

Effectiveness of Pregabalin Treatment for Neuropathic Pain in Patients with Spine Diseases: A Pooled Analysis of Two Multicenter Observational Studies in Japan

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Toshihiko Taguchi¹
Shogo Nakano²
Kazutaka Nozawa²

¹Japan Organization of Occupational Health and Safety, Yamaguchi Rosai Hospital, Sanyo-Onoda, Yamaguchi, Japan;

²Pfizer Japan, Inc., Tokyo, Japan

Purpose: Neuropathic pain (NeP) is common among patients with chronic pain associated with spine diseases. Practical effectiveness of pregabalin, one of the first-line treatments for NeP, has not been evaluated in an entire population of patients with spine diseases, including various pathophysiological conditions. This pooled analysis aimed to evaluate the therapeutic value of pregabalin for chronic pain with NeP component in patients with spine diseases in routine primary care settings.

Patients and Methods: We pooled data from two 8-week prospective observational cohort studies for patients with chronic low back pain with accompanying lower limb pain (NeP component), and patients with chronic cervical pain and accompanying upper limb radiating pain (NeP component) in routine primary care settings in Japan. For both studies, patients were treated for 8 weeks with pregabalin (alone/with other analgesics) or usual care with conventional analgesics (eg, non-steroidal anti-inflammatory drugs). Changes in pain numerical rating scale (NRS), Pain-Related Sleep Interference Scale (PRSIS), and EuroQol 5-dimension 5-level (EQ-5D-5L) scores from baseline to week 8 were summarized and compared between the pregabalin and usual care groups, and also for subgroups of primary diagnosis. Safety was evaluated by adverse events (AEs) in the pregabalin group.

Results: The pooled dataset comprised 700 patients (pregabalin group: 302; usual care group: 398). All patient-reported outcomes (PRO) scores significantly improved from baseline to week 8 in the pregabalin than in the usual care group (NRS: $P < 0.0001$; PRSIS: $P < 0.0001$, and EQ-5D-5L: $P = 0.0006$). Overall, all three PRO measures showed greater improvement in the pregabalin than in the usual care group, irrespective of the primary diagnosis. AEs were reported in 36.1% of the pregabalin group.

Conclusion: This analysis suggested multi-faceted effectiveness of treatment with pregabalin from the patient's perspectives under a "real-world" practice in all patients with chronic NeP from various spine diseases.

Keywords: neuropathic pain, chronic pain, spine diseases, pregabalin, pooled analysis

Introduction

Low back pain and cervical pain are common health problems in developed countries. About 83% of the population in Japan experience low back pain at some point in their lives,¹ and 48.3% of adults have neck or shoulder pain each year.² Neuropathic pain (NeP), defined as "pain caused by a lesion or disease of the somatosensory nervous system"³ is caused by various etiologies including

Correspondence: Kazutaka Nozawa
Email kazutaka.nozawa@pfizer.com

spine diseases, such as radiculopathy and cauda equina lesions,⁴ and cervical spondylotic myelopathy.⁵ NeP from these spine diseases is often experienced as low back pain and cervical pain with pain radiating down to the legs and arms, respectively.

According to an Internet-based survey in Japan, the prevalence of NeP was estimated to be 6.4% among the general population.⁶ NeP is common among patients with chronic pain associated with spine diseases, with a reported prevalence as high as 53.3%.⁵ Involvement of NeP further increases the burden of chronic pain in patients, including pain intensity,^{7–9} quality of life (QOL),^{8–11} and sleep interference,^{9,10} and interference with daily activities,¹⁰ when compared to chronic pain without an NeP component. Considering the indirect effect of pain on QOL (T Taguchi, personal unpublished data),^{12,13} pain relief with pharmacological treatment is a cornerstone for NeP management to reduce the multifaceted burdens.¹⁴

Pregabalin, a ligand of $\alpha 2\text{-}\delta$ subunits of voltage-gated calcium channels,¹⁵ reduces plasma membrane expression of calcium channels and calcium influx as well as inhibits the release of neurotransmitters, such as glutamate.^{16,17} Activation of descending noradrenergic and serotonergic pathways also contributes to the analgesic effects of pregabalin.^{18,19} Pregabalin was approved for NeP and pain associated with fibromyalgia in Japan²⁰ and has also been recommended as one of the first-line pharmacological treatments for NeP¹⁴ in some other countries.^{21,22} Several randomized controlled trials (RCTs) have shown that pregabalin reduces pain intensity and improves sleep, health status, or other patient-reported outcomes (PROs) in patients with various types of NeP.^{23–29} Recently, however, some RCTs demonstrated that pregabalin was not more effective than placebo in reducing pain and other relevant PROs in patients with sciatica,³⁰ lumbosacral radiculopathy,³¹ and lumbar spinal stenosis with neurogenic claudication,³² partially because of the high placebo response and possible involvement of the nociceptive component of pain, or unlikely or little involvement of NeP component of the target conditions of these studies.

To evaluate the effectiveness of pregabalin in chronic NeP from spine diseases, reflecting pain management in Japanese routine clinical practice, we previously conducted non-interventional studies in patients with chronic low back pain (CLBP) with accompanying lower limb pain below the knee (NeP component) (CLBP with NeP component, hereinafter)³³ or chronic cervical pain

accompanying upper limb radiating pain (NeP component) (chronic cervical pain with NeP component, hereinafter).³⁴ In both studies, pain and pain-related sleep interference, function, and health status significantly improved in patients treated with pregabalin (alone or in combination with other analgesics) than in those with usual care, using conventional analgesics.^{33,34} Generally, pregabalin was well tolerated in both studies.^{33,34} These results provided clinically important information on the effectiveness and benefits of treatment using pregabalin in routine clinical practice.

At the same time, our previous observational studies revealed that $\geq 90\%$ of the patients were treated with non-steroidal anti-inflammatory drugs (NSAIDs), and not treated with the first-line NeP treatments, that is, pregabalin, duloxetine, and tricyclic antidepressive agents,¹⁴ despite the involvement of the neuropathic component in the “real-world” setting.^{33,34} Evidence in an entire population of patients encompassing different diagnoses of spine diseases may help to guide better treatment strategies. However, to date, most of the observational studies have targeted patients with specific diagnoses (eg, cervical, lumbar, or lumbosacral radiculopathy),^{35–37} or pain location (back or low back),^{38,39} no study has investigated the practical effectiveness of pregabalin in an entire population of patients with spine diseases, including various pathophysiological conditions, a common NeP population encountered in daily clinical practice.

