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ORIGINAL RESEARCH ARTICLE

Pregabalin for Neuropathic Pain: Why Benefits Could Be Expected for Multiple Pain Conditions

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Abstract

Background and Objective Limited research exists to support the extrapolation of the analgesic efficacy of pregabalin from one neuropathic pain condition to another. This retrospective analysis evaluated similarities in the efficacy of pregabalin for treating neuropathic pain associated with post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (DPN), and spinal cord injury (SCI) in a Japanese population, as a basis for considering the extrapolation of these data to other neuropathic pain conditions.

Methods Data were analysed across pregabalin doses within each pain condition, from three comparable 13- to 16-week, randomized, double-blind, placebo-controlled trials (RCTs) and the corresponding 52-week, open-label extension trials of pregabalin in Japanese patients with PHN, DPN or SCI. Efficacy outcomes in the RCTs included endpoint and weekly mean pain and sleep interference scores; endpoint proportions of responders in pain; Patient Global Impression of Change scores; and 36-Item Short Form Health Survey (SF-36) scores or Hospital Anxiety and Depression Scale (HADS) assessments. Study discontinuation rates were compared between treatment groups. The extension trials assessed pain intensity, using the Short-Form McGill Pain Questionnaire.

Results In the RCTs for all pain conditions, significant improvements in comparison with placebo in mean pain and sleep interference scores were evident after 1 week with pregabalin and were sustained throughout the treatment periods ($p < 0.05$). At the study endpoint, in comparison with placebo, a significantly greater percentage of pregabalin-treated patients experienced a ≥30 % reduction in pain across the RCTs ($p < 0.05$), and pregabalin significantly improved six of 16 SF-36 subscale scores in the PHN and DPN trials ($p < 0.05$). In the SCI trial, pregabalin-treated patients had numerically better outcomes of HADS scores. In the extension trials, improvements in pain intensity were maintained over a 52-week period.

Conclusion Similarities in the pregabalin efficacy profiles, including time to onset and magnitude of response, were confirmed regardless of the neuropathic pain condition. These data support the potential for extrapolating analgesic efficacy to other neuropathic pain conditions.

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Key Points

Pregabalin was consistently efficacious in treating peripheral and central neuropathic pain (post-herpetic neuralgia, diabetic peripheral neuropathy and spinal cord injury) in Japanese patients.

The similarity in the observed efficacy profiles across these three indications supports the extrapolation of analgesic treatment efficacy to other neuropathic pain conditions.

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1 Introduction

Neuropathic pain results from a lesion or disease of the somatosensory nervous system and, depending on the origin, is either categorized as peripheral or central pain [1]. Among peripheral neuropathic pain conditions, post-herpetic neuralgia (PHN), a complication of herpes zoster (HZ), and diabetic peripheral neuropathy (DPN), a complication of type 1 and type 2 diabetes mellitus, are common. Central neuropathic pain can be associated with spinal cord injury (SCI). In Japan, 26.4 % of adults are estimated to have chronic pain, with 24.1 % of these adults estimated to have neuropathic pain (6.4 % of the whole population) [2]. On the basis of limited epidemiological evidence for each neuropathic pain condition in Japan, 10–15 % of HZ patients develop PHN [3], 20–40 % of diabetes patients develop DPN [4, 5] and 65 % of SCI patients experience central neuropathic pain [6].

Chronic neuropathic pain is considered a complex multidimensional condition, which is challenging to manage because of its associated comorbidities affecting many aspects of the patient's life, including sleep disturbance, depression, anxiety, disrupted daily routines, reduced social activities, absenteeism, presenteeism and low health-related quality of life (QoL) [7–10]. Because of the low health-related QoL reported by many patients with neuropathic pain, improvements in functioning and well-being are considered to be important therapeutic targets [11, 12]. Sleep disturbance is specifically recognized as an important dimension to assess and manage [13–16]. Patients with DPN, PHN or SCI are highly susceptible to pain-related sleep interference [17–21].

Pregabalin binds to the alpha-2-delta subunit of voltage-gated calcium channels in the central nervous system and is indicated for the management of neuropathic pain associated with painful DPN, PHN and SCI in the United States, and for the treatment of peripheral and central neuropathic pain in Europe and Japan [22–24]. Clinical trials have shown that pregabalin has positive effects on both pain and pain-related sleep interference in patients with DPN, PHN and SCI [25–27].

Although specific neuropathic pain conditions, notably PHN and DPN, have been frequently investigated for treatment efficacy, limited research exists to support the extrapolation of analgesic efficacy from one pain condition to another. The US Food and Drug Administration (FDA) recognizes the importance of understanding the types of evidence that would be required for the extrapolation of analgesic efficacy to pain conditions in which a treatment has not been studied [28, 29]. Exploring the generalization of efficacy across replicated, adequate and well-controlled neuropathic pain studies may suggest, depending on the outcome, that a pharmacological treatment could exert positive effects in other neuropathic pain conditions.

To help provide more meaningful evaluations of treatments for chronic pain, the IMMPACT initiative identified research design considerations for confirmatory chronic pain clinical trials, including trial subject selection, trial phases, treatment groups, dosing regimens and types of trials [30]. Variation in the characteristics of trial subjects, including ethnic factors, can impact a drug's efficacy and safety [31]. For these reasons, the current analysis assessed the efficacy of pregabalin in Japanese patients (a patient population with reduced variability in ethnic and demographic characteristics) across three neuropathic pain conditions (PHN, DPN and SCI), using similar clinical trial study designs. The potential similarities of treatment responses were evaluated to address the possibility that pregabalin, by extrapolation, may exert analgesic effects in other neuropathic pain conditions.

