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ORIGINAL RESEARCH ARTICLE

Effectiveness of Pregabalin as Monotherapy or Combination Therapy for Neuropathic Pain in Patients Unresponsive to Previous Treatments in a Spanish Primary Care Setting

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Abstract

Background and Objective Patients from a previous study of neuropathic pain (NP) in the Spanish primary care setting still had symptoms despite treatment. Subsequently, patients were treated as prescribed by their physician and followed up for 3 months. Since pregabalin has been shown to be effective in NP, including refractory cases, the objective of this study was to assess the effectiveness of pregabalin therapy in patients with NP refractory to previous treatments.

Methods This was a post hoc analysis of pregabalin-naïve NP patients treated with pregabalin in a 3-month follow-up observational multicenter study to assess symptoms and satisfaction with treatment. Patients were evaluated with the *Douleur Neuropathique en 4 questions* (DN4), the Brief Pain Inventory (BPI) and the Treatment Satisfaction for Medication Questionnaire (SATMED-Q) overall satisfaction domain.

Results 1,670 patients (mean age 58 years, 59 % women), previously untreated or treated with ≥1 drug other than pregabalin, were treated with pregabalin (37 % on monotherapy). At 3 months, pain intensity and its interference with activities decreased by half ($p < 0.0001$), while the number of days with no or mild pain increased by a mean of 4.5 days ($p < 0.0001$). Treatment satisfaction increased twofold ($p < 0.0001$). Patients with a shorter history of pain and those with neuralgia and peripheral nerve compression syndrome (PCS) as etiologies had the highest proportion on monotherapy and showed the greatest improvements in pain-related parameters in their respective group categories.

Conclusion Treatment with pregabalin (as monotherapy or combination therapy) provides benefits in pain and treatment satisfaction in patients with NP, including refractory cases. Shorter disease progression and neuralgia and PCS etiologies are favorable factors for pregabalin treatment response.

1 Introduction

Chronic pain affects one in five European adults and represents a major healthcare problem [1]. Neuropathic pain (NP) is defined as pain arising from a lesion or disease affecting the somatosensory pathways within the peripheral or central nervous system. It usually persists after lesion healing [2–5], becoming a frequent cause of chronic pain. This type of pain is difficult to diagnose and treat [5–8]. Chronic pain in general, and NP specifically, are frequently associated with anxiety, depression, and sleep disorders [9–12], which not only contribute to the negative impact of NP on quality of life [13, 14] but can also negatively affect the response to analgesic treatment. Therapies should therefore treat these concomitant symptoms along with pain [15], as recommended first-line NP treatments (anticonvulsants and tricyclic antidepressants) do [16–18]. However, NP management still represents a therapeutic challenge, especially in refractory

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patients [1, 8]. According to a very recent consensus by a group of experts, to classify NP as refractory "it should have had a trial of treatment with at least four drugs of known effectiveness, each drug should have been tried for at least 3 months or until side effects prevent adequate dosage, and despite the above treatment, the intensity of pain should have been reduced by less than 30% or should remain at a level of at least 5 on a 0-10 scale and/or it should continue to contribute significantly to poor quality of life" [19].

Primary care physicians (PCPs) are usually the first physicians visited by patients with chronic pain and NP [1, 20–22]. In a previous cross-sectional study conducted in a Spanish primary care setting, NP prevalence according to the *Douleur Neuropathique en 4 questions* (DN4) was 45.7 % in patients with pain visiting primary care centers [23]. These NP patients experienced moderate pain and high levels of pain interference with their activities of daily living and showed little satisfaction with treatment. The two pharmacologic treatments most frequently used were non-steroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics (53 and 51 %, respectively), which are not recommended for NP, while recommended first-line (anticonvulsants and antidepressants) and second-line (opioids) treatments [16, 24, 25] were being administered at lower percentages. Following the previous cross-sectional study, these patients were managed as prescribed by their physician and followed up for 3 months.

Pregabalin is an anticonvulsant that has been shown to be effective in randomized clinical trials for a wide array of painful neuropathic conditions. Pregabalin has level A evidence for efficacy in patients with postherpetic neuralgia and painful polyneuropathies [26–28], and has been shown to be effective in central NP [29] as well as in a broad range of peripheral NP etiologies [30]. Pregabalin not only reduces pain but also improves anxiety and pain-related sleep interference [31–33], and it is safe and effective in both older and younger patients [34].

In addition, pregabalin is indicated for the treatment of generalized anxiety disorder (GAD). Pregabalin use is becoming widespread in psychiatry and addiction-related treatments. Evidence derived from different studies suggests that pregabalin is an efficacious therapy for GAD [35] and social anxiety disorder [36], with some preliminary evidence for its efficacy in relapse prevention. It is also used as adjunctive therapy in many other psychiatric conditions, such as obsessive compulsive disorder [37], post-traumatic stress disorder, schizophrenia, bipolar mania [38], and major depression [39].

Pregabalin has been shown to have positive effects on benzodiazepine dependence in both the withdrawal phase and for discontinuation of long-term use, and it is considered a potentially useful new drug for treatment of alcohol withdrawal syndrome [40].

Furthermore, pregabalin has been successfully used in patients with refractory NP [41, 42], which may be the case in some patients in the current study, since they were symptomatic despite using a mean 2.4 drugs. Specifically, in the Spanish primary care setting, pregabalin was shown to be an effective therapy for the treatment of peripheral NP in patients refractory to at least one previous analgesic in routine clinical practice [43, 44]. Therefore, from the previous cross-sectional study [23], of all the patients followed for 3 months, this publication focuses on those who were treated with pregabalin to confirm the beneficial effect of this treatment, with the aim of improving the management of NP. This publication presents original data as it is a naturalistic study of a large number of patients in the primary care environment.

2 Methods

Patients from a previous NP prevalence study [23] were followed up for 3 months to assess the progression of pain-related parameters and treatment satisfaction. This publication is a post hoc analysis performed in patients from the previous NP prevalence study treated with pregabalin [23] who had not been exposed to the drug in the previous 3 months. The study protocol was approved by the Clinical Research Ethics Committee of Virgen de las Nieves Hospital (Granada, Spain) in 2008 and complied with all ethical considerations involving human subjects in accordance with the Declaration of Helsinki, and followed standard security and confidentiality measures in compliance with Spanish legislation.

The aforesaid previous study was an observational, epidemiologic, cross-sectional, multicenter study carried out to assess the prevalence of NP according to the DN4 in primary care centers in Spain, and to characterize NP patients diagnosed by clinical judgment [23]. All of the participating physicians (792) enrolled the first 25 patients over 18 years of age presenting at primary care centers with pain of any origin and after giving their informed consent. Of the patients who met the DN4 diagnosis criteria of NP, the first five with clinical confirmation and who gave their informed consent were selected and included in this post hoc analysis. After 57 patients were excluded because of non-compliance with the screening criteria, this left a total of 3,836 patients eligible for analysis.