Therefore, this study aimed to obtain a comprehensive picture of therapeutic values of pregabalin for chronic pain with NeP component in patients with spine diseases from the patient’s perspective. In this analysis, using the pooled dataset of our previous studies in patients with CLBP with NeP component³³ and chronic cervical pain with NeP component³⁴ in routine primary care settings in Japan, we evaluated the effectiveness of pregabalin on PRO measures. Moreover, we conducted sub-group analyses to further explore patient profiles associated with treatment response.

Patients and Methods

Study Overview

This was a retrospective, pooled analysis of two prospective observational cohort studies conducted in Japan, with similar study design and methods, with one major difference in target pain site: the low back (Study A0081333, referred to as Study 1333,

Table 1 Summary of the Studies Included in the Pooled Analysis

Study Number/ ClinicalTrials.gov Identifier	Target Condition	Treatment Duration	Eligibility Criteria	Evaluation	Number of Patients	
					Pregabalin	Usual Care
Study 1333 (A0081333)/ NCT02273908	CLBP with accompanying lower limb pain (NeP component)	8 weeks	Inclusion: 1. Age: at least 18 years 2. CLBP with accompanying lower limb pain below the knee, refractory to prior analgesics for at least 3 months 3. Pain intensity of ≥ 5 on the NRS ^a Exclusion: 1. Pregabalin treatment within the past 2 weeks	NRS PRSIS EQ-5D-5L RMDQ PGIC CGIC WPAI	157	174
Study 1354 (A0081354)/ NCT02868359	Chronic cervical pain with accompanying upper limb radiating pain (NeP component)	8 weeks	Inclusion: 1. Age: at least 20 years 2. Chronic cervical pain with accompanying radiating pain to superior limbs with an NeP component, refractory to prior analgesics for at least 12 weeks 3. Pain intensity of ≥ 5 on NRS ^a 4. Sleep disturbance of ≥ 1 at baseline on PRSIS ^b Exclusion: 1. Pregabalin treatment within the past 12 weeks or regular nerve block treatment	NRS PRSIS EQ-5D-5L NDI PGIC CGIC WPAI	145	224

Notes: ^aPain was required to be refractory to previous analgesics and self-rated as ≥ 5 on an 11-point NRS (0–3=mild pain; 4–6=moderate pain; and 7–10=severe pain), based on recall over the past week. ^bPatients must have reported sleep disturbance of a ≥ 1 score on the PRSIS at baseline based on recall over the past week on an NRS ranging from 0 (did not interfere with sleep) to 10 (completely interferes with sleep).

Abbreviations: CGIC, Clinical Global Impressions of Change; CLBP, chronic low back pain; EQ-5D-5L, EuroQol 5-dimension 5-level; NDI, Neck Disability Index; NeP, neuropathic pain; NRS, numerical rating scale; PGIC, Patient Global Impression of Change; PRSIS, Pain-Related Sleep Interference Scale; RMDQ, Roland Morris Disability Questionnaire; WPAI, Work Productivity and Activity Impairment.

hereinafter)³³ and cervical region (Study A0081354, referred to as Study 1354, hereinafter)³⁴ (Table 1).

Individual studies included in this analysis were registered with clinicaltrials.gov (Study 1333: NCT02273908; Study 1354: NCT02868359), approved by the Byoin-Godo Ethical Review Board, and conducted in accordance with the Declaration of Helsinki. All patients included in both studies provided written informed consent.

Study Design

Detailed methods have been published previously.^{33,34}

Individual studies were 8-week, multicenter, prospective, observational studies that evaluated the effectiveness of pregabalin for the treatment of CLBP with NeP component (Study

1333)³³ or chronic cervical pain with NeP component (Study 1354)³⁴ in primary care settings under routine clinical practice (Table 1). Study 1333 was conducted in 2014, while Study 1354 was conducted between October 2016 and October 2017.

The inclusion and exclusion criteria for individual studies were generally similar (Table 1). Briefly, Study 1333 included patients aged ≥ 18 years who had CLBP with accompanying lower limb pain below the knee, and with pain that was refractory to prior analgesics for at least 3 months with an intensity rating of ≥ 5 on a numerical rating scale (NRS). Study 1354 included patients aged ≥ 20 years who had chronic cervical pain with accompanying radiating pain to the upper limbs with an NeP component, with pain that was refractory to previous analgesics for at least

12 weeks, and had an intensity of ≥ 5 on the NRS. In study 1354, patients were also required to have sleep interference by pain, rated ≥ 1 on Pain-Related Sleep Interference Scale (PRSIS), a detailed description of which is provided in the section below.

To reduce selection bias, both studies consecutively enrolled all patients who met the eligibility criteria during the enrollment period of individual studies at each site. Study sites were screened and selected based only on feasibility from the medical institutions that had contracted with a site management organization and had accepted support by clinical research coordinators across Japan.

For both studies, enrolled patients were treated for 8 weeks with pregabalin (alone or in combination with other analgesics) or usual care with conventional analgesics, such as paracetamol (acetaminophen), NSAIDs, antidepressants, other antiepileptic agents, and opioids. Selection of these treatments and their dose was solely rested on the physician's best clinical judgment based on the package insert in the original studies to investigate the effectiveness of treatment with pregabalin under the settings reflecting the Japanese routine clinical practice. For the same reason, treatment compliance was not assessed in the original studies and the participants were not included or excluded based on a particular dose or compliance level.

Outcome Measures

In both studies, effectiveness was evaluated by PRO measures, including NRS, PRSIS, and EuroQol 5-dimension 5-level (EQ-5D-5L), administered at baseline, week 4, and week 8 (or at discontinuation). These three measures were included in the present analysis as PRO measures of treatment effectiveness.

NRS, an 11-point pain rating scale (ranging from 0 to 10), was used to evaluate average pain intensity over the past week. An NRS score of 0–3 was considered mild, 4–6 as moderate, and 7–10 as severe pain.³⁴ PRSIS, a patient-completed measure, is used to evaluate the extent to which pain interferes with a patient's sleep over the past week on an NRS (ranging from 0 [did not interfere with sleep] to 10 [completely interfered with sleep]). It is derived from the Pain Interference with Sleep item of the Brief Pain Inventory – Short Form.⁴⁰ EQ-5D-5L, a standardized, self-administered questionnaire, consists of five-dimension descriptive system (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and visual analog scale. Each dimension has five levels of severity (ie, no

problems, slight problems, moderate problems, severe problems, and extreme problems).⁴¹ The severity level against each dimension is combined to calculate a single utility index value. The index score for the Japanese population ranged from -0.025 to 1.00 (1 denotes “perfect health” and 0 “death”).⁴² For this analysis, only the data from the EQ-5D-5L index score were used to assess health status.