2 Methods

2.1 Data Sources

Data were analysed from three randomized, double-blind, placebo-controlled trials (RCTs) of pregabalin published in patients with PHN, DPN and neuropathic pain due to SCI. Safety and efficacy outcome data were previously published for the PHN [32, 33] and DPN trials [32, 34], which were both conducted in Japan. The SCI study was conducted in ten countries worldwide, including Japan, and the total population data have previously been published [35]. Only the Japanese subpopulation data from the SCI trial was selected for the current analyses (not previously published).

2.1.1 Study Designs

The three RCTs shared similar design features (Table 1). Participants in the PHN trial were randomized to receive pregabalin 150, 300 or 600 mg/day or placebo, administered twice daily (BID) for the 12-week, fixed-dose period following a 1-week titration phase. Participants in the DPN trial were randomized to receive pregabalin fixed doses of 300 or 600 mg/day or placebo, also administered BID, for 12 weeks following 1 week of titration. Participants in the SCI trial were randomized to receive pregabalin, dosed flexibly at 150–600 mg/day, or placebo for the 12-week dose-maintenance period, following a 4-week dose-optimization phase.

To assess the long-term efficacy of pregabalin, patients who had completed the PHN and DPN RCTs were enrolled into 52-week, open-label extension trials [36, 37]

Table 1 Neuropathic pain studies

Study [references]	Treatment period (week) (total dose titration or optimization[c]/maintenance)	Administration	Dose/day, mg	Participants, *n*		
				Placebo	Pregabalin	Total
RCTs						
PHN[a] [32, 33]	13 (1/12)	BID fixed	150, 300, 600[d]	97	272	369
DPN[a] [32, 34]	13 (1/12)	BID fixed	300, 600[d]	135	179	314
SCI[a] [35]	16 (4/12)	BID flexible	150–600	27	32	59
Open-label extension trials						
PHN[b] [36]	52	BID flexible	150–600[d]	–	126	126
DPN[b] [37]	52	BID flexible	150–600[d]	–	123	123
SCI[b] [38]	52	BID flexible	150–600	–	38	38

BID twice daily, CL_{CR} creatinine clearance, *DPN* diabetic peripheral neuropathy, *PHN* post-herpetic neuralgia, *RCT* randomized, controlled trial, *SCI* spinal cord injury

[a] Efficacy analysis was performed on the pre-specified analysis populations that were defined in the original protocols, although analyses of the SCI trial were based on the Japanese subpopulation. This included all randomized patients who had received at least one dose of the study medication and who had at least one post-baseline entry in the daily pain diary

[b] Efficacy analysis was performed on the pre-specified analysis populations that were defined in the original protocols, although analyses of the SCI trial were based on the SCI subpopulation. This included all patients who received at least one dose of the study medication and had both baseline and at least one post-baseline efficacy measurements

[c] The PHN and DPN RCTs included a 1-week titration phase: patients received 150 mg/day (BID) and were titrated up to 300 and 600 mg/day respective to the treatment group. The SCI RCTs included a 4-week dose-optimization phase: patients received 150 mg/day (BID) for 1 week; on the basis of efficacy and tolerability, the dose was increased to 600 mg/day

[d] Patients assigned to pregabalin 600 mg/day who had low CL_{CR} (defined as ≤60 mL/min) received 300 mg/day BID

(Table 1). Similarly, Japanese patients who completed the SCI RCT were enrolled into a 53-week, open-label trial of pregabalin in patients with central neuropathic pain due to SCI, multiple sclerosis or cerebral stroke [38].

2.1.2 Patient Population

In all three RCTs, patients were aged ≥18 years. An average pain score ≥4 on an 11-point numeric rating scale (NRS) from 0 = 'no pain' to 10 = 'worst possible pain', in the week prior to randomization was used to select patients with moderate to severe pain. Additional inclusion criteria identified patients with chronic persistent baseline neuropathic pain: patients in the PHN trial had pain persisting ≥3 months after the HZ rash healed; patients in the DPN trial were diagnosed at baseline with type 1 or 2 diabetes ≥1 year before the start of the trial and were diagnosed with painful, distal, symmetrical, sensorimotor polyneuropathy due to diabetes. Entry criteria for patients with SCI included complete or incomplete C2–T12 SCI with a duration of ≥12 months. Patients with traumatic and non-traumatic SCI pain were included. Patients were required to have below-level neuropathic pain (according to the Bryce/Ragnarsson SCI pain taxonomy [39]) that was continuous for ≥3 months or remitting/relapsing for ≥6 months.

All patients who had any condition that may have confounded the assessment of neuropathic pain associated with DPN, PHN or SCI, as applicable per trial, were excluded. Patients with a creatinine clearance rate (CL_{CR}) ≤30 mL/min were excluded, as were patients with a malignancy within the past 1–2 years. For each study, the use of therapies that may have impaired efficacy evaluations was prohibited or restricted.

The studies were registered with ClinicalTrials.gov (study sponsor identifiers/Clinical Trials.gov identifiers: A0081120/NCT00394901, A0081163/NCT00553475, A0081107/NCT00407745, A0081121/NCT00424372, A0081164/NCT00553280, A0081252/NCT01202227).

2.2 Outcome Measures

The key efficacy measures were (1) the study endpoint and weekly mean pain score derived from the pain diary ratings using an 11-point NRS and (2) the study endpoint and weekly mean sleep interference scores assessed also using an 11-point NRS, where 0 = 'pain did not interfere with sleep' to 10 = 'pain completely interfered with sleep'.

