ORIGINAL ARTICLE

Does Duration of Neuropathic Pain Impact the Effectiveness of Pregabalin?

Concepción Pérez, PhD*; Mark Latymer, BSc†; Mary Almas, MS‡; Marie Ortiz,‡; Andrew Clair, PhD‡; Bruce Parsons, MD, PhD‡; Roxana Varvara, MD†

Pain Clinic, Hospital de la Princesa, Madrid, Spain; †Pfizer Ltd, Tadworth, Surrey U.K.; ‡Pfizer, New York, New York, U.S.A

■ **Abstract**

Background: Patients with chronic pain conditions such as neuropathic pain frequently experience delays in diagnosis and treatment. Ideally, all patients should be treated in a timely manner, but in those patients with more established disease it is important to know that approved treatments remain effective.

Methods: This was a pooled analysis of 19 randomized placebo-controlled trials of pregabalin for peripheral neuropathic pain conditions, including diabetic peripheral neuropathy, postherpetic neuralgia, and post-traumatic/postsurgical pain. Patients were divided into 5 pain duration categories based on time since onset of pain (< 6 months, 6 months to < 1 year, 1 year to < 2 years, 2 years to < 5 years, and ≥ 5 years). Mean change in pain score at endpoint, vs. placebo, was assessed for each category, together with changes in Patient Global Impression of Change (PGIC) responders ("very much" or "much" improved at endpoint).

Results: The analysis included 5,783 patients (n = 3,619 pregabalin; n = 2,164 placebo). Mean baseline pain scores were similar across the pain duration categories (range 6.3 to 6.5). Pregabalin significantly improved pain score at endpoint, vs. placebo, in all patients together (treatment difference [95% confidence interval], −0.59 [−0.67, −0.52], $P < 0.0001$) and similarly in each pain duration category ($P < 0.0001$ for each). There were significantly more PGIC responders with pregabalin, vs. placebo, for all patients (45.0% vs. 30.9%, $P < 0.0001$) and each category separately ($P < 0.001$ for each). There were no consistent, significant differences in treatment response between the different pain duration categories.

Conclusions: Pregabalin significantly improves pain irrespective of the length of time since onset of neuropathic pain. ■

Key Words: neuropathic pain, pregabalin, pain duration

INTRODUCTION

Neuropathic pain is a common chronic pain condition that can be particularly challenging to treat due to its severity and associated comorbidities. The incidence of pain with neuropathic characteristics in the general population has been estimated to be between 6.9% and 10%,[1] although it is responsible for an even larger proportion of visits to primary care physicians and pain clinics.[2,3] As a consequence, neuropathic pain represents a significant economic burden on patients and healthcare systems.[4–6]

Patients with chronic pain frequently experience delays in receiving treatment that, when wait times are longer than 6 months, have been shown to result in significant deterioration in health-related quality of life and psychological well-being.[7] As such, pathways for care emphasize timely review of patients with neuropathic pain in order to reduce suffering.[8]

Address correspondence and reprint requests to: Concepción Pérez, PhD, Pain Clinic, Hospital de la Princesa, Madrid, Spain. E-mail: cphernandez@salud.madrid.org.

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Pregabalin, an $\alpha_2\delta$ ligand, is approved for the treatment of peripheral and central neuropathic pain in Europe.[9] It is also approved for the treatment of general anxiety disorder and partial onset seizures in Europe,[9] and partial onset seizures, fibromyalgia, and neuropathic pain due to diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), and spinal cord injury (SCI) in the United States.[10] Pregabalin is recommended as a first-line treatment for indicated neuropathic pain conditions by the International Association for the Study of Pain,[11] the European Federation of Neurological Societies,[12] and the American Academy of Neurology,[13,14] and the worldwide exposure to pregabalin up to the end of 2014 has been estimated to be over 28 million patient-years.[15]

As noted above, pathways for care prescribe diagnosing and treating patients with neuropathic pain in a timely manner in order to reduce suffering.[8] Initiating treatment with pregabalin earlier after diagnosis can also result in significant cost savings, with lower healthcare costs and fewer lost workdays.[16] At the same time, an observational study of a mixed population of patients with neuropathic pain in a Spanish primary care setting found that treatment with pregabalin improved measures of pain and that this improvement was significantly greater in those patients with a shorter duration of pain.[17] While these data may suggest further cause to initiate treatment earlier, there is little other evidence to suggest that, once established, peripheral neuropathic pain conditions become less amenable to treatment over time.

It is important for physicians treating patients with neuropathic pain to know whether patients will respond differently to pregabalin based on their duration of pain; however, additional data are required to determine whether patients with different durations of pain do respond differently to treatment with pregabalin. This analysis pooled individual patient-level data from 19 randomized placebo-controlled studies of pregabalin in patients with neuropathic pain to assess the impact of duration of pain on the response to pregabalin.