Moreover, at baseline, all enrolled patients underwent the self-reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)⁴³ after a physical examination; however, it was later not used for diagnosis.

Safety was evaluated by reports of adverse events (AEs). AEs were considered treatment-related when there was a reasonable possibility of a causal relationship between the treatment and AE. Any AEs in patients administered with pregabalin of any dose that met the following conditions were considered serious: resulted in death; life-threatening; required inpatient hospitalization or prolongation of hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to perform normal life functions); or resulted in congenital anomaly/birth defect.

Statistical Analyses

A dataset of patients with chronic pain with an NeP component from spine diseases was created by pooling data from individual studies (Study 1333 and Study 1354) and were grouped according to the treatment received (pregabalin or usual care group). All patients who received at least one dose of pregabalin or usual care were included in the dataset, and baseline characteristics were summarized for these patients.

Analysis of PROs was conducted on the full analysis set (FAS), which comprised all pooled patients who received at least one dose of pregabalin or usual care and had at least one post-baseline evaluable PRO assessment. Changes in PRO scores from baseline at weeks 4 and 8 were summarized and compared between pregabalin and usual care groups, using the mixed effect model for repeated measurements, including fixed categorical effects of treatment, visit, and treatment-by-visit interaction as well as a fixed continuous effect of baseline value. A shift in the pain intensity level, based on the NRS score, from baseline to week 8 was described in patients with NRS data at week 8 available. The proportion of patients reporting pain intensity level as mild, moderate, or severe, based on the NRS score at week 8, was summarized by baseline pain intensity level (moderate or severe) for each treatment group. PRO score changes

were also summarized for subgroups of patients stratified by primary diagnosis.

To explore patient profiles associated with treatment response, treatment response state was summarized for subgroups of patients stratified by whether their main pain was perceived as radiating, and by pain duration. Treatment responder was defined by an NRS reduction of $\geq 30\%$. Patients' perception of whether their main pain was radiating or not was defined, according to areas on the S-LANSS body maps the patients marked ([Supplementary Figure 1](#)). Patients in Study 1333 were considered to perceive their main pain radiating if they marked on ipsilateral adjacent areas of the lower half of the body; those in Study 1354 were considered as such when they marked the ipsilateral adjacent areas of the upper half of the body. Patients who did not perceive their main pain radiating had other patterns, including marks on a single area, multiple distant areas, and bilateral or contralateral areas, for both studies. We assessed the association between perception of radiating main pain and treatment responder state by using logistic regression analysis, adjusted for sex, age, and NRS at baseline, and calculated adjusted odds ratio (OR) of the responder state and its 95% confidence interval (CI). The logistic regression analysis included patients with NRS data available at week 8.

For safety analysis, AEs reported were summarized in the safety analysis set. The safety analysis set included all patients who received at least one dose of pregabalin.

$P < 0.05$ was considered statistically significant for the overall population. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

In this study, pooled data comprised of 331 patients from Study 1333 and 369 patients from Study 1354. In total, 700 patients were treated with pregabalin (pregabalin group, $n = 302$) or usual care (usual care group, $n = 398$). Of these, excluding 24 and 9 patients without post-baseline evaluable PRO assessment data from the pregabalin and usual care groups, respectively, 667 patients (pregabalin group, $n = 278$ and usual care group, $n = 389$) were included in the FAS. All 302 patients in the pregabalin group were included in the safety analysis set.

Baseline characteristics of the pooled patients are provided by the treatment group in [Table 2](#). In the pregabalin group, male and female proportions were almost similar

(female: 53.0%), whereas in the usual care group, females accounted for a larger proportion (65.8%). Mean (standard deviation [SD]) age was slightly higher in the usual care group than in the pregabalin group (68.3 [14.4] years vs 63.9 [15.9] years). The distribution pattern of primary diagnosis was mostly similar between both treatment groups, and the most common diagnosis was cervical spondylotic radiculopathy (28.1% for pregabalin and 27.9% for usual care). Mean pain duration was slightly shorter in the pregabalin group than in the usual care group (50.4 months vs 56.7 months). At baseline, most of the patients in both treatment groups had received NSAIDs (95.0% for pregabalin and 92.0% for usual care). At baseline, the mean (SD) NRS and PRSIS were higher in the pregabalin group than in the usual care group (NRS: 6.2 [1.2] vs 5.8 [1.1]; PRSIS: 3.2 [2.5] vs 2.8 [2.2]), while the mean (SD) EQ-5D-5L scores were comparable between both treatment groups (pregabalin: 56.9 [18.1]; usual care: 57.0 [15.6]). During the study period, the median (min–max) pregabalin dose administered per patient was 50 mg/day (25–300 mg/day).

Effectiveness Based on PRO Measures

Least squares (LS) mean change (95% CI) in NRS scores continued to decrease from baseline through week 8 in both treatment groups (pregabalin: -1.50 [95% CI: -1.71 , -1.29] at week 4 and -2.21 [95% CI: -2.44 , -1.98] at week 8; usual care: -0.77 [95% CI: -0.94 , -0.60] at week 4 and -1.15 [95% CI: -1.34 , -0.96] at week 8) ([Figure 1A](#)). The improvement was significantly greater in the pregabalin group than in the usual care group (between-treatment difference in LS mean from baseline) both at week 4 (-0.73 [95% CI: -1.00 , -0.46]; $P < 0.0001$) and at week 8 (-1.06 [95% CI: -1.36 , -0.76]; $P < 0.0001$).

[Figure 2](#) summarizes the shift in the pain intensity level from baseline to week 8. The proportion of patients who continued to have the same pain intensity level from baseline at week 8 was smaller in the pregabalin group than in the usual care group (moderate pain: 49.7% vs 69.3% ([Figure 2A](#)); severe pain: 21.3% vs 42.5% ([Figure 2B](#))). Correspondingly, the proportion of patients who had a shift in the pain intensity level towards lower severity was higher in the pregabalin group than in the usual care group (shift from moderate to mild: 44.7% [72/161 patients] vs 23.0% [63/274 patients]; shift from severe to moderate or mild: 78.7% [59/75 patients] vs 57.5% [46/80 patients]).