Secondary efficacy outcome measures for the RCTs included the responder rate (defined as a ≥30 % reduction in mean pain score from baseline to endpoint) and the Patient Global Impression of Change (PGIC) [40] score at

the endpoint. The PGIC measures change in overall patient status on a scale from 1 (very much improved) to 7 (very much worse). Additional efficacy measures included the 36-Item Short Form Health Survey (SF-36) [41] for the PHN and DPN trials and the Hospital Anxiety and Depression Scale (HADS [-A/-D]) [42] for the SCI trial. The proportion of patients who discontinued participation in the trials early for treatment-related reasons (defined as adverse events [AEs] or lack of efficacy) was also assessed.

In the extension trials, change from baseline in pain intensity at each time point rated on a 100-mm visual analogue scale (VAS) was evaluated using the Short-Form McGill Pain Questionnaire (SF-MPQ) [43].

2.3 Statistical Analyses

For the PHN and DPN RCTs, data from the pregabalin dose groups were extracted into one pregabalin treatment group per trial to preserve comparability among the trials analysed, on the basis of the two treatment groups (placebo versus pregabalin). Descriptive statistics were calculated to characterize baseline and demographic characteristics of the treatment groups.

The mean change from baseline in pain and sleep interference scores at each study week were analysed using a mixed model for repeated measures. The model included the fixed continuous effect of the baseline value and fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and CL_{CR} strata for the PHN and DPN RCTs. The model included the fixed continuous effect of the baseline value (and the baseline Pain Catastrophizing Scale [PCS] score for pain) and fixed categorical effects of treatment, visit, and treatment-by-visit interaction for the SCI RCT. Change from baseline to endpoint was analysed using an analysis of covariance (ANCOVA), which included the fixed categorical effects of treatment (and CL_{CR} strata for the PHN and DPN RCTs), as well as the fixed continuous effect of the baseline value (and baseline PCS score for pain in the SCI RCT). Responder data were analysed using a logistic regression model, which included treatment as the categorical factor and baseline pain (and baseline PCS score for the SCI RCT) as the covariates. SF-36 and HADS were analysed using the same ANCOVA. In the PHN and DPN trials, seven change categories of PGIC data were analysed using the Cochran–Mantel–Haenszel test with a modified ridit score adjusted for the CL_{CR} stratum. In the SCI trial, PGIC data were analysed using a chi-squared test with a modified ridit score. All efficacy outcome measures in the RCTs, except for weekly change from baseline in pain and sleep scores, used a last-observation-carried-forward (LOCF) approach to missing data. No imputation was performed for missing VAS scores (observed data were used) in the extension trials.

All efficacy analyses were conducted using the pre-specified analysis populations that were defined in the original protocols, although analyses for the SCI trial were based on the Japanese subpopulation. This included all patients who received at least one dose of study treatment and had at least one post-baseline efficacy measurement. For all efficacy measures, significance was declared if the two-tailed test for the difference between treatment groups was significant at the 0.05 level.

3 Results

Total numbers of 369 participants (placebo, $n = 97$; pregabalin, $n = 272$), 314 participants (placebo, $n = 135$; pregabalin, $n = 179$) and 59 participants (placebo, $n = 27$; pregabalin, $n = 32$) were included in the efficacy analyses of the PHN, DPN and SCI trials, respectively (Table 1). The median dose of pregabalin during the treatment fixed-dose/maintenance phase was 300 mg/day in the PHN and DPN trials and 449 mg/day in the SCI trial.

The majority of patients were male (54, 75 and 83 % in the PHN, DPN and SCI trials, respectively) and the mean ages were 70, 61 and 53 years, respectively (Table 2). The mean baseline pain scores were ≥6 for patients in the placebo and pregabalin groups in each trial.

Significant pain improvement was evident after 1 week of pregabalin treatment in the pooled population in all three trials ($p < 0.05$; Fig. 1a–c) and lasted for the duration of the trial. At the endpoint, the least-squares (LS) mean pain scores (LOCF) were statistically significantly reduced with pregabalin in all three trials (Table 3). The LS mean difference (95 % confidence interval [CI]) from placebo was −0.60 (−1.03 to −0.17; $p = 0.0065$) in the PHN trial, −0.66 (−1.09 to −0.23; $p = 0.0028$) in the DPN trial and −1.10 (−2.00 to −0.21; $p = 0.0168$) in the SCI trial. Similarly, pregabalin treatment was associated with improved sleep interference scores after 1 week in comparison with placebo in all three trials ($p < 0.05$; Fig. 1d–f). Improved sleep scores were observed for pregabalin versus placebo throughout the treatment phase. The mean sleep scores at the endpoint were statistically significantly reduced with pregabalin in all three trials (Table 3). The LS mean difference (95 % CI) from placebo was −0.84 (−1.21 to −0.47; $p < 0.0001$) in the PHN trial, −0.80 (−1.16 to −0.43; $p < 0.0001$) in the DPN trial and −1.46 (−2.34 to −0.58; $p = 0.0015$) in the SCI trial.

In all trials, from baseline to endpoint, the proportion of patients experiencing a ≥30 % decrease in pain score was significantly higher in the pregabalin-treated groups relative to the placebo-treated groups (all $p < 0.05$; Table 3). More than one third of pregabalin-treated patients achieved a ≥30 % reduction in pain from baseline across the trials.