The first 25 patients, 18 years of age or older, seen at primary care centers for pain of any origin were registered. The 792 physicians enrolled 16,115 patients complaining of pain, of whom 7,327 (45.7 %) had NP according to the DN4. The first five patients with clinically confirmed NP were recruited after giving their informed consent, resulting in a total of 3,893 patients. After excluding 57 for

non-compliance with screening criteria, 3,836 patients were eligible to be characterized.

As a post hoc analysis from a previous cross-sectional study, the decision of the PCP on the most appropriate medical treatment for his or her patient was never influenced. They were followed up for 3 months to assess the progression of pain-related parameters and satisfaction with treatment. In the current post hoc analysis, only patients treated with pregabalin who had previously not been exposed to it (patients who had received no treatment or had been treated with a drug other than pregabalin during the previous 3 months) were analyzed. The patient disposition is shown in Fig. 1. These patients had a baseline and a 3-month visit. At baseline, the DN4 questionnaire was administered and sociodemographic and pain characteristic (etiology, duration) data were gathered; at baseline and also at 3 months, Brief Pain Inventory (BPI) Short Form (BPI-SF), pharmacologic and non-pharmacologic treatment, and treatment satisfaction data were collected.

2.1 Questionnaires Used

The DN4 [45, 46] is a ten-item questionnaire, which consists of pain descriptors and sensory dysfunctions that are systematically compared in order to identify patients with a high probability of NP. Individual item scores are added to obtain a maximum score of 10, with a screening breakpoint of 4.

The BPI [47, 48] is a self-administered tool to assess the intensity of pain and its impact on activities of daily living. The Spanish version has been validated [51]. The BPI-SF was used in the current study and was completed by the patient. The BPI-SF contains 11 items rated on a 0 (no pain/no interference) to 10 (worst possible pain/total interference) numeric rating scale, grouped in two dimensions: pain intensity (mean of the first 4 items: worst, least and average pain during the last week and pain now) and interference with life activities (mean of the last 7: interference with general activity, mood, walking ability, normal work, social relations, and enjoyment of life). Pain intensity is classified as mild or no pain (0–3), moderate (4–6), and severe (7). Patients are classified as responders when pain intensity decreases ≥50 % from the baseline score [49, 50].

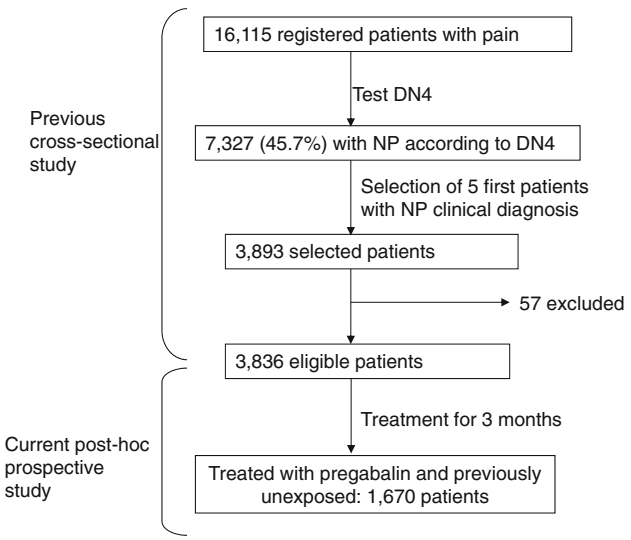

Fig. 1 Patient disposition in the previous and current study. *DN4* Douleur Neuropathique en 4 questions, *NP* neuropathic pain

Satisfaction with treatment was measured by self-administration of the generic Treatment Satisfaction for Medication Questionnaire (SATMED-Q) [52]. This questionnaire consists of 17 items on a Likert-type scale from 0 to 4 points (0 = no, not at all, 1 = somewhat, 2 = moderately, 3 = very, 4 = yes, extremely). The total score is the mean of the 17 items; scores are standardized from 0 (no satisfaction at all) to 100 (total or maximum satisfaction). The 17 items are grouped in six domains or dimensions (each with 2–3 items) of treatment satisfaction. The domain explored in the current study was "overall opinion", which includes items 15 (intention to continue treatment), 16 (feeling at ease with treatment), and 17 (overall satisfaction with treatment). Scores were also standardized (*Z*) with respect to the scores of the normal Spanish population.

2.2 Statistics

Descriptive statistics were applied to all variables, including measures of central tendency and statistical variability for quantitative variables, in addition to absolute and relative frequencies for qualitative variables, at baseline and 3 months, as well as for all changes from baseline. Some data were missing and results were obtained only from subjects with available data. Size samples were therefore smaller than the population sample and differed among variables.

Student's t-test was used to compare independent data for quantitative variables and the chi-square test was used for qualitative variables. For pair-wise data (final scores vs. baseline), Student's t-test was used for quantitative variables, Wilcoxon test for quantitative non-parametric variables, and McNemar test for dichotomic qualitative variables.

Patients were grouped post hoc according to pain duration (<1, 1–3, 3–6, 6–12, and >12 months), etiology [radiculopathy, neuralgia, neuropathy, peripheral nerve compression syndrome (PCS), complex regional pain syndrome (CRPS), plexopathy, NP in cancer, central pain, phantom limb syndrome (PLS) and other by deafferentation, atypical facial pain, and others] and baseline pain intensity (mild, moderate, severe). In each group category, an ANCOVA adjusted for baseline values was performed to compare changes in among-group scores (BPI-SF,

SATMED-Q, and number of days with no or mild pain). Only those subjects who had a baseline and a 3-month score were included.

The statistics program SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis and all statistics tests were bilateral with significance levels of 5 %.

3 Results

Of 3,836 NP patients from a previous prevalence study in the Spanish primary care setting, 3,516 (91.7 %) completed the study. Reasons for dropping out (8 %) were lost to follow-up (84; 2.2 %), at patient's request (54; 1.4 %), researcher's decision (35; 0.9 %), death (17; 0.4 %), adverse events (16; 0.4 %), exacerbation of disease (13; 0.3 %), unknown reasons (40; 1 %), protocol violations (8; 0.2 %), and other reasons (59; 1.5 %). Of 3,516 patients, 1,670 were treated with pregabalin for 3 months who had not been exposed to the drug in the previous 3 months [173 patients (10.4 %) had not received any treatment and 1,497 (89.6 %) had been treated with at least one drug other than pregabalin]. Fifty-nine percent were women, mean age was 58 years, and 71 % were overweight (Table 1). Patients had taken the DN4 questionnaire with a mean number of six positive answers. Pain had been chronic for almost a year. The most frequent etiology was radiculopathy (55 %) and the most frequent NP diagnosis was lumbar spinal cord and nerve root disorders (22 %).