Table 2 Baseline Characteristics of Studies Included in the Pooled Analysis

Characteristics	Total (n = 700)	Pregabalin (n = 302)	Usual Care (n = 398)
Gender, n (%)			
Female	422 (60.3)	160 (53.0)	262 (65.8)
Age (years)			
Mean (SD)	66.4 (15.2)	63.9 (15.9)	68.3 (14.4)
Median (min, max)	71 (20, 93)	67 (20, 92)	72 (20, 93)
Age group (years), n (%)			
< 65	265 (37.9)	138 (45.7)	127 (31.9)
65–74	170 (24.3)	69 (22.8)	101 (25.4)
≥ 75	265 (37.9)	95 (31.5)	170 (42.7)
Duration of pain (months)			
Mean (SD)	54.0 (73.5)	50.4 (67.2)	56.7 (77.9)
Median (min, max)	25 (2, 588)	22 (2, 480)	28 (3, 588)
Any medical condition and comorbidities ^a , n (%)			
Yes	20 (2.9)	3 (1.0)	17 (4.3)
No	680 (97.1)	299 (99.0)	381 (95.7)
Complications, n (%)			
Yes	670 (95.7)	299 (99.0)	371 (93.2)
No	30 (4.3)	3 (1.0)	27 (6.8)
Surgical history, n (%)			
Yes	23 (3.3)	9 (3.0)	14 (3.5)
No	677 (96.7)	293 (97.0)	384 (96.5)
Pain medication use, n (%)			
NSAIDs	653 (93.3)	287 (95.0)	366 (92.0)
Antidepressants	20 (2.9)	11 (3.6)	9 (2.3)
Antiepileptics	1 (0.1)	1 (0.3)	0
Weak opioids	51 (7.3)	21 (7.0)	30 (7.5)
Potent opioids	2 (0.3)	1 (0.3)	1 (0.3)
Other	209 (29.9)	102 (33.8)	107 (26.9)
Primary diagnosis, n (%)			
Cervical spondylotic radiculopathy	196 (28.0)	85 (28.1)	111 (27.9)
Others (cervical pain)	117 (16.7)	38 (12.6)	79 (19.8)
Lumbar spinal stenosis	113 (16.1)	49 (16.2)	64 (16.1)
Osteoarthritis of lumbar spine	108 (15.4)	54 (17.9)	54 (13.6)
Others (low back pain)	57 (8.1)	27 (8.9)	30 (7.5)
Cervical disk herniation	41 (5.9)	14 (4.6)	27 (6.8)
Lumbar disc herniation	39 (5.6)	22 (7.3)	17 (4.3)
Cervical spondylotic myelopathy	14 (2.0)	7 (2.3)	7 (1.8)
Spondylolysis and spondylolisthesis	10 (1.4)	2 (0.7)	8 (2.0)
Compression fracture due to osteoporosis	4 (0.6)	3 (1.0)	1 (0.3)
Cervical spondylosis	1 (0.1)	1 (0.3)	0
S-LANSS			
Mean (SD)	11.4 (5.9)	10.7 (6.1)	11.9 (5.7)
Median (min, max)	13 (0, 24)	11 (0, 24)	13 (0, 24)
NRS			
Mean (SD)	6.0 (1.2)	6.2 (1.2)	5.8 (1.1)
Median (min, max)	6 (5, 10)	6 (5, 10)	5 (5, 10)

(Continued)

Table 2 (Continued).

Characteristics	Total (n = 700)	Pregabalin (n = 302)	Usual Care (n = 398)
PR SIS			
Mean (SD)	3.0 (2.4)	3.2 (2.5)	2.8 (2.2)
Median (min, max)	2 (0, 10)	3 (0, 10)	2 (0, 10)
EQ-5D-5L score			
Mean (SD)	57.0 (16.7)	56.9 (18.1)	57.0 (15.6)
Median (min, max)	55 (0, 100)	55 (0, 99)	55 (10, 100)

Note: ^aHistory of any medical condition and all the comorbidities at baseline, reported based on the patient's medical chart.

Abbreviations: EQ-5D-5L, EuroQol 5-dimension 5-level; max, maximum; min, minimum; NRS, numerical rating scale; NSAID, non-steroidal anti-inflammatory drug; PRSIS, Pain-Related Sleep Interference Scale; SD, standard deviation; S-LANSS, self-reported Leeds Assessment of Neuropathic Symptoms and Signs.

LS mean change (95% CI) in PRSIS scores from baseline decreased at both week 4 and week 8 in the pregabalin group, while there was not much change observed in the usual care group during the same time period (pregabalin: -0.83 [95% CI: -1.07 , -0.60] at week 4 and -1.23 [95% CI: -1.46 , -0.99] at week 8; usual care: -0.14 [95% CI: -0.33 , 0.06] at week 4 and -0.32 [95% CI: -0.52 , -0.13] at week 8) (Figure 1B). Significantly greater improvement in PRSIS scores was

observed in the pregabalin group than in the usual care group (LS mean treatment difference: -0.69 [95% CI: -1.00 , -0.39 ; $P < 0.0001$] at week 4 and -0.90 [95% CI: -1.21 , -0.60 ; $P < 0.0001$] at week 8).

LS mean change (95% CI) in EQ-5D-5L scores continued to improve from baseline through week 8 in both treatment groups (pregabalin: 0.06 [95% CI: 0.05 , 0.08] at week 4 and 0.08 [95% CI: 0.07 , 0.09] at week 8; usual care: 0.02 [95% CI: 0.01 , 0.03] at week 4 and