Table 2 Patient demographics and baseline characteristics

Characteristic	PHN trial		DPN trial		SCI trial	
	Placebo n = 97	Pregabalin n = 272	Placebo[a] n = 135	Pregabalin n = 179	Placebo n = 27	Pregabalin n = 32
Sex, n (%)						
Male	57 (58.8)	141 (51.8)	103 (76.3)	134 (74.9)	25 (92.6)	24 (75.0)
Female	40 (41.2)	131 (48.2)	32 (23.7)	45 (25.1)	2 (7.4)	8 (25.0)
Age, years						
Mean (SD)	71.0 (8.6)	69.8 (10.7)	61.3 (9.6)	61.5 (10.3)	52.3 (14.1)	54.3 (12.2)
Range	29–88	24–92	35–85	35–85	27–81	28–72
Weight, kg						
Mean (SD)	57.7 (10.5)	57.4 (10.9)	64.9 (12.8)	65.7 (12.8)	64.0 (11.6)	64.3 (11.5)
Range	33–101	34–98	41–104	31–113	43–93	47–92
Baseline pain score						
Mean (SD)	6.2 (1.5)	6.2 (1.5)	6.1 (1.4)	6.0 (1.3)	6.6 (1.5)	6.8 (1.4)
Range	4–10	4–10	4–9	4–10	4–10	4–9
Estimated CL_{CR} at screening, mL/min						
Mean (SD)	74.6 (23.3)	73.9 (24.4)	97.3 (37.1)	97.6 (33.0)	111.5 (33.8)	121.5 (35.3)
Median	71.0	70.5	91.0	96.0	111.7	111.6
Range	39–183	31–159	33–258	31–240	62–183	66–211
Duration of pain, months						
Mean	33.3	35.1	50.5	51.9	87.5	121.3
Median	18.2	18.9	41.3	36.1	45.0	74.5
Range	3–210	3–370	12–233	13–250	10–271	14–396

CL_{CR} creatinine clearance, *DPN* diabetic peripheral neuropathy, *PHN* post-herpetic neuralgia, *SCI* spinal cord injury, *SD* standard deviation

[a] Placebo data from the DPN study have previously been presented by Satoh et al. [34] and Ogawa et al. [32]

The proportion of patients reporting their overall status as 'very much', 'much' or 'minimally' improved at the endpoint was higher with pregabalin versus placebo across the trials. The differences between treatment groups across all seven change categories were statistically significant ($p < 0.05$; Table 3).

In the PHN trial, the endpoint SF-36 subscale scores were statistically significantly improved in the pregabalin group versus the placebo group for physical role limitations, bodily pain, general health perception, vitality and mental health (all $p < 0.05$). In the DPN trial, social functioning was statistically significantly improved in the pregabalin group versus placebo ($p < 0.05$). In the SCI trial, a non-significant numerical difference in comparison with placebo was observed for the HADS anxiety and depression subscale scores in the pregabalin-treated group. A summary of efficacy endpoints is shown in Table 3.

For all three conditions, a notably smaller number of patients discontinued participation because of lack of efficacy in the pregabalin-treated group than in the placebo group. In contrast, discontinuations due to treatment-related AEs occurred at a rate approximately three times greater in the pregabalin-treated groups than in the placebo groups across indications (Table 4). The most common treatment-related AEs with pregabalin in the DPN and PHN trials were dizziness (DPN 43/179 [24.0 %]; PHN 85/273 [31.1 %]), somnolence (DPN 46/179 [25.7 %]; PHN 78/273 [28.6 %]), peripheral oedema (DPN 23/179 [12.8 %]; PHN 32/273 [11.7 %]) and weight gain (DPN 20/179 [11.2 %]; PHN 29/273 [10.6 %]); each occurred more frequently in patients treated with pregabalin compared with placebo (previously published data) [32]. In the SCI trial, the most common treatment-related AEs reported more frequently with pregabalin compared with placebo were somnolence (18/32, 56.3 %), dizziness (8/32, 25.0 %) and oedema (4/32, 12.5 %).

Of the patients who reached week 52 in the long-term trials (PHN, 74.6% [n = 94/126]; DPN, 78.9% [n = 97/123]; SCI, 89.5% [n = 34/38]), mean (standard deviation [SD]) SF-MPQ VAS pain scores were improved from baseline by −12.5 (17.4) mm, −13.9 (23.3) mm and −13.6 (20.8) mm, respectively. In all three long-term trials, improvements in SF-MPQ VAS scores for pregabalin patients were sustained throughout the treatment period (Fig. 2). These findings suggest an analgesic effect of pregabalin when used over a long period for PHN, DPN and SCI.