This subgroup of 1,670 patients treated with pregabalin (average dose 202 mg/day) are the target sample group of this post hoc analysis. Of those 1,670 patients, 617 (36.9 %) were taking pregabalin monotherapy, 517 (30.9 %) received one concomitant treatment, and 536 (32.1 %) received two or more (up to 5). The mean number of drugs used "within 3 months before the study" was 2.2 ± 1.1 and "during the study" was 2.1 ± 1.1. Three months before the study, anticonvulsants were used in only 9 % of patients, with gabapentin as the only glutamate and GABA analog, and the most frequently used pharmacologic treatments were NSAIDs (61 %) and non-opioid analgesics (58 %), both reduced by half during the course of the study (Table 2). Non-pharmacologic treatment was used in 43.4 % of patients in the previous 3 months and in 34.3 % during the study, with physiotherapy and local administration of heat being the most frequent ones used in both periods.

Figure 2 and Table 3 show the progression of pain parameters and satisfaction with treatment from baseline to the end of the study. After adjusting for baseline scores, pain intensity and its interference with activities were significantly ($p < 0.0001$) reduced by half, while the number of days with no or mild pain increased by a mean of 4.5 days ($p < 0.0001$). There were 843 (51.6 %) responders (patients whose pain intensity decreased by ≥50 %) (data not shown), 22 % of patients had severe pain and 75 % moderate pain at baseline, and these percentages decreased to 1 and 31 %, respectively, at 3 months. The proportion of patients with no or mild pain, which was 3 % at baseline, increased to 67 % (data not shown). Regarding satisfaction with treatment, the overall opinion doubled (from 35.2 to 76.8; $p < 0.0001$), and the standardized score rose to the level of the general population at 3 months of treatment ($p < 0.0001$), from 2 points below at baseline.

Table 1 Socio-demographic characteristics of the target sample population (3,836 patients)

Women	981 (59.4)
Age (years)	58.5 ± 13.7
Bodyweight (kg)	74.2 ± 11.9
Height (cm)	165 ± 8.5
BMI (kg/m^2)	27.2 ± 3.9
≤18.5 (low weight)	7 (0.4)
18.5–25 (normal weight)	474 (28.7)
25–30 (obesity grade I)	816 (49.5)
30–35 (obesity grade II)	301 (18.2)
35–40 (obesity grade III)	41 (2.5)
≥40 (obesity grade IV)	11 (0.7)
DN4 positive questions (no.)	6.3 ± 1.5
Pain duration (years)	0.9 ± 1.8
Age at pain initiation (years)	57.5 ± 13.7
Etiology[a]	
Radiculopathy	916 (55.14)
Neuralgia	279 (16.8)
Neuropathy	197 (11.9)
Peripheral nerve compression syndrome	178 (10.71)
Complex regional pain syndrome	53 (3.2)
Plexopathy	44 (2.6)
Other	43 (2.6)
Central pain	29 (1.7)
Oncology-associated pain	27 (1.6)
Phantom limb syndrome and other deafferentation pain	16 (1.0)
Atypical facial pain	13 (0.8)

Values expressed as *n* (%) or mean ± SD

BMI Body Mass Index, *DN4* Douleur Neuropathique en 4 questions

[a] Some patients indicated more than one etiology

3.1 Progression According to Pain Duration

Patients were divided according to their pain duration: <1 month (356 patients), 1–3 months (226), 3–6 months (292), 6–12 months (308) and >12 months (430) groups.

The mean number of drugs administered during the study was significantly ($p = 0.0025$) different among groups,

Table 2 Treatments used previously (within 3 months before the study) or during the study period by ≥1 % of patients

Treatment	Previously (n = 1,497)	Study period (n = 1,670)
Anticonvulsant		
Pregabalin	–	1,670 (100)
Gabapentin	87 (5.8)	17 (1.0)
Carbamazepine	37 (2.5)	–
NSAIDs		
Ibuprofen	411 (27.5)	183 (10.0)
Diclofenac	286 (19.1)	104 (6.2)
Dexketoprofen	59 (3.9)	30 (1.8)
Aceclofenac	45 (3.0)	18 (1.1)
Celecoxib	37 (2.5)	41 (2.5)
Naproxen	37 (2.5)	19 (1.1)
Meloxicam	21 (1.4)	–
Aspirin	18 (1.2)	–
Non-opioid analgesic		
Paracetamol	620 (41.4)	374 (22.4)
Metamizol	268 (17.9)	128 (7.7)
Opioid		
Tramadol	248 (16.6)	158 (9.5)
Fentanyl	30 (2.0)	30 (1.8)
Non-opioid analgesic/opioid combination		
Paracetamol/tramadol	69 (4.6)	68 (4.1)
Codeine/paracetamol	15 (1.0)	–
Benzodiazepine		
Tetrazepam	124 (8.3)	48 (2.9)
Lorazepam	20 (1.3)	24 (1.4)
Alprazolam	16 (1.1)	–
Diazepam	–	55 (3.3)
Antidepressant		
Amitriptyline	79 (5.3)	51 (3.1)
Paroxetine	15 (1.0)	–
Other		
Omeprazole	70 (4.7)	55 (3.3)
Hydroxocobalamin/pyridoxine/thiamine	29 (1.9)	18 (1.1)
Metformin	24 (1.6)	19 (1.1)
Aciclovir	22 (1.5)	–
Cyanocobalamin/dexamethasone/lidocaine/thiamine	19 (1.3)	–
Pantoprazole	19 (1.3)	18 (1.1)
Pharmacologic groups[a]		
NSAIDs	907 (60.6)	428 (25.6)
Non-opioid analgesics	864 (57.7)	535 (32)
Opioids	362 (24.2)	265 (15.9)
Anticonvulsants	136 (9.1)	1,670 (100)
Antidepressants	133 (8.9)	108 (6.5)
Benzodiazepines	259 (17.3)	153 (9.2)
Other	340 (22.7)	234 (14)
Non-pharmacologic treatment		
Any	674 (43.4)	502 (34.3)
Physiotherapy[b]	328 (48.7)	294 (58.6)
Local administration of heat[b]	368 (54.6)	204 (40.6)
Local administration of cold[b]	71 (10.5)	38 (7.6)
Vibrations/massages[b]	121 (18.0)	78 (15.5)
Acupuncture[b]	69 (10.2)	28 (5.6)
Other[b]	60 (8.9)	45 (9.0)

Data expressed as n (%) patients

NSAIDs non-steroidal anti-inflammatory drugs

[a] Some drugs are classified in more than one group

[b] Percentage based on the total number of patients using any non-pharmacologic treatment

ranging from 2.0 in the <1 month group to 2.3 in the >12 months group. There were also significant differences ($p = 0.0211$) in the proportion of patients on pregabalin monotherapy or combination therapy among groups, with the groups with shorter disease progression showing higher patient percentages on monotherapy: 40 % in the <1 month group, 43 % in 1–3 months, 38 % in 3–6 months, 37 % in 6–12 months, and 31 % in >12 months.