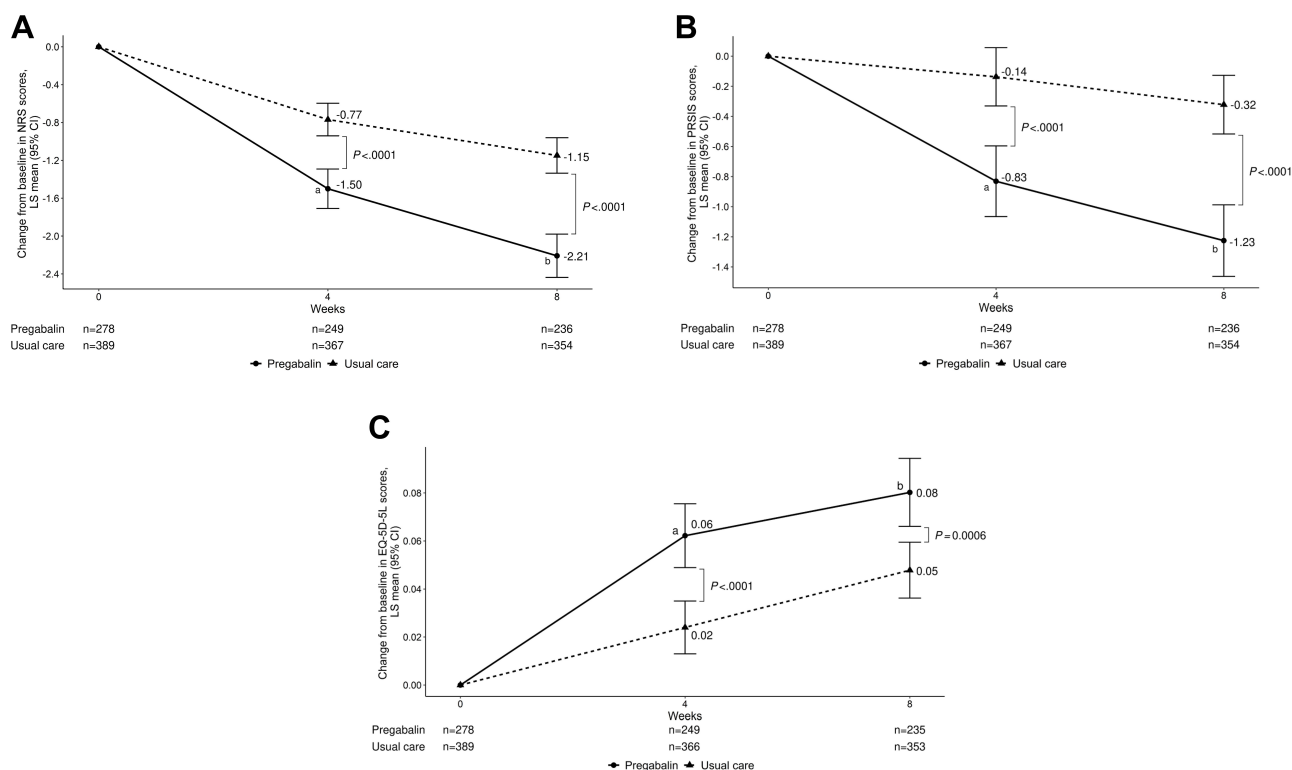


Figure 1 Least-squares mean change in NRS scores (A), PRSIS scores (B), and EQ-5D-5L scores (C) from baseline at week 4 and week 8.

Notes: Data from the FAS are presented. LS mean (95% CI) treatment difference (pregabalin vs usual care) in (A) ^aWeek 4: -0.73 (-1.00 , -0.46); ^bWeek 8: -1.06 (-1.36 , -0.76), (B) ^aWeek 4: -0.69 (-1.00 , -0.39); ^bWeek 8: -0.90 (-1.21 , -0.60), (C) ^aWeek 4: 0.04 (0.02 , 0.06); ^bWeek 8: 0.03 (0.01 , 0.05).

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension 5-level; FAS, full analysis set; LS, least-squares; NRS, numerical rating scale; PRSIS, Pain-Related Sleep Interference Scale.

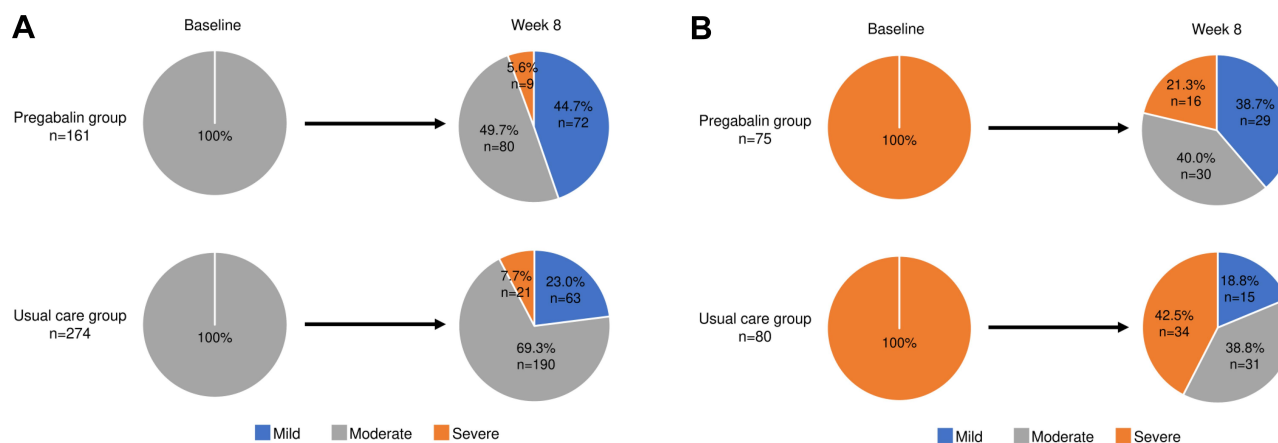


Figure 2 Shift in the pain intensity level from baseline to week 8 by intensity level at baseline (A) moderate and (B) severe.

Note: Pain intensity level was based on NRS: mild (0–3), moderate (4–6), and severe (7–10). Patients included were those with available NRS data at Week 8.

Abbreviation: NRS, numerical rating scale.

0.05 [95% CI: 0.04, 0.06] at week 8) (Figure 1C). However, the improvement was significantly greater in the pregabalin group than in the usual care group (LS mean treatment difference: 0.04 [95% CI: 0.02, 0.06; $P < 0.0001$] at week 4 and 0.03 [95% CI: 0.01, 0.05; $P = 0.0006$] at week 8).

Subgroup Analysis by Primary Diagnosis

Stratification by primary diagnosis yielded a small number of patients for each diagnosis subgroup (Figure 3A–C). Although the change in NRS (Figure 3A), PRSIS (Figure 3B), and EQ-5D-5L scores (Figure 3C) from baseline at week 8 varied by each diagnosis, the overall trend was greater improvement across all three PRO measures in the pregabalin group compared with the usual care group, irrespective of the primary diagnosis. Changes in PRO scores from baseline at week 8 favoring usual care over pregabalin tended to be seen in very small diagnosis subgroups.

