† Sum of three disability items scores.
SD = standard deviation; SF-MPQ = Short Form McGill Pain Questionnaire; VAS = visual analog scale; PPI = present pain intensity; MOS = Medical Outcomes Study; HADS = Hospital Anxiety Depression Scale; SDI = Sheehan Disability Inventory.

frequency of drug use. Thus, NSAIDs were more frequently used in the pregabalin-add-on group, and antiepileptic drugs (AEDs) in the other treatments group (the most frequent was gabapentin: 32 [19.2%] vs 100 [16.7%] pregabalin-monotherapy and 74 [12.6%] pregabalin-add-on, while opioids were less frequently used in the pregabalin-monotherapy group [Table 3]). No statistically significant differences were observed between groups with regard to the doses of the drugs used.

A significantly larger number of patients of the other-treatments group underwent infiltrations and iontophoresis compared with the pregabalin groups ($P < 0.05$), while a higher percentage of pregabalin-add-on patients were treated with microwaves ($P < 0.05$; Table 3). Some diagnostic tests were prescribed significantly less frequently for the other-treatments patients ($P < 0.001$; Table 3). Other-treatments patients had to be hospitalized more often than the other patient groups ($P = 0.001$). However, other-treatments patients also reported, on average, a lower number of total and primary care visits, while the pregabalin-add-on group had the highest number of all types of visits ($P < 0.05$; Table 3).

Work productivity losses expressed in LWDE was significantly lower in the other-treatments group than in the pregabalin groups ($P < 0.001$) (Figure 1). This was mainly a consequence of a significantly lower mean number of days working with pain (35.0 [29.0] other-treatments, 40.3 [30.2] pregabalin-monotherapy, 43.2 [29.9] pregabalin-add-on [$P = 0.012$]), better work productivity on days working with pain (48.1 [21.3] other-treatments, 46.9 [21.1] pregabalin-monotherapy, 43.4 [21.6] pregabalin-add-on [$P = 0.007$]), or fewer days of absenteeism than the pregabalin groups, especially the pregabalin-add-on group (15.7 [21.7] other-treatments, 19.1 [23.4]

Table 3 Health resources utilization

Resource	Other Treatments (N = 167)*	Pregabalin Monotherapy (N = 598)*	Pregabalin Add-on (N = 589)*	*P*
Drug treatment				
Mean number (SD)	2.4 (1.3)	2.0 (1.1)	2.6 (1.4)	<0.001
Number of previous treatments, N (%)				
1	48 (28.7)	239 (40.0)	127 (21.6)	
2	48 (28.7)	190 (31.8)	182 (30.9)	
3	40 (24.0)	112 (18.7)	156 (26.5)	
4	17 (10.2)	42 (7.0)	71 (12.1)	
≥5	14 (8.4)	15 (2.5)	53 (9.0)	
Previous treatments†, N (%)				
NSAID	109 (65.3)	388 (64.9)	479 (81.3)	<0.001
Acetaminophen	73 (43.7)	232 (38.8)	273 (46.3)	0.030
Opioids	74 (44.3)	159 (26.6)	250 (42.4)	<0.001
AED	46 (27.5)	133 (22.2)	111 (18.8)	0.043
TCAs	18 (10.8)	61 (10.2)	69 (11.7)	0.704
Other	13 (7.8)	36 (6.0)	81 (13.8)	<0.001
Non-pharmacological treatments; N (%)*				
Physiotherapy	45 (30.8)	168 (34.1)	194 (38.2)	0.180
TENS	16 (11.4)	45 (9.6)	52 (10.7)	0.766
Infiltrations	21 (14.9)	51 (10.8)	72 (14.8)	0.154
Electrotherapy	18 (12.9)	30 (6.5)	48 (10.0)	0.033
Blockade	3 (2.2)	8 (1.7)	5 (1.1)	0.552
Iontophoresis	4 (2.9)	1 (0.2)	7 (1.5)	0.019
Spinal stimulator	1 (0.7)	2 (0.4)	4 (0.8)	0.727
Pumps	1 (0.8)	0 (0.0)	3 (0.6)	0.214
Hydrotherapy	3 (1.8)	10 (1.7)	15 (2.5)	0.552
Short wave	3 (1.8)	7 (1.2)	22 (3.7)	0.013
Magnetotherapy	1 (0.6)	3 (0.5)	6 (1.0)	0.568
Acupuncture	1 (0.6)	4 (0.7)	3 (0.5)	0.938
Complementary tests; N (%)				
CT	25 (15.0)	155 (25.9)	193 (32.8)	<0.001
Resonance	60 (35.9)	193 (32.3)	224 (38.0)	0.114
Electromyogram	40 (24.0)	164 (27.4)	215 (36.5)	0.001
ECHO Doppler	12 (7.2)	50 (8.4)	59 (10.0)	0.424
Thermogram	6 (3.6)	4 (0.7)	13 (2.2)	0.016
X-rays	111 (66.5)	363 (60.7)	410 (69.6)	0.005
General analysis	124 (74.3)	427 (71.4)	450 (76.4)	0.146
Gammagram	12 (7.2)	41 (6.9)	51 (8.7)	0.491
Number of medical visits, mean (SD)*				
Total	8.8 (7.0)	9.6 (8.1)	10.3 (7.1)	0.050
Primary care	5.9 (4.1)	6.7 (4.9)	7.1 (4.8)	0.011
Pain unit	0.5 (0.9)	0.7 (1.6)	0.6 (1.2)	0.164
Specialist	1.4 (1.7)	1.2 (1.5)	1.5 (1.7)	0.033
Emergency room	1.6 (2.8)	1.5 (3.1)	1.6 (2.4)	0.847
Hospitalized* (N, %)	11 (7.7)	9 (1.8)	34 (6.4)	0.001