From baseline to the endpoint, pain intensity and interference with daily life decreased significantly ($p < 0.0001$) and the number of days with no or mild pain increased significantly ($p < 0.0001$) within each group. Among-group significant differences ($p < 0.0001$) were observed for changes in the adjusted scores of the three parameters, with the <1 and 1–3 months groups showing the largest decreases in pain intensity and pain interference with daily activities and the largest increases in number of days with no or mild pain (Table 4; Fig. 3a, b). Significant ($p < 0.0001$) differences were also observed among groups in the proportion of responders, which decreased as the duration of pain increased (Fig. 3c). The overall within-group opinion of satisfaction with treatment increased significantly ($p < 0.0001$) and the among-group changes were significantly ($p = 0.0386$) different, with the 1–3 and <1 month groups showing the largest increases (Fig. 3d); the within-group changes for the standardized score were also significant ($p < 0.0001$) and significant ($p = 0.0362$) differences were observed in the among-group changes, with the 1–3 months group showing the highest increase (Fig. 3e).

3.2 Progression According to Etiology

Patients were divided according to their pain etiology into radiculopathy (841 patients), neuralgia defined as pain in

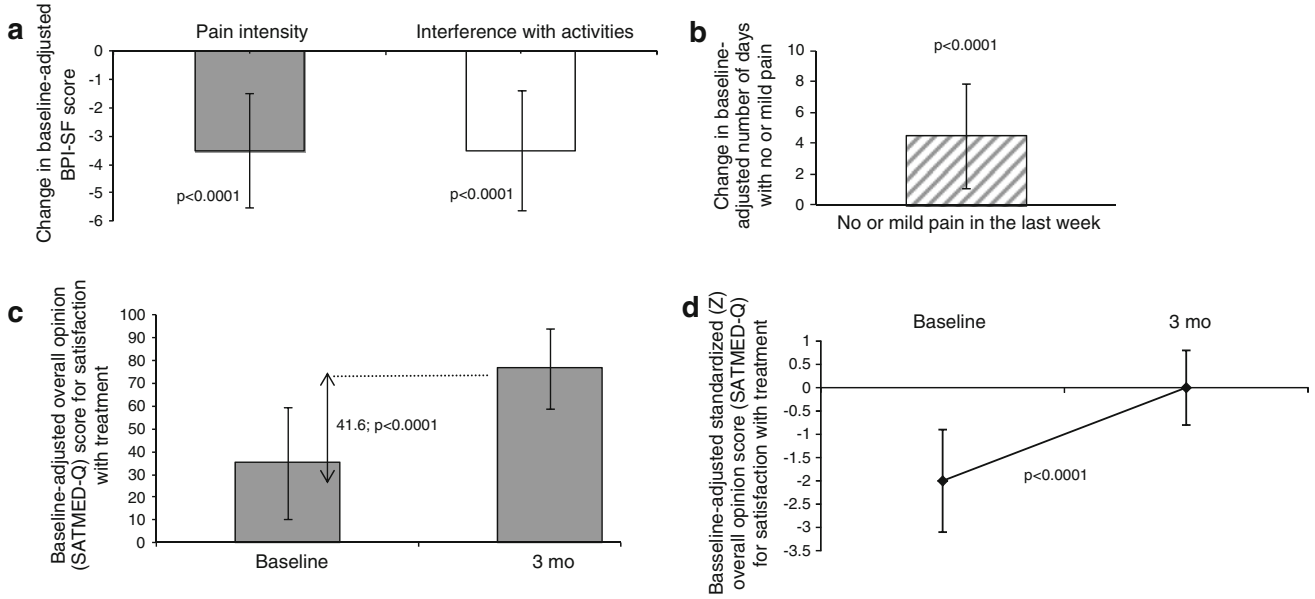

Fig. 2 Progression of pain parameters and satisfaction with treatment during the study: **a** change in mean ± SD baseline-adjusted BPI-SF scores for pain intensity and pain interference with activities; **b** change in mean ± SD baseline-adjusted number of days with no or mild pain in the last week; **c** mean ± SD overall opinion score for satisfaction with treatment (SATMED-Q) at baseline and 3 months (baseline-adjusted); **d** mean ± SD overall opinion score for satisfaction with treatment (SATMED-Q) standardized for the Spanish population at baseline and 3 months. All *p* values vs. baseline. *BPI-SF* Brief Pain Inventory-Short Form, *SATMED-Q* Treatment Satisfaction for Medication Questionnaire, *SD* standard deviation

Table 3 Pain-related parameters and satisfaction with treatment at baseline and endpoint (3 months)

Outcomes	*n*	Baseline	3 months	Change (95 % CI)	*p* value
BPI-SF					
Pain intensity (score)	1,636	6.4 ± 1.5	2.9 ± 1.7	−3.5 (−3.6 to −3.4)	<0.0001
Interference with activities (score)	1,621	6.3 ± 1.8	2.8 ± 2	−3.5 (−3.6 to −3.4)	<0.0001
No or mild pain last week (days)	1,647	0.3 ± 1.4	4.8 ± 3.3	4.5 (4.3–4.7)	<0.0001
SATMED-Q					
Overall satisfaction (score)	1,517	35.2 ± 24.4	76.8 ± 17.5	41.6 (40.1–43)	<0.0001
Standardized overall satisfaction (*Z* score)	1,502	−2.0 ± 1.1	−0.0 ± 0.8	1.9 (1.9–2.0)	<0.0001

Data are observed means ± SD with 95 % confidence intervals; *p* values are adjusted by baseline values

BPI-SF Brief Pain Inventory Short Form, *SATMED-Q* Treatment Satisfaction for Medication Questionnaire

the distribution of a nerve or nerves (265), neuropathy defined as a disturbance of function or pathologic change in a nerve (161), PCS (142), CRPS (32), plexopathy (27), NP in cancer (21), central pain (19), PLS and other deafferentation pain (13), atypical facial pain (11), and others (35).

The mean number of drugs used during the study was significantly ($p = 0.001$) different among groups, with "NP in cancer" having the highest number (2.8) and "atypical facial pain" the lowest (1.8). There were also significant differences ($p = 0.0447$) in the proportions of patients on pregabalin monotherapy or combination therapy among groups. The proportions of patients on monotherapy were as follows: NP in cancer 19 %, PLS and other deafferentation pain 23 %, other 31 %, central pain 32 %, CRPS 34 %, radiculopathy 35 %, atypical facial pain 36 %, neuropathy 37 %, plexopathy 41 %, neuralgia 45 %, and PCS 46 %.