Responder Analysis

Slightly over half of the patients in the pregabalin group achieved “responder” status for pain relief (ie, $\geq 30\%$ reduction in NRS), irrespective of whether or not the patients perceived their main pain radiating (55.5% vs 55.9% (Table 3); OR: 0.976 [95% CI: 0.59, 1.61]). In the usual care group, the proportion of patients who achieved “responder” status tended to be slightly lower in those who perceived their main pain radiating than those who did not (26.0% vs 34.8%; OR: 0.653 [95% CI: 0.42, 1.03]).

In the pregabalin group, more than 50% of patients achieved “responder” status for pain relief, irrespective of pain duration (Table 3). In the usual care group, a majority of patients were “non-responders”, irrespective of pain duration. No linear increase or decrease in the trend was observed for responder rate by pain duration in either treatment group.

Safety

In the safety analysis set patients (pregabalin group), 36.1% reported AEs (Table 4). AEs reported in 20.9% of the patients were considered treatment-related and none was serious. Treatment-related AEs led to discontinuation in 7.0% of the patients. The most common treatment-related AEs in the pregabalin group were dizziness (10.3%) and somnolence (8.9%). Other treatment-related AEs were reported in less than 1% of patients in the pregabalin group.

Discussion

In this pooled analysis, we aimed to obtain a comprehensive picture of therapeutic values of pregabalin for chronic pain with NeP component in patients with spine diseases. All the PROs, pain intensity, pain-related sleep interference, and health status significantly improved from baseline through week 8 in the pregabalin group (alone or in combination with other analgesics), compared with the usual care group. Multi-dimensional effectiveness of treatment using pregabalin, previously separately demonstrated in the original observational studies,^{33,34} was shown to be evident in the entire population of patients with chronic pain with NeP

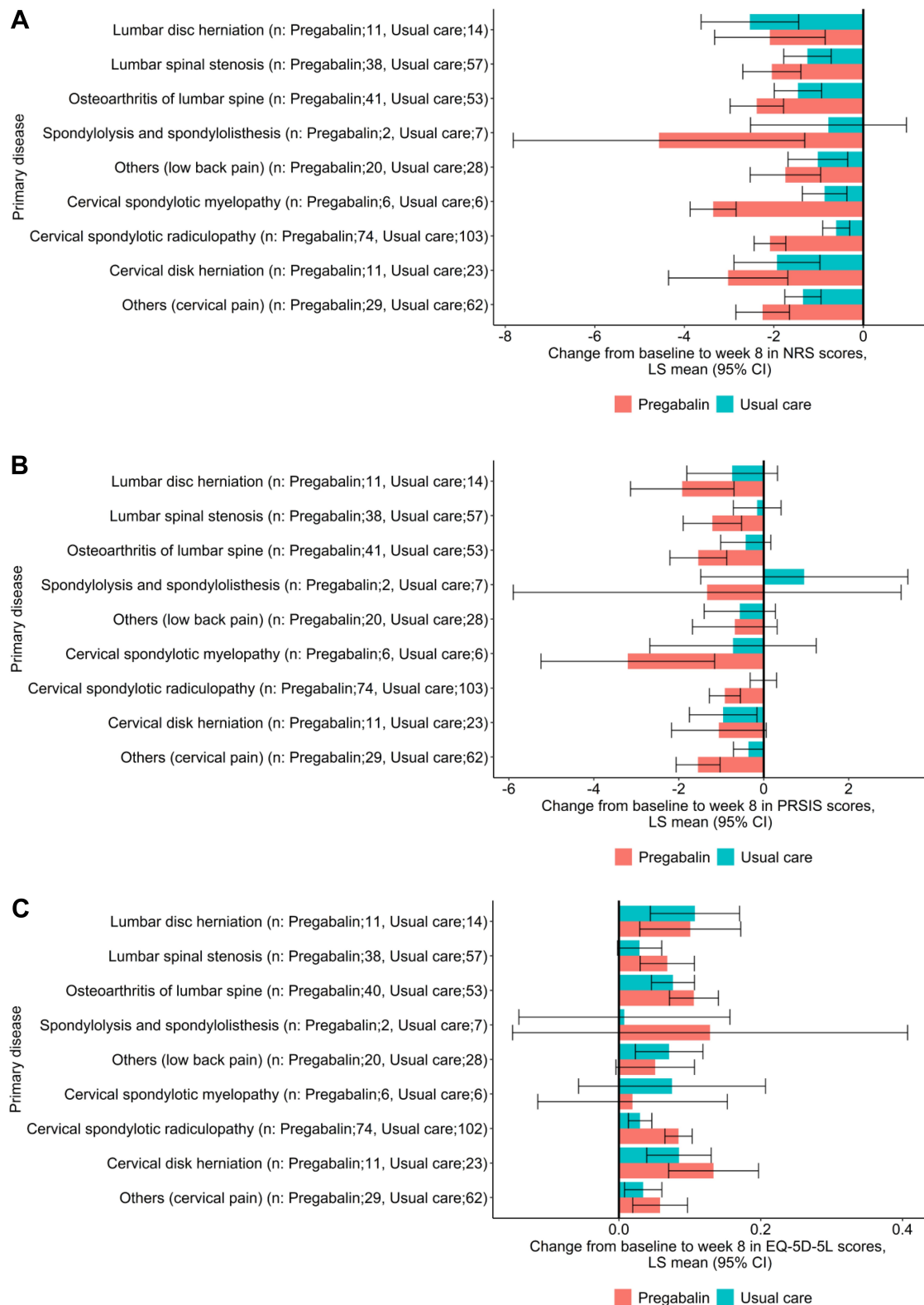


Figure 3 Change in NRS scores (A), PRSIS scores (B), and EQ-5D-5L scores (C) from baseline by primary diagnosis at week 8.

Notes: Data from the FAS are presented. The number of patients diagnosed with compression fracture due to osteoporosis or cervical spondylolysis was too small to estimate the treatment effects in the model, and thus these subgroups were not included in this analysis.

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension 5-level; FAS, full analysis set; LS, least-squares; NRS, numerical rating scale; PRSIS, Pain-Related Sleep Interference Scale.