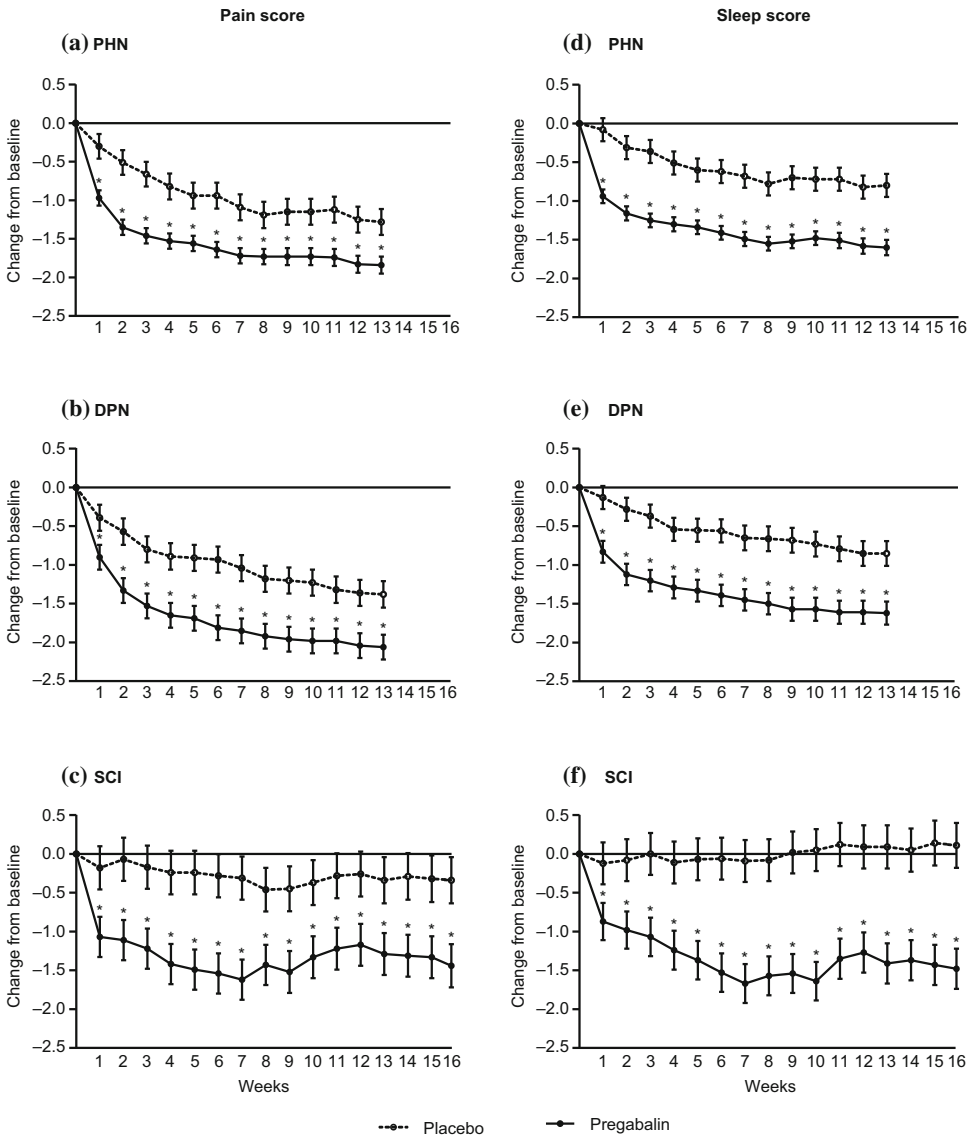

Fig. 1 Least-squares mean (standard error) changes in **a–c** pain scores and **d–f** sleep scores at each study week. *$p <$ 0.05 versus placebo. Pain scores range from 0 = 'no pain' to 10 = 'worst possible pain'. Sleep scores range from 0 = 'pain did not interfere with sleep' to 10 = 'pain completely interfered with sleep'. Analysed using a mixed model for repeated measures, with fixed categorical effects of treatment, visit and treatment-by-visit interaction (and creatinine clearance strata in the post-herpetic neuralgia [PHN] and diabetic peripheral neuropathy [DPN] randomized, controlled trials [RCTs]) and the fixed continuous effect of the baseline value (and the baseline Pain Catastrophizing Scale score in the spinal cord injury [SCI] RCT [for pain])

4 Discussion

In this retrospective analysis of RCTs, pregabalin was consistently efficacious in treating peripheral and central neuropathic pain (PHN, DPN and SCI) in Japanese patients. Significant improvements in comparison with placebo in mean pain and sleep interference scores were observed over 13- to 16-week treatment periods, with improvements evident after 1 week of treatment ($p < 0.05$). In addition, a significantly greater percentage of pregabalin-treated patients experienced a $\geq$30 % reduction in pain in comparison with placebo across the RCTs ($p < 0.05$), a milestone considered moderate, clinically relevant pain relief [44]. Findings from the published extension trials were assessed to highlight any similarities in treatment response that may exist between the three types of neuropathic pain conditions. Improvements in VAS values obtained using SF-MPQ were maintained over a 52-week period, suggesting a long-term analgesic effect of pregabalin in patients with PHN, DPN or SCI. These findings support the clinically meaningful short- and long-term efficacy of pregabalin in treating neuropathic pain associated with PHN, DPN and SCI. Pregabalin was also associated with improving other efficacy outcomes related to function and QoL in Japanese patients with PHN, DPN or SCI.

In the United States, pregabalin currently has separate approvals for managing neuropathic pain associated with PHN, DPN and SCI [22]. The FDA recognizes the importance of generalizing efficacy across neuropathic pain conditions and has drafted an evidence-based approach for an overall indication of the treatment of (both central and peripheral) neuropathic pain [29]. Identifying patterns of findings from clinical trials could serve as a basis for the