METHODS

Source Data

Patient-level data were pooled from 19 phase II, III, and IV randomized placebo-controlled trials of pregabalin for the treatment of peripheral neuropathic pain. Selected studies included all Pfizer-sponsored studies of pregabalin for peripheral neuropathic pain completed at the time of this analysis, with the exception of open-label, methodological, or pharmacokinetic studies; studies that did not confirm diagnosis of neuropathic pain; studies that did not collect data on the duration since diagnosis of pain; and studies that terminated before sufficient data were collected. Studies conducted in patients with HIV infection or cancer were excluded because of the complexities of their pathophysiologies.

The studies included in the analysis included patients with DPN, PHN, and post-traumatic or postsurgical pain (PT/PS; Table 1). Eight trials were conducted in patients with DPN: 1008-149[18], A0081030 (Clinical Trials.gov: NCT00156078)[19], A0081060 (NCT00159679)[20], A0081071 (NCT00143156)[19], A0081163 (NCT00553475)[21], A0081265 (NCT01332149), A0081268 (NCT01455415)[22], and A0081269 (NCT01474772).[23] There were 7 trials conducted in patients with PHN: 1008-030[24], 1008-045[25], 1008-127[26], 1008-196[27], A0081004 (NCT00159666)[28], A0081120 (NCT00394901)[29], and A0081276 (NCT01455428).[30] Two trials were conducted in patients with either DPN or PHN: 1008-155[31] and A0081081 (NCT00301223).[32] One trial was conducted in patients with PT/PS pain: A0081064 (NCT00292188).[33] One trial was conducted in patients with DPN, PHN, or PT/PS: A0081037 (NCT00141219).[34] Some historical trials are not recorded at ClinicalTrials.gov. Two of the above studies were placebo-controlled crossover trials (A0081268 [NCT01455415][22] and A0081269 [NCT01474772][23]), with only the first period of these trials (6 weeks of placebo-controlled treatment) included in the analysis, while all other studies were parallel, double blind, and placebo controlled.

The trials were conducted between October 1998 and April 2014 and included patients from Asia, Australia, Europe, the Middle East, North and South America, and South Africa. Rates of discontinuation with pregabalin in these studies ranged from 9.3% to 37.0%. Patients were treated with fixed doses of 150 mg/day, 300 mg/day, or 600 mg/day, or with flexible dosing (150 to 600 mg/day) for between 4 and 13 weeks. Data were assessed with all doses of pregabalin (including flexible dosing) and durations of treatment together. In a separate analysis, patients treated with flexible-dose pregabalin alone were assessed. Flexible dosing most closely reflects the recommended approach in clinical practice in which pregabalin should be carefully escalated to the highest tolerable dose,[10,12,35] and this

Table 1. Studies Included in the Analysis

Study	Clinical Trials Identifier	Condition	Study Dates	Duration
1008-149[18]	—	DPN	Nov 2000 to May 2002	12 weeks
A0081030[19]	NCT00156078	DPN	Jan 2005 to Apr 2006	12 weeks
A0081060[20]	NCT00159679	DPN	Sep 2004 to Oct 2005	13 weeks
A0081071[19]	NCT00143156	DPN	May 2005 to May 2007	13 weeks
A0081163[21]	NCT00553475	DPN	Oct 2007 to Mar 2009	13 weeks
A0081265	NCT01332149	DPN	Jul 2011 to Apr 2014	9 weeks
A0081268[22]	NCT01455415	DPN	Dec 2011 to Dec 2013	2 × 6 weeks crossover study*
A0081269[23]	NCT01474772	DPN	Dec 2011 to Jul 2013	2 × 6 weeks crossover study*
1008-030[24]	—	PHN	Oct 1998 to Jul 1999	5 weeks
1008-045[25]	—	PHN	Feb 1999 to Jun 2000	8 weeks
1008-127[26]	—	PHN	Dec 1999 to May 2000	8 weeks
1008-196[27]	—	PHN	Nov 2001 to Oct 2002	13 weeks
A0081004[28]	NCT00159666	PHN	Oct 2004 to Jun 2006	4 weeks
A0081120[29]	NCT00394901	PHN	Sep 2006 to Nov 2007	13 weeks
A0081276[30]	NCT01455428	PHN	Dec 2011 to Jan 2014	8 weeks
A0081064[33]	NCT00292188	PT/PS	Jan 2006 to May 2008	8 weeks
1008-155[31]	—	DPN or PHN	Jul 2001 to Dec 2002	12 weeks
A0081081[32]	NCT00301223