Table 3 Responder Analysis ($\geq 30\%$ Reduction in NRS) by Patient Characteristics

	Pregabalin		Usual Care	
	Non-Responder	Responder	Non-Responder	Responder
	n (%)	n (%)	n (%)	n (%)
Main pain indicated perceived radiating pain over at least two parts^a				
No	56 (44.1)	71 (55.9)	120 (65.2)	64 (34.8)
Yes	61 (44.5)	76 (55.5)	145 (74.0)	51 (26.0)
Duration of pain				
3 months ^b to 1 year	50 (47.2)	56 (52.8)	94 (74.0)	33 (26.0)
1–2 years	15 (48.4)	16 (51.6)	34 (66.7)	17 (33.3)
2–3 years	9 (45.0)	11 (55.0)	26 (68.4)	12 (31.6)
3–4 years	7 (46.7)	8 (53.3)	15 (51.7)	14 (48.3)
4–5 years	6 (37.5)	10 (62.5)	12 (70.6)	5 (29.4)
5–6 years	4 (33.3)	8 (66.7)	12 (66.7)	6 (33.3)
6–7 years	3 (37.5)	5 (62.5)	12 (60.0)	8 (40.0)
7–8 years	3 (42.9)	4 (57.1)	7 (70.0)	3 (30.0)
8–9 years	1 (12.5)	7 (87.5)	8 (88.9)	1 (11.1)
9–10 years	4 (36.4)	7 (63.6)	11 (73.3)	4 (26.7)
>10 years	15 (50.0)	15 (50.0)	34 (73.9)	12 (26.1)

Notes: ^aPatients' perception of whether their main pain was radiating or not was defined, according to areas on the S-LANSS body maps the patients marked (Supplementary Figure 1). Patients in Study 1333 (patients with CLBP with accompanying lower limb pain below the knee [NeP component]) were considered to perceive their main pain radiating if they marked on ipsilateral adjacent areas of the lower half of the body; those in Study 1354 (patients with chronic cervical pain and accompanying upper limb radiating pain [NeP component]) were considered as such when they marked the ipsilateral adjacent areas of the upper half of the body. Patients who did not perceive their main pain radiating had other patterns, including marks on a single area, multiple distant areas, and bilateral or contralateral areas, for both studies. ^bInclusion criteria stipulated that pain duration be at least 3 months in Study 1333 and at least 12 weeks in Study 1354. Data from the FAS are presented.

Abbreviations: CLBP, chronic low back pain; FAS, full analysis set; NeP, neuropathic pain; NRS, numerical rating scale; S-LANSS, self-reported Leeds Assessment of Neuropathic Symptoms and Signs.

Table 4 Adverse Events Reported in the Pregabalin Group in the Pooled Analysis (n = 302)

All Causality Adverse Events	n	(%)
Number of events	181	(59.9)
Number of patients	109	(36.1)
Serious events	2	(0.7)
Discontinuation due to events	23	(7.6)
Dose reduction or temporary discontinuation due to the events	30	(9.9)
Treatment-Related Adverse Events	n	(%)
Number of events	82	(27.2)
Number of patients	63	(20.9)
Serious events	0	
Discontinuation due to events	21	(7.0)
Dose reduction or temporary discontinuation due to the events	28	(9.3)
Common events ^a		
Dizziness	31	(10.3)
Somnolence	27	(8.9)

Notes: ^aAdverse events reported by $>1\%$ of patients in the pregabalin group. Data from the safety analysis set are presented.

component from spine diseases in routine primary care settings.

The goal of NeP treatment is not only to reduce pain, but also to improve daily living and QOL, rather than to eliminate the pain since a cure for the condition has not yet been established.¹⁴ When interpreted in reference to the minimal important difference (MID) and clinically meaningful improvement previously reported,^{44–48} the degree of improvement in all PRO measures in the present analysis suggests that patients may have achieved not only statistically significant but also clinically meaningful improvement in pain and various aspects of their lives after 8 weeks of pregabalin treatment. NRS scores improved at week 8 by -2.21 in the pregabalin group and by -1.15 in the usual care group. The pregabalin group exceeded 2.0, reported as the clinically important difference associated with much improvement or greater on Patient Global Impression of Change (PGIC) in patients with chronic pain⁴⁴ and as the value associated with much better improvement in chronic musculoskeletal pain,⁴⁵ and was also determined as a key

threshold score, associated with improvement or much improvement on PGIC, in treatment for Japanese patients with CLBP.⁴⁶ Similarly, improvement in PRSIS by -1.23 and EQ-5D-5L scores by 0.08 at week 8 in the pregabalin group exceeded the MID of $1-2$ ⁴⁷ and 0.061 ,⁴⁸ respectively, but not in the usual care group (PRSIS and EQ-5D-5L score improvement from baseline: -0.32 and 0.05 , respectively). It should be noted that the MID for PRSIS referred to Daily Sleep Interference Scale, similar to PRSIS with an 11-point NRS of sleep interference by pain, except for a recall period of the past 24 h.⁴⁷ Even though the data were not utilized in the present pooled analysis, the original studies^{33,34} reported functional improvement measured by the Roland-Morris Disability Questionnaire and Neck Disability Index both exceeded the MID (3.5 ⁴⁹ and 8.5 ,⁵⁰ respectively). The present and original study results suggest the effectiveness of pregabalin treatment not only for pain relief but also for improvement in various aspects, including pain-related sleep interference, function, and QOL. Furthermore, the pathway by which pain, pain-related sleep interference, and function influence QOL was clarified in another study using data from the pregabalin group patients from the same original studies.^{33,34} It was demonstrated that the impact of pain reduction on QOL improvement achieved after treatment with pregabalin consisted of direct and indirect effects, but with greater contribution of indirect impact via functional improvement (Unpublished data, Taguchi et al 2020). Therefore, treatment with pregabalin may play an important role, not only from the perspective of pain relief but also QOL, to achieve a treatment goal of NeP to reduce the multifaceted burdens of patients beyond pain itself.

Focusing on pain relief, one of the essentials of NeP treatment, pain was alleviated to a lower level for more patients in the pregabalin group than in the usual care group, regardless of whether it was moderate or severe at baseline. This trend is consistent with observations from pooled analysis of RCTs in Japanese patients with postherpetic neuralgia, diabetic neuropathy, and spinal cord injury.⁵¹ Improvement in persistent pain that had not been relieved with other analgesics for at least 3 months after 8-week treatment with pregabalin, without unknown or any major safety concerns may be promising for patients.