Table 3 Summary of efficacy outcome measures

Parameter, scale	PHN trial		DPN trial		SCI trial	
	Placebo	Pregabalin	Placebo	Pregabalin	Placebo	Pregabalin
Pain (change from baseline)[a,b]						
n	97	272	135	179	27	32
LS mean change (SE)	−1.12 (0.19)	−1.72 (0.12)	−1.20 (0.21)	−1.85 (0.20)	−0.25 (0.33)	−1.35 (0.30)
Difference (95 % CI)	–	−0.60 (−1.03 to −0.17)	–	−0.66 (−1.09 to −0.23)	–	−1.10 (−2.00 to −0.21)
p value	–	0.0065	–	0.0028	–	0.0168
Sleep (change from baseline)[b,c]						
n	97	272	135	179	27	32
LS mean change (SE)	−0.67 (0.17)	−1.51 (0.10)	−0.74 (0.18)	−1.53 (0.17)	0.14 (0.32)	−1.32 (0.30)
Difference (95 % CI)	–	−0.84 (−1.21 to −0.47)	–	−0.80 (−1.16 to −0.43)	–	−1.46 (−2.34 to −0.58)
p value	–	<0.0001	–	<0.0001	–	0.0015
Pain responders (at the endpoint)[d]						
n	97	272	135	179	27	32
≥30 %, *n* (%)	29 (29.9)	125 (46.0)	49 (36.3)	92 (51.4)	3 (11.1)	11 (34.4)
OR (95 % CI)	–	2.05 (1.24 to 3.40)	–	1.85 (1.17 to 2.93)	–	5.20 (1.16 to 23.22)
p value	–	0.0053	–	0.0087	–	0.0309
PGIC (at the endpoint)[e]						
n	95	262	135	178	27	32
Improved, *n* (%)	41 (43.2)	176 (67.2)	74 (54.8)	122 (68.5)	7 (25.9)	24 (75.0)
p value	–	<0.0001	–	0.0158	–	0.0010
SF-36 (at the endpoint)[f]						
Physical functioning, *n*	95	262	135	178	–	–
LS mean (SE)	76.18 (1.28)	77.90 (0.80)	75.25 (1.57)	75.33 (1.46)	–	–
Difference (95 % CI)	–	1.72 (−1.16 to 4.59)	–	0.09 (−3.08 to 3.25)	–	–
p value	–	0.2410	–	0.9570	–	–
Physical role limitations, *n*	95	262	135	178	–	–
LS mean (SE)	67.94 (2.27)	73.64 (1.43)	76.72 (2.47)	75.05 (2.30)	–	–
Difference (95 % CI)	–	5.70 (0.58 to 10.81)	–	−1.67 (−6.65 to 3.30)	–	–
p value	–	0.0291	–	0.5091	–	–
Bodily pain, *n*	95	262	135	178	–	–
LS mean (SE)	47.43 (1.83)	51.75 (1.14)	55.39 (1.97)	57.16 (1.82)	–	–
Difference (95 % CI)	–	4.33 (0.23 to 8.42)	–	1.77 (−2.19 to 5.74)	–	–
p value	–	0.0386	–	0.3801	–	–
General health perception, *n*	95	262	135	178	–	–
LS mean (SE)	52.37 (1.48)	56.70 (0.93)	43.82 (1.44)	45.08 (1.33)	–	–
Difference (95 % CI)	–	4.33 (1.00 to 7.65)	–	1.26 (−1.63 to 4.16)	–	–
p value	–	0.0110	–	0.3922	–	–
Social functioning, *n*	95	262	135	178	–	–
LS mean (SE)	75.23 (2.21)	79.10 (1.38)	77.49 (2.39)	83.33 (2.22)	–	–
Difference (95 % CI)	–	3.87 (−1.08 to 8.82)	–	5.84 (1.03 to 10.65)	–	–
p value	–	0.1255	–	0.0175	–	–
Emotional role limitations, *n*	95	262	135	178	–	–
LS mean (SE)	69.98 (2.40)	74.78 (1.50)	78.95 (2.51)	80.20 (2.34)	–	–
Difference (95 % CI)	–	4.81 (−0.58 to 10.19)	–	1.25 (−3.82 to 6.32)	–	–
p value	–	0.0801	–	0.6279	–	–
Vitality, *n*	95	262	135	178	–	–
LS mean (SE)	54.14 (1.89)	59.84 (1.19)	55.17 (1.94)	56.31 (1.81)	–	–
Difference (95 % CI)	–	5.71 (1.45 to 9.97)	–	1.14 (−2.78 to 5.06)	–	–
p value	–	0.0087	–	0.5672	–	–
Mental health, *n*	95	262	135	178	–	–
LS mean (SE)	61.89 (1.94)	67.15 (1.22)	65.57 (1.83)	67.70 (1.70)	–	–
Difference (95 % CI)	–	5.26 (0.90 to 9.62)	–	2.12 (−1.58 to 5.82)	–	–

Table 3 continued

Parameter, scale	PHN trial		DPN trial		SCI trial	
	Placebo	Pregabalin	Placebo	Pregabalin	Placebo	Pregabalin
p value	–	0.0182	–	0.2598	–	–
HADS (change from baseline)[g]						
Anxiety, *n*	–	–	–	–	27	32
LS mean change (SE)	–	–	–	–	0.49 (0.61)	−0.78 (0.56)
Difference (95 % CI)	–	–	–	–	–	−1.27 (−2.94 to 0.40)
p value	–	–	–	–	–	0.1339
Depression, *n*	–	–	–	–	27	32
LS mean change (SE)	–	–	–	–	0.24 (0.57)	−1.14 (0.53)
Difference (95 % CI)	–	–	–	–	–	−1.39 (−2.95 to 0.17)
p value	–	–	–	–	–	0.0798

ANCOVA analysis of covariance, *CI* confidence interval, CL_{CR} creatinine clearance, *DPN* diabetic peripheral neuropathy, *HADS* Hospital Anxiety and Depression Scale, *LS* least-squares, *OR* odds ratio, *PCS* Pain Catastrophizing Scale, *PGIC* Patient Global Impression of Change, *PHN* post-herpetic neuralgia, *SCI* spinal cord injury, *SE* standard error, *SF-36* 36-Item Short Form Health Survey

[a] Pain scores range from 0 = 'no pain' to 10 = 'worst possible pain'

[b] ANCOVA with fixed categorical effects of treatment (and the CL_{CR} strata for the PHN and DPN trials), and the fixed continuous effect of the baseline value (and baseline PCS score for the SCI trial [for pain])

[c] Sleep scores range from 0 = 'pain did not interfere with sleep' to 10 = 'pain completely interfered with sleep'

[d] Patients with a ≥30 % reduction in the weekly mean pain score from baseline to endpoint. Exponentiation of the log OR and 95 % CI corresponding to the treatment contrast in the logistic regression model, with treatment (and the CL_{CR} strata for the PHN and DPN trials) as the categorical factor and baseline pain (and the baseline PCS score for the SCI trial) as the covariates

[e] Based on the Cochran–Mantel–Haenszel test with a modified ridit score adjusted for the CL_{CR} stratum for the PHN and DPN trials, and a chi-squared test with a modified ridit score for the SCI trial

[f] Scores range from 0 to 100, with higher scores indicating better patient status. Analysed using the same ANCOVA

[g] Scores range from 0 to 21, with lower scores indicating better patient status. Analysed using the same ANCOVA

extrapolation of analgesic efficacy from one chronic neuropathic condition to another [28]. The similarity in the observed efficacy profiles regardless of the neuropathic pain conditions, including the time to onset of response and magnitude of response, are consistent with the data required to serve as a basis for the extrapolation of analgesic efficacy to other neuropathic pain conditions [28].