* Some patients did not report all data (<10%).

SD = Standard deviation; NSAID = non-steroidal anti-inflammatory drug; TCAs = Tricyclic antidepressant drugs; AED = antiepileptic drug; † Patients might be receiving more than one previous treatment. TENS = transcutaneous electric neurostimulation; CT = Computerized tomography.

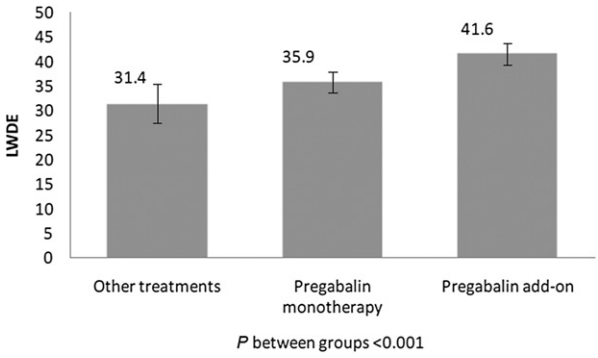

Figure 1 Lost workdays equivalents (LWDE).

pregabalin-monotherapy, 24.4 [26.9] pregabalin-add-on [$P = 0.001$]).

Greater use of direct health care and indirect resources by the pregabalin-add-on group resulted in significantly higher direct, indirect, and overall costs ($P < 0.001$) than the two other groups (Table 4). The costs of diagnostic tests and pharmacological treatments administered to the other-treatments group were significantly lower, yet it was the pregabalin-monotherapy group that had the lowest total direct costs ($P = 0.001$; Table 4).

Discussion

Understanding the medical profile and current treatment patterns in patients with NeP is crucial to the development of effective pain management strategies [23]. For refractory conditions, placebo-controlled clinical trials cannot replicate the real clinical world. In these circumstances, observational studies, incorporating the advantages of multiple measures pre- and post-intervention, can yield important new information [22]. Data presented in this study describe the baseline demographics, clinical characteristics, and expenditures due to NeP in the pregabalin-naïve population of an observational study [24]. Baseline patient characteristics were not balanced among treatment groups. Our patient-reported health outcomes data show that subjects not receiving pregabalin, in general, had better clinical conditions at baseline, with lower levels of pain intensity and disability, which resulted in better social and work activity and quality of life, quite the opposite of what was observed in the pregabalin-add-on group. Likewise, when compared with patients who received pregabalin, those patients also had significantly lower scores in pain-related mood symptoms. Similar baseline characteristics have been observed in other observational studies of pregabalin-naïve and refractory patients with painful lumbar or cervical radiculopathy [39].

The expenditures due to NeP were also unbalanced among groups at baseline. Pregabalin seems to be prescribed to patients who, at baseline, reported significantly more prescribed diagnostic tests, more medical visits, more expensive pharmacological treatment, as well as more LWDEs. Mean total expenditures were significantly higher among pregabalin-add-on patients than in the other groups (about €3,100/patient vs €2,400/patient). The direct costs were lower in the pregabalin-monotherapy group (a mean of about €150/patient) than in the other-treatments group; €834 vs €984/patient, respectively, probably due to the high percentage of hospitalized other-treatments patients, similar to the pregabalin-add-on group. This observational study did not record NeP-non-related comorbidities, which could provide additional information about patient clinical profiles and a possible reason for hospitalization expenditures. The magnitude of the baseline costs observed in this trial were similar to those observed in other studies conducted in our context and in Canada, supporting the validity of the "real-world" health costs obtained in the present study [14,40,41].