Greater improvement in all the PRO measures in pregabalin than in the usual care group was also generally demonstrated across different primary diagnoses by subgroup analysis (Figure 3). Minor variations in the trend in some subgroups may largely be attributed to the small

number of patients included in the subgroup. In addition, considering the greater burden associated with chronic NeP than those without an NeP component,⁷⁻¹¹ the degree of involvement of NeP may also contribute to the variations. When comparing the results of the original studies, more patients with CLBP with an NeP component responded to usual care³³ than those with chronic cervical pain with an NeP component.³⁴ It was suggested that more patients in Study 1333 had CLBP of greater involvement of nociceptive and less of NeP, while more patients in Study 1354 had cervical pain with greater involvement of NeP and less nociceptive pain. Therefore, the degree of burden and responses to treatment may be different, relative to chronic cervical pain.

To explore who can benefit from treatment with pregabalin, we further conducted a responder analysis by stratifying patients according to their perceptions of whether the main pain was radiating or not, and their pain duration (Table 3). Based on the trend described, it is inferred that more than half of the patients may be able to equally benefit from treatment using pregabalin, regardless of whether their main pain was radiating or not, or regardless of how many years they had been suffering from the pain. In contrast, the majority of patients in all the subgroups did not seem to respond to usual care; even in patients who considered that their main pain was not radiating, only 34.8% of patients achieved $\geq 30\%$ pain relief. Considering varying etiologies of NeP and characteristics of each patient, the finding that practical effectiveness of pregabalin across diverse diagnoses of spine diseases, pain, and patient characteristics may provide useful information for the use of pregabalin, one of the first-line treatment for NeP, in daily clinical practice.

Based on the accumulated evidence in various conditions associated with an NeP component, such as postherpetic neuralgia,²³⁻²⁶ diabetic neuropathy,^{27,28,52,53} spinal cord injury,²⁹ and painful lumbar or cervical radiculopathy,³⁵⁻³⁷ pregabalin is recommended as one of the first-line treatments for NeP.^{14,21,22} However, in some RCTs in patients with NeP associated with spine diseases, the efficacy of pregabalin was not shown to be greater than that obtained in the placebo group,³⁰⁻³² partially due to a high placebo response. For example, the RCT in patients with acute or chronic sciatica, reported pain intensity was reduced by about 50% from baseline to week 8 in both the pregabalin and placebo groups, and nearly two-thirds of both groups were satisfied with their treatments.³⁰ Their study population comprised mostly of acute cases (pain <

3 months in 80.2%).³⁰ Considering that the sciatica pain resolves early (2 weeks in 36% and 12 weeks in 73%) without surgery,⁵⁴ these improvements in both groups may have reflected spontaneous recovery. Moreover, in an RCT in patients with chronic lumbosacral radiculopathy,³¹ pain relief during the single-blinded pregabalin treatment phase may have been carried over to the following double-blind treatment phase, leading to a lack of separation of treatment effect by pregabalin from those by placebo. Furthermore, the possible involvement of the nociceptive component of the target conditions (sciatica,³⁰ lumbosacral radiculopathy,³¹ and lumbar spinal stenosis³²) may have affected the treatment response. For example, in an RCT in patients with sciatica, the baseline PainDETECT score suggested that most of the patients were likely to have had predominantly nociceptive pain or unlikely/uncertain neuropathic pain component.³⁰ Taken together, the possibility of pregabalin's effectiveness for chronic pain with an NeP component from spine diseases may not be completely excluded, and may require further consideration.

Adverse events reported were consistent with the known safety profile of pregabalin in the Japanese patient population.⁵⁵ However, prescriptions should be made based on careful consideration of overall benefits and risks. Less-than recommended dose of pregabalin administered during the study period (150–600 mg/day)^{33,34} suggests that physicians may have carefully adjusted the pregabalin dose according to each patient based on the renal function because the included study population was relatively old (mean age: 66.4 years), and most of them were concomitantly prescribed other analgesics, such as NSAIDs.

This study has some limitations. First, inclusion criteria of moderate to severe cases refractory to analgesics may limit the generalizability of the dataset. Nevertheless, pain resolves without the need for pharmacological intervention for some patients, while for others, it is not until NeP becomes chronic that treatment with pregabalin is successfully introduced. Second, the potential for bias in treatment selection because the decision rested on the physician's discretion, but at the same time, this approach reflects “real-world” treatment practice, which does not necessarily endorse balanced treatment strategies. Third, this study may not conclude the effectiveness solely attributed to pregabalin, since other analgesics were permitted to be used in combination with pregabalin. In Studies 1333³³ and 1354,³⁴ most of the patients received concomitant medications at baseline and during study periods (pregabalin group: at least 91% in Study 1333 and at least 72%

in Study 1354, respectively; usual care group: at least 99% in both studies), most of which were NSAIDs³⁴ (data of Study 1333 not shown). Lastly, whether the main pain was perceived radiating or not was identified when the marks of the worst pain site made by a patient were spreading to the adjacent areas. On the other hand, diagnosis of radiating pain by physicians may be different, as it usually follows a specific dermatome. There may remain a possibility that our definition underestimates patients who could not recognize their main pain radiating.

Conclusions

This pooled analysis suggests multi-faceted effectiveness of treatment with pregabalin, alone or in combination with other analgesics, from the patient's perspectives under a “real-world” practice in all patients with chronic NeP from spine diseases, a common but previously under-appreciated population. The trends observed across the subgroups may suggest that patients with various diagnoses and profiles (irrespective of whether the main pain was perceived as radiating, or how long the pain had persisted) possibly benefit from treatment with pregabalin. These findings suggest important therapeutic values of pregabalin as one of the first-line treatments for chronic pain with an NeP component in patients with spine diseases.

Abbreviations

AEs, adverse events; CI, confidence interval; CLBP, chronic low back pain; EQ-5D-5L, EuroQol 5-dimension 5-level; FAS, full analysis set; LS, least squares; MID, minimal important difference; NeP, neuropathic pain; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PGIC, Patient Global Impression of Change; PRO, patient-reported outcome; PRSIS, Pain-Related Sleep Interference Scale; QOL, quality of life; RCT, randomized controlled trial; SD, standard deviation; S LANS, self-reported Leeds Assessment of Neuropathic Symptoms and Signs.

Data Sharing Statement

Upon request, and subject to certain criteria, conditions and exceptions (see <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (ie,

development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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