Findings from the present analysis are consistent with those from multiple clinical trials conducted across the globe, which demonstrate the positive effects of pregabalin on pain and patient QoL outcomes in PHN [27, 45–47], DPN [27, 48–52] and SCI [21, 26, 53], and also for a broader range of neuropathic pain aetiologies, including neuropathic pain associated with post-trauma/post-surgery [54, 55], stroke [53] and hereditary/idiopathic peripheral neuropathy [56].

In an observational, non-interventional study in Japanese patients with chronic lower back pain (CLBP) with a neuropathic pain component, significantly greater improvement in pain-related sleep interference was observed with pregabalin at the study endpoint (8 weeks) relative to usual care alone (conventional analgesic care). The treatment difference from usual care was −0.9 (95 % CI −1.5 to −0.4; $p < 0.001$). In comparison with usual care, pregabalin also significantly improved pain scores and PGIC scores at the endpoint (both $p < 0.001$) [57]. In the open-label, long-term trial conducted in Japan, the mean (SD) SF-MPQ VAS pain score at the study endpoint (52 weeks) was improved from baseline (68.0 [16.7] mm) by −26.3 (26.1) mm in the post-stroke patient subpopulation [38]. The efficacy demonstrated in these patient populations further supports the generalizability of results across the neuropathic pain conditions.

Not all neuropathic pain trials have demonstrated improvements with pregabalin, and this issue should be discussed during consideration of the extrapolation of efficacy between different pain conditions. In a central pain, post-stroke trial conducted across 11 countries in the Asia-Pacific region (except for Japan), pregabalin 600 mg/day did not significantly reduce pain at the endpoint (13 weeks) in comparison with placebo, although improvements in other efficacy measures, including sleep, anxiety and the Clinical Global Impression of Change, did suggest some clinical benefits in these patients [58]. A trial in patients with painful HIV neuropathy conducted in the United States and Puerto Rico failed to show superiority of pregabalin in any efficacy endpoint [59]. In a trial in chronic lumbosacral radiculopathy conducted across eight countries in Europe and North America, although 58 % of patients experienced a ≥30 % pain reduction in the single-blind pregabalin treatment phase

Table 4 Treatment failures: proportions of patients in the randomized, controlled trials who discontinued participation because of treatment-related adverse events (AEs) or lack of efficacy

Parameter	PHN		DPN		SCI	
	Placebo $n = 98$	Pregabalin $n = 273$	Placebo $n = 135$	Pregabalin $n = 179$	Placebo $n = 27$	Pregabalin $n = 32$
Lack of efficacy, *n* (%)	6 (6.1)	8 (2.9)	7 (5.2)	1 (0.6)	2 (7.4)	0
Treatment-related AEs, *n* (%)	3 (3.1)	36 (13.2)	6 (4.4)	22 (12.3)	1 (3.7)	3 (9.4)

DPN diabetic peripheral neuropathy, *PHN* post-herpetic neuralgia, *SCI* spinal cord injury

of the randomized, placebo-controlled withdrawal design, the primary endpoint (time to loss of response) did not significantly differ between the pregabalin and placebo groups in the double-blind treatment phase [60]. The reduced ability of these trials to demonstrate efficacy could have been a reflection of the heterogeneity of the patient populations studied, which may have compromised the 'assay sensitivity' [30].

The high placebo response identified in each negative trial would have limited the potential for pregabalin to demonstrate efficacy. Placebo response rates are known to be highly variable in pain trials, in part because of the different underlying pathophysiology of the conditions. An IMMPACT analysis found that mean improvements with placebo were consistently greater in trials of patients with painful DPN than in trials of patients with painful PHN [61]. In addition, higher levels of placebo response were suggested in peripheral neuropathic pain than in central neuropathic pain [62, 63]. The findings from the current analysis further support this idea, with a numerically greater proportion of placebo-treated patients with PHN and DPN experiencing a ≥30 % pain reduction and improvement in PGIC scores than placebo-treated patients with SCI.

Making comparisons across clinical trials requires consistent study design and methodology [61, 64, 65]. The present analysis used data from trials with similar methodological aspects. A racially homogenous study population (Japanese patients) and comparable inclusion/exclusion criteria reduced the variability in demographic characteristics, and the timing of the trials was also comparable (the duration of the first subject, first visit for the first trial to the last subject, last visit for the last trial was within 4.5 years).

However, there were some differences in the trial designs. The PHN and DPN trials used a fixed-dose design, which is commonly used in these trials. The SCI trial used a flexible-dose design, which is suggested to better reflect clinical practice, as dosages can be adjusted in response to effectiveness and tolerability. Flexible-dose designs may have greater 'assay sensitivity' (the ability of the trial to demonstrate a treatment effect in comparison with placebo) than fixed designs [30]. Efficacy and safety studies of pregabalin in PHN and DPN demonstrated that both fixed and flexible dosing significantly improved pain reduction in comparison with placebo, with patients administered flexible dosage experiencing fewer withdrawals from treatment due to AEs in comparison with the fixed dosage [66, 67]. Freynhagen et al. [66] reported endpoint treatment differences in comparison with placebo of −1.38 (95 % CI −2.11 to −0.65; $p < 0.001$) and −1.17 (95 % CI −1.90 to −0.45; $p = 0.002$) with pregabalin 600 mg/day fixed dosage and pregabalin 150–600 mg/day flexible dosage, respectively [66, 68]. The difference in pain reduction was likely attributable to the difference in average pregabalin dosages in the fixed- and flexible-dosage groups (554.8 vs 457.0 mg/day). In the current analysis, a larger treatment difference in comparison with placebo was observed in the SCI trial than in the peripheral pain trials, which may have been attributable to the difference in pregabalin dosage between the trials. Patients in the fixed-dosage group assigned to pregabalin 600 mg/day would likely have received doses higher than required to achieve meaningful pain relief and acceptable tolerability [66].