As it is the most prevalent group, it is worth noting that in the group of patients with radiculopathy as the cause of NP, of the 841 patients who reported radicular NP, 65 % were treated with pregabalin as part of a combination therapy and 35 % with pregabalin alone.

Regarding the pregabalin add-on group, more than half took a combination with one other drug (52 %) and 32 % received two other drugs, while 10 % received a combination of pregabalin plus three other drugs (mean number of drugs 2.1, standard deviation 1.1, 95 % CI 2.0–2.2).

Table 4 Outcomes according to pain duration

Outcomes	<1 month ($n = 355$)	1–3 months ($n = 226$)	3–6 months ($n = 296$)	6–12 months ($n = 309$)	>12 months ($n = 432$)	p value[b]
BPI-SF score for pain intensity						
Baseline, mean [SD]	6.5 [1.5]	6.3 [1.4]	6.3 [1.4]	6.4 [1.4]	6.3 [1.5]	0.2198
Change (95 % CI)	−4.5 (−4.7 to −4.3)	−3.8 (−4.0 to −3.5)	−3.3 (−3.5 to −3.1)	−3.3 (−3.5 to −3.1)	−2.8 (−3.0 to −2.6)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
BPI-SF score for pain interference with activities						
Baseline, mean [SD]	6.1 [1.9]	6.0 [1.8]	6.3 [1.7]	6.4 [1.8]	6.5 [1.8]	0.0002
Change (95 % CI)	−4.2 (−4.4 to −4.0)	−3.6 (−3.9 to −3.4)	−3.6 (−3.8 to −3.3)	−3.5 (−3.7 to −3.2)	−3.0 (−3.2 to −2.8)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Number of days with no or mild pain						
Baseline, mean [SD]	0.3 [1.5]	0.2 [1.2]	0.3 [1.3]	0.3 [1.5]	0.3 [1.3]	0.8402
Change (95 % CI)	5.7 (5.4–6.0)	5.0 (4.6–5.4)	4.7 (4.4–5.1)	4.2 (3.8–4.5)	3.5 (3.2–3.8)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Overall opinion score for satisfaction with treatment (SATMED-Q)						
Baseline, mean [SD]	30.7 [26.1]	34.8 [25.5]	36.2 [23.0]	34.1 [23.5]	38.5 [23.9]	0.001
Change (95 % CI)	47.8 (44.2–51.4)	44.4 (40.7–48.1)	41.7 (38.4–45.0)	42.1 (39.0–45.3)	36.6 (33.7–39.5)	0.0386
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Overall opinion score for satisfaction with treatment (SATMED-Q) standardized for the Spanish population						
Baseline, mean [SD]	−2.2 [1.2]	−2 [1.2]	−1.9 [1.1]	−2 [1.1]	−1.8 [1.1]	0.001
Change (95 % CI)	2.2 (2.1–2.4)	2.1 (1.9–2.3)	1.9 (1.8–2.1)	2.0 (1.8–2.1)	1.7 (1.6–1.8)	0.0362
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

BPI-SF Brief Pain Inventory-Short Form, *SATMED-Q* Treatment Satisfaction for Medication Questionnaire

[a] Data are observed means ± SD with 95 % confidence intervals; p values are adjusted by baseline values and represent within-group comparisons

[b] Data are observed means ± SD with 95 % confidence intervals; p values are adjusted by baseline values and represent between-group comparisons

Thirty-four percent of the patients received at least one non-opioid analgesic, 31 % took NSAIDs, 15 % took opioids, and 12 % took benzodiazepines.

Pain intensity and interference with daily life decreased ($p < 0.0001$), while the number of days with no or mild pain increased ($p < 0.0001$) significantly within groups at 3 months. Significant among-group differences ($p < 0.0001$) were observed for the changes in the adjusted scores of pain intensity, interference with activities, and days with no or mild pain, with neuralgia and PCS groups showing the largest changes in all three parameters (Table 5; Fig. 4a, b). Significant ($p = 0.0002$) differences in the number of responders were observed among groups, with the CRPS (65.6 %) and neuralgia (62.9 %) groups showing the highest percentages of responders (Fig. 4c).

Regarding satisfaction with treatment, there were significant among-group differences at baseline on the scores obtained on the three questions of the SATMED-Q overall opinion domain. On "Intention to continue treatment" ($p < 0.0001$), scores ranged from 1.2 ± 1.0 to 2.1 ± 1.1; on "Feeling at ease with treatment" ($p = 0.0014$), from 0.9 ± 1.0 to 1.7 ± 1.0; and on "Overall satisfaction with treatment" ($p = 0.0060$), from 0.9 ± 0.8 to 1.6 ± 1.2. After 3 months of pregabalin treatment, the scores for "Intention to continue treatment" were similar among groups ($p = 0.0741$), ranging from 2.8 ± 1.1 to 3.5 ± 0.5. The scores for "Feeling at ease with treatment" were significantly different ($p = 0.0039$) among groups, ranging from 2.6 ± 1.1 to 3.2 ± 0.8, with neuralgia and PLS showing the highest mean score. The scores for "Overall satisfaction with treatment" were also significantly different ($p = 0.0011$), ranging from 2.7 ± 1.1 to 3.3 ± 0.7, with neuralgia showing the highest mean score (data not shown).

3.3 Progression According to Baseline Pain Intensity

Patients were divided according to their baseline pain intensity as mild or no pain (364 patients), moderate (1,120), and severe (364).

Significant differences were observed in the mean number of drugs administered during the study ($p = 0.0012$) among groups, with the severe pain group having the highest number (2.3) and the no or mild pain group the lowest (1.9), but the proportion of patients on pregabalin monotherapy or on combination therapy was similar ($p = 0.4028$) among groups.