Our findings may indicate a preferred pattern of prescribing pregabalin as a switch drug in refractory patients who have poorer health and thus higher health costs. This pattern could also suggest that an individual patient baseline characteristic may strongly influence prescriber decisions regarding selection of a switch treatment option.

Table 4 Overall and by components costs expressed in 2006 Euros

Costs (€/patient/quarter)	Other Treatments (N = 167)	Pregabalin Monotherapy (N = 598)	Pregabalin Add-on (N = 589)	*P*
Pharmacological treatment	66.8 (93.1)	82.3 (106.9)	96.8 (120.2)	0.004
Non-pharmacological treatment	258.8 (1,211.6)	168.5 (525.9)	290.9 (983.1)	0.043
Medical visits and hospitalizations	430.3 (702.8)	351.3 (572.6)	497.5 (1,044.6)	0.010
Complementary tests	228.2 (257.0)	231.5 (247.2)	282.1 (254.9)	0.001
Total direct costs	984.1 (1,684.3)	833.6 (934.4)	1,167.3 (1,666.4)	0.001
Indirect costs (LWDE)	1,412.5 (1,339.7)	1,636.1 (1,382.9)	1,942.2 (1,485.4)	<0.001
Total costs	2,396.6 (2,308.0)	2,469.7 (1,856.8)	3,109.5 (2,495.8)	<0.001

Values expressed as means (standard deviation).
LWDE = lost workdays equivalents.

Observational study designs have limitations such as possible bias in patient selection, group balance in number of patients, or other confounding factors [22]. One confounding factor, called "confounding by indication bias," inherent in observational drug studies, explains that in clinical practice, there is always a reason for a prescription, which is often associated with the outcome of interest [42]. This would explain the significant differences in baseline clinical characteristics of the three groups selected for this analysis and also the prescription pattern observed in this study. The unbalanced sample size of the nonpregabalin group in comparison with the other two groups might reflect a possible selection of patients receiving pregabalin. The investigators may have tested the most efficacious drug [25,43–45] in the most seriously ill patients, so patients in the pregabalin-monotherapy and pregabalin-add-on groups showed significantly more severe symptoms in intensity and descriptors of pain.

Interestingly, in accordance with recent guidelines and recommendations [42,46], it appears that a substantial proportion of subjects in the study were receiving inappropriate drug regimens for a neuropathic condition before starting the trial. In this population, a large percentage of patients were treated with NSAIDs or acetaminophen (at least 65% and 40%, respectively). These drugs are ineffective in NeP, although they may help with a coexisting nociceptive condition [39,46]. In contrast, only about 20% of the refractory patients received AEDs and about 10% tricyclic antidepressants (TCAs), both drugs considered first line drugs for NeP [42,46]. In fact, of the total population analyzed, 167 (12.3%) patients did not receive pregabalin as a switch drug (other-treatments group), despite the fact that only 46 (27.5%) were treated with some AED (32 [70%] received gabapentin but were apparently non-responders) and 18 (11%) with TCAs. This situation is almost analogous to the ones described by other authors, likewise in PCS, where NSAIDs are widely used (65%), while the use of drugs with proven clinical efficacy in the treatment of NeP, such as AEDs or TCAs, is more limited (10% and 3%) [18,23,39,47]. Thus, our study raises questions about the optimality of NeP treatment in a routine PCS, as our results, consistent with the findings of several recent studies, point towards inadequate use of medications for the management of NeP in general practice [18,23,43,48]. Berger et al. recently demonstrated that NSAIDs were widely used for patients with NeP and theorized that clinicians may be more comfortable prescribing "traditional" analgesics to treat pain regardless of its etiology [18]. Among other possible reasons, we may speculate that this is due to a failure in continuing medical education at the primary care level, the scarcity of resources in these settings resulting in an inability to devote enough time to patient care, and saturated waiting lists.

The ability to reliably identify a specific patient profile can supply important information to primary care providers and lead to opportunities to optimize NeP care. Pregabalin may have been perceived by prescribers as having a better efficacy profile, so it would be preferentially prescribed to patients who tended to have a more severe NeP profile and thus higher spending on diagnostic tests and medical visits, as well as more LWDEs. In summary, these findings suggest that primary care physicians chose pregabalin as an option for treating refractory patients who tended to have much more severe NeP profiles, costing society more than when they chose other therapeutic strategies not including pregabalin.

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