In the current analysis, the proportion of patients who withdrew from the study because of treatment-related AEs was slightly higher in the peripheral pain trials, which used fixed designs, than in the SCI trial, which used a flexible design. These results are likely attributable to the differences in dosing regimens; therefore, comparability between the trials is not thought to be significantly affected by these differences.

Additional limitations associated with the current analysis need to be considered. Unlike the individual studies, the treatment groups were not balanced for the number of patients, with fewer patients evaluated in the SCI study than in the PHN and DPN studies. The total number of QoL assessment tools utilized was small, and different tools

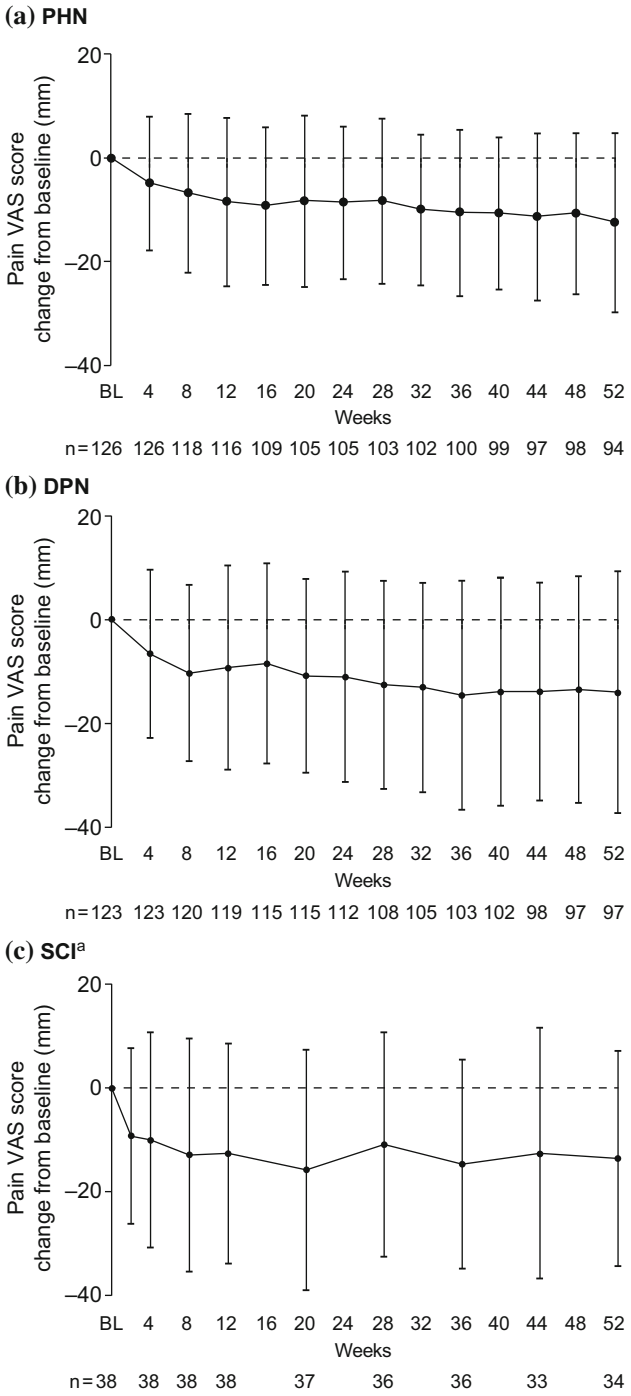

Fig. 2 Mean (standard deviation) change from baseline (BL) in Short-Form McGill Pain Questionnaire visual analogue scale (VAS) scores by week. [a]Spinal cord injury (SCI) figure adapted from Onouchi et al. [38], an open-access article distributed under the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/3.0/legalcode). *DPN* diabetic peripheral neuropathy, *PHN* post-herpetic neuralgia

were applied per trial (SF-36 versus HADs). Finally, the findings may not be extrapolated beyond the duration of the trials.

5 Conclusion

Because efficacy was consistently demonstrated in treating neuropathic pain associated with PHN, DPN and SCI in this analysis, the type of neuropathic pain condition may have a limited impact on treatment response for these pain aetiologies. These findings support the potential for extrapolating analgesic treatment efficacy between neuropathic pain conditions and the need for further research to specify the boundaries for the generalization of efficacy, especially for pain conditions with different pathophysiological mechanisms.

Compliance with Ethical Standards

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Conflict of interest Akio Arakawa, Kazuhiro Hayakawa and Tamotsu Yoshiyama are all full-time employees of Pfizer and hold stock in Pfizer. Setsuro Ogawa has received consultancy fees or lecture fees from Janssen, Hisamitsu, Pfizer, Nippon Shinyaku and Showa Yakuhin Kakou.

Ethical approval All trials included in the current analyses were approved by the appropriate institutional review board or independent ethics committee at each investigational centre. All trials were conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonisation Good Clinical Practice Guidelines.

Informed consent All patients provided written informed consent prior to participation in any trial procedures.

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