The adjusted scores for pain intensity and pain interference with activities decreased significantly ($p < 0.0001$) within groups but the changes were similar among groups

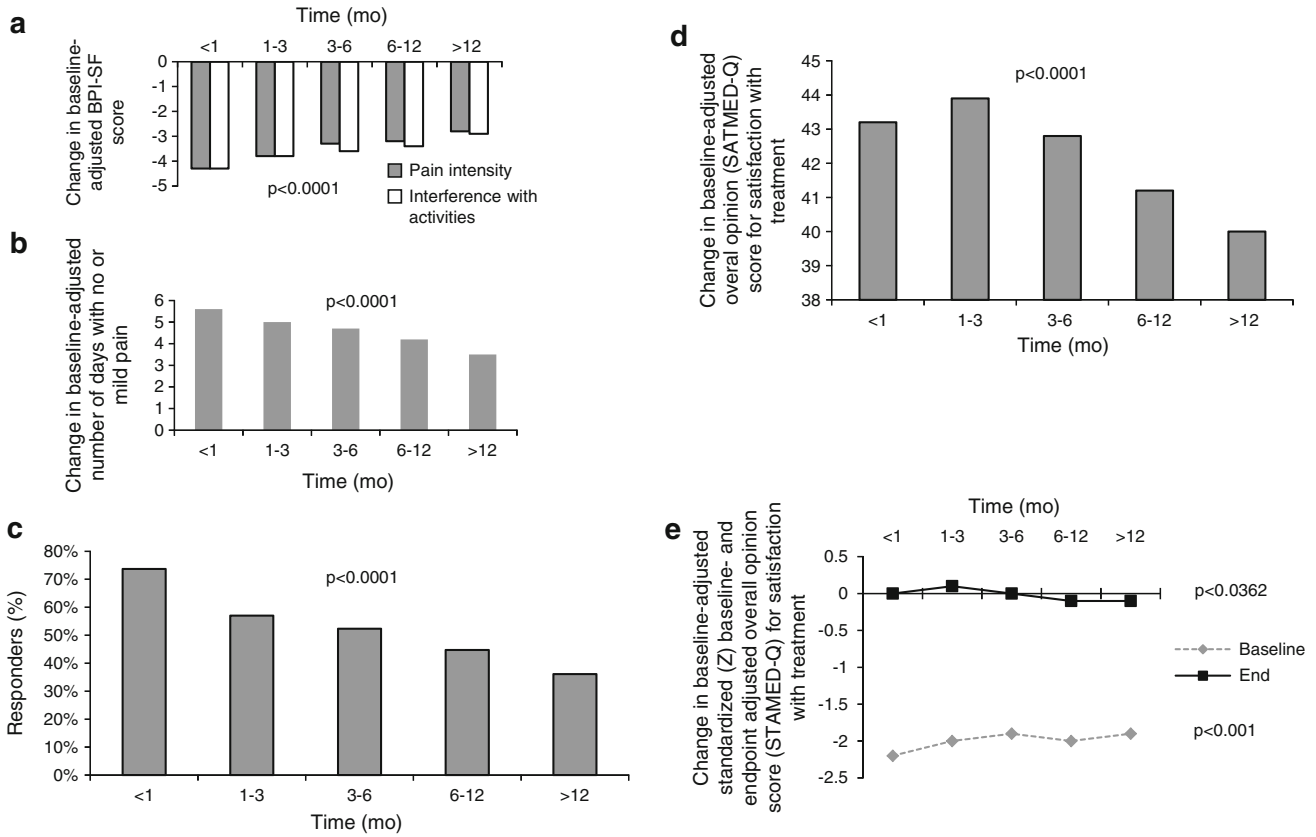

Fig. 3 Pain outcomes according to disease progression: **a** change in mean baseline-adjusted BPI-SF scores for pain intensity and pain interference with activities; **b** change in mean baseline-adjusted number of days with no or mild pain; **c** responders to treatment; **d** change in baseline-adjusted overall opinion score for satisfaction with treatment (SATMED-Q); **e** mean baseline- and endpoint-adjusted overall opinion score for satisfaction with treatment (SATMED-Q) standardized for the Spanish population. *p* values represent among-group differences. *BPI-SF* Brief Pain Inventory-Short Form, *SATMED-Q* Treatment Satisfaction for Medication Questionnaire

($p = 0.2047$ for pain intensity and $p = 0.9956$ for pain interference with activities) (Table 6; Fig. 5a). Likewise, there were significant ($p < 0.0001$) within-group increases in the number of days with no or mild pain; however, the change in number of days was significantly ($p < 0.0001$) different among groups, increasing in size as the intensity of baseline pain decreased (Table 6; Fig. 5b). Regarding satisfaction with treatment, the adjusted overall opinion scores increased significantly ($p < 0.0001$) within groups but no significant ($p = 0.4204$) among-group changes were observed (data not shown).

4 Discussion

A cross-sectional study carried out in the primary care setting [23] highlighted the non-appropriate management of NP patients, with over half of them being treated with NSAIDs and non-opioid analgesics. Patients had moderate pain intensity and interference with activities, and although many were inappropriately treated, others may have been treatment-refractory cases. These patients were treated for 3 months at the discretion of their physicians, and we focused on those treated with pregabalin, since this treatment had been shown to be effective in NP patients refractory to at least one previous analgesic in the Spanish primary care setting [43, 44]. Data obtained (significant reduction in pain intensity and interference with activities and significant increase in overall satisfaction with treatment) confirmed the beneficial effect of pregabalin as monotherapy or combination therapy in this setting.

The target pregabalin-unexposed population demographically reflected the overall NP population, since 59 % were women and the mean age was 58 years, in keeping with previous Spanish and European studies showing that women and middle-age patients suffer more frequently from NP [12, 53, 54]. Radiculopathy was also the most frequent etiology (55 %) in this population, as is the case in the overall NP population in Spanish pain units [53].

Pregabalin treatment as monotherapy and combination therapy was effective in pregabalin-unexposed patients, most (90 %) of whom were previously treated with at least one other treatment. At 3 months of treatment, pain intensity and its interference with activities were

Table 5 Outcomes according to neuropathic pain etiology

Outcomes	Neuro ($n = 161$)	Neuralgia ($n = 262$)	Radic ($n = 835$)	Plexo ($n = 26$)	PCS ($n = 141$)	CRPS ($n = 32$)	PLS ($n = 13$)	Central ($n = 19$)	AFP ($n = 11$)	Oncology ($n = 21$)	Other ($n = 32$)	p value[b]
Mean dose [SD] (mg/day)	224.3 (157.1)	206.1 (121.2)	194.0 (111.0)	238.5 (164.2)	192.1 (123.7)	190.6 (132.1)	242.3 (153.6)	256.6 (137.6)	197.7 (107.5)	306.3 (220.3)	202.1 (164.6)	–
BPI-SF score for pain intensity												
Baseline mean [SD]	6.3 [4.5]	6.6 [1.6]	6.3 [1.4]	6.4 [1.6]	6.0 [1.6]	6.2 [1.4]	6.6 [1.2]	6.7 [1.3]	6.1 [1.7]	4.1 [1.6]	6.6 [1.5]	0.002
Change (95 % CI)	−3.0 (−3.2 to −2.7)	−4.2 (−4.5 to −3.9)	−3.5 (−3.6 to −3.4)	−3.1 (−3.9 to −2.3)	−3.4 (−3.8 to −3.1)	−3.2 (−3.7 to −2.6)	−2.8 (−4.0 to −1.7)	−2.7 (−3.7 to −1.6)	−3.2 (−4.9 to −1.5)	−2.8 (−3.9 to −1.6)	−2.7 (−3.4 to −2.1)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
BPI-SF score for pain interference with activities												
Baseline mean [SD]	6.5 [1.8]	6.1 [1.8]	6.4 [1.7]	6.4 [1.4]	5.2 [1.9]	6.0 [2.1]	6.9 [1.8]	7.4 [1.3]	5.6 [1.9]	7.1 [2.1]	6.9 [1.6]	<0.0001
Change (95 % CI)	−3.1 (−3.4 to −2.8)	−4.0 (−4.3 to −3.7)	−3.7 (−3.8 to −2.5)	−3.5 (−4.4 to −2.7)	−3.1 (−3.5 to −2.8)	−3.1 (−3.7 to −2.4)	−2.9 (−4.6 to −1.2)	−2.8 (−4.0 to −1.7)	−3.1 (−4.7 to −1.5)	−2.8 (−4.0 to −1.5)	−2.7 (−3.5 to −1.9)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Number of days with no or mild pain												
Baseline mean [SD]	0.3 [1.4]	0.3 [1.5]	0.3 [1.3]	0.5 [1.9]	0.5 [1.9]	0.4 [1.7]	6.6 [1.2]	6.7 [1.3]	0.6 [2.1]	4.1 [1.6]	6.6 [1.5]	0.3875
Change (95 % CI)	3.9 (3.4–4.7)	5.1 (4.7–5.5)	4.7 (4.5–4.9)	3.6 (2.2–5.0)	4.8 (4.2–5.3)	4.4 (3.1–5.6)	3.2 (1.0–5.4)	2.9 (1.2–4.7)	3.8 (1.4–6.3)	3.3 (1.6–5.0)	3.6 (2.4–4.8)	0.0002
p value[a]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	

AFP atypical facial pain, *BPI-SF* Brief Pain Inventory-Short Form, *CRPS* complex regional pain syndrome, *Neuro.* neuropathy, *PCS* peripheral nerve compression syndrome, *Plexo.* plexopathy, *PLS* phantom limb syndrome and other deafferentation pain, *Radic.* radiculopathy, *SD* standard deviation

[a] Data are observed means ± SD with 95 % confidence intervals; p values are adjusted by baseline values and represent within-group comparisons

[b] Data are observed means ± SD with 95 % confidence intervals; p values are adjusted by baseline values and represent between-group comparisons

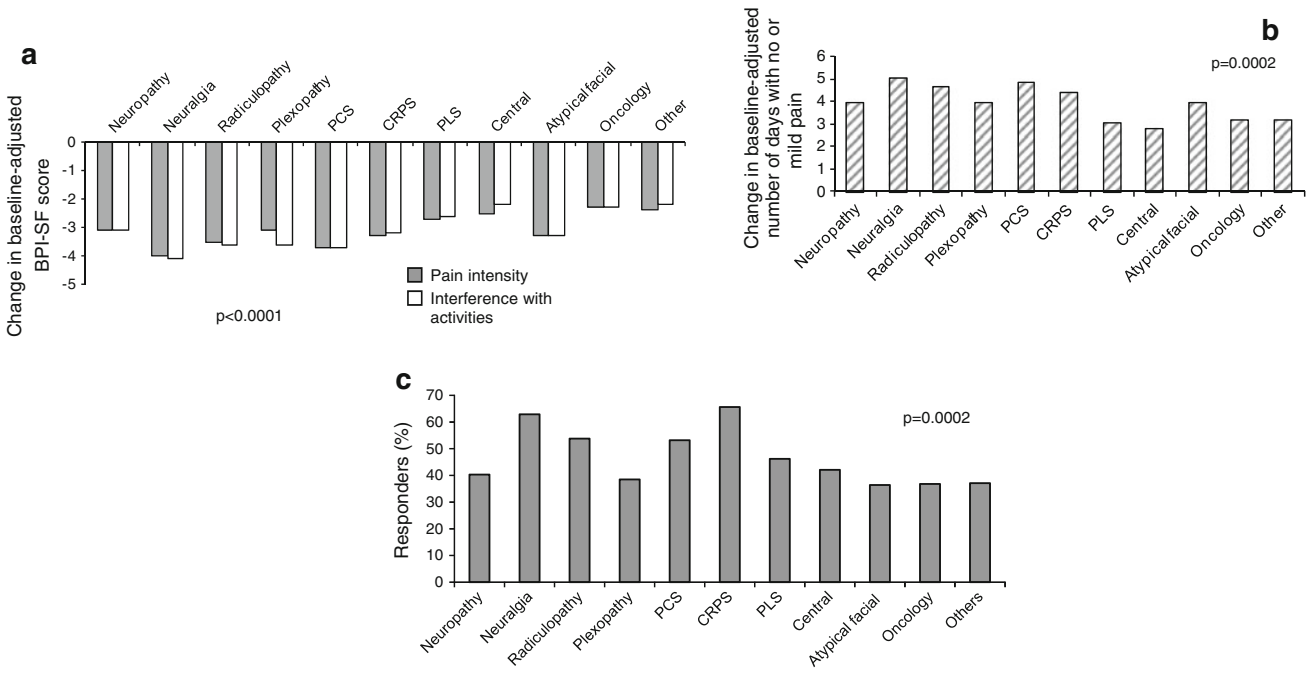

Fig. 4 Pain outcomes according to etiology: **a** change in mean baseline-adjusted BPI-SF scores for pain intensity and pain interference with activities; **b** change in mean baseline-adjusted number of days with no or mild pain; **c** responders to treatment. *p* values represent among-group differences. *BPI-SF* Brief Pain Inventory-Short Form, *CRPS* complex regional pain syndrome, *PCS* peripheral nerve compression syndrome, *PLS* phantom limb syndrome

Table 6 Outcomes according to baseline pain intensity

Outcomes	Intense ($n = 364$)	Moderate ($n = 1,220$)	No or mild ($n = 52$)	*p* value[b]
BPI-SF score for pain intensity				
Baseline mean [SD]	8.3 [0.5]	6 [1.0]	2.6 [0.7]	<0.0001
Change (95 % CI)	−4.9 (−5.1 to −4.7)	−3.2 (−3.3 to −3.1)	−1.2 (−1.5 to −0.9)	0.2047
p value[a]	<0.0001	<0.0001	<0.0001	
BPI-SF score for pain interference with activities				
Baseline mean [SD]	7.7 [1.2]	6 [1.6]	2.9 [1.6]	<0.0001
Change (95 % CI)	−4.4 (−4.6 to −4.1)	−3.4 (−3.5 to −3.3)	−1.5 (−1.9 to −1.1)	0.9956
p value[a]	<0.0001	<0.0001	<0.0001	
Number of days with no or mild pain				
Baseline mean [SD]	0 [0.0]	0.1 [0.9]	6.2 [2.3]	<0.0001
Change (95 % CI)	3.9 (3.5 to 4.3)	4.8 (4.7 to 5.0)	0.7 (−0.0 to 1.4)	<0.0001
p value[a]	<0.0001	<0.0001	<0.0001	

BPI-SF Brief Pain Inventory-Short Form, *SD* standard deviation

[a] Data are observed means ± SD with 95 % confidence intervals; *p* values are adjusted by baseline values and represent within-group comparisons

[b] Data are observed means ± SD with 95 % confidence intervals; *p* values are adjusted by baseline values and represent between-group comparisons

significantly reduced, resulting in a significant increase in the number of days with no or mild pain. The percentage of responders (51.6 %) was closer to that observed in patients receiving pregabalin in the study by Navarro et al. [44] (55 % overall; including 52.1 % of responders to pregabalin combination therapy and 57.9 % of responders to pregabalin monotherapy). As a result of the pain reduction by half, satisfaction with treatment (overall opinion) doubled, with the standardized score reaching the level of the Spanish general population.

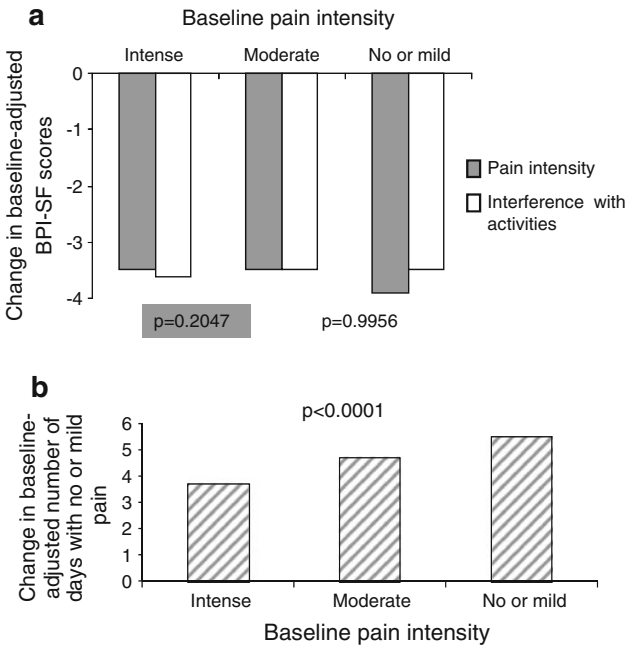

Fig. 5 Pain outcomes according to baseline BPI-SF pain intensity: **a** change in mean baseline-adjusted BPI-SF scores of pain intensity and pain interference with activities; **b** change in mean baseline-adjusted number of days with no or mild pain. *p* values represent among-group differences. *BPI-SF* Brief Pain Inventory-Short Form

Patients with shorter disease progression (≤3 months) and those with neuralgia and PCS etiology seemed to respond better to pregabalin treatment. The possibility of distinct NP subtypes depending on etiology has been discussed [55]. The study by Attal et al. [55] investigating the relationship between positive NP symptoms and etiologies found some associations, such as the association of trigeminal neuralgia and postherpetic neuralgia with absence of tingling and pins and needles, and that of amputation pain and plexopathy with presence of electric shocks and stabbing pain. Thus, neuralgia may be a distinct NP subtype with better response to pregabalin than other etiologies, and so may be the case for PCS. Regarding pain duration, a short duration between symptom onset and treatment has already been associated with NP improvement in other neuropathy cases [56]. On the other hand, it is important to point out that those groups were also the ones with the highest proportion of patients on pregabalin monotherapy. Combination treatment is usual clinical practice in NP and may result in greater pain relief [57]; however, these groups showed better treatment response despite being the ones with the lowest proportion of patients on combination therapy. Pregabalin monotherapy may be more effective than combination therapy in these patients. In the study by Navarro et al. [44], at least numerically, there were more responders in the pregabalin monotherapy group than in the combination therapy group (57.9 vs. 52.1 %). Therefore, we cannot establish how much of the among-group change differences observed are due to time since disease onset and etiology type and how much to the proportion of monotherapy/combination therapy.

The per baseline pain intensity groups, which had similar proportions of patients on combination therapy or monotherapy, did not show any significant among-group differences in the score changes for pain intensity, interference with activities, and satisfaction with treatment. These data seem to support the possible effect of monotherapy or combination therapy over treatment response, since among-group changes were significantly different only in group categories with significantly different percentages of monotherapy and combination therapy among groups. However, having no or mild pain at baseline still resulted in more pain-free (or mild pain) days after 3 months of pregabalin treatment, which suggests a positive association between low baseline pain intensity and pregabalin treatment response.

Overall, at 3 months, satisfaction with treatment seemed to be improved, since the lowest mean score for each SATMED-Q overall opinion question was higher than the highest score for that same question at baseline. Patients with neuralgia seemed to be the most satisfied with pregabalin treatment, in keeping with the largest improvement in pain intensity, interference with daily life, and number of days with no or mild pain in this group.

Our study has some limitations. The observational design introduces different confounding factors including "confounding by indication", where prognostic factors may influence treatment decisions [58, 59]. Also, psychiatric co-morbidities were not assessed and this could influence the outcomes.

The current post hoc analysis assessed only patients treated with pregabalin; however, in the analyses of the per pain duration and per etiology groups, the proportion of patients receiving monotherapy or combination therapy differed among groups, which may act as another confounding factor for the outcomes observed. This will have to be further analyzed. Also, in each group category, baseline values were significantly different among groups for most variables. However, the analyses were adjusted for baseline values to even out possible bias. Since we focused on pregabalin-treated patients, outcomes could not be compared with those of patients on other treatments; however, in the study by Navarro et al. [43, 44], patients on pregabalin monotherapy or combination therapy showed greater reductions in pain severity than those on non-PGB therapy.

Whether or not the proportion of patients on monotherapy or combination therapy influences the outcomes, most patients were treated with non-opioid analgesics and

NSAIDs (32 and 26 % of all patients) as concomitant treatments, and only 22 % were treated with another NP recommended treatment (antidepressants or opioids); thus, in most patients (78 %) the reduction in pain intensity and interference with activities observed is most likely due to pregabalin.

5 Conclusion

Our analysis suggests that treatment with pregabalin, both as monotherapy or in combination with other drugs, provides benefits for pain and treatment satisfaction in patients with NP, including refractory cases. Shorter disease progression, neuralgia and PCS etiologies, and low baseline pain intensity seem to be favorable variables for pregabalin treatment response. The possible effect of monotherapy or combination therapy on treatment response should be further investigated.

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Author contributions All authors had complete access to the data, participated in the analysis and/or interpretation of results, and drafted and approved the content of the manuscript. María Pérez and Vanessa López-Gómez participated in the design and concept of the original study and in the interpretation of data and drafting the manuscript. All authors were responsible for review of the literature and extraction of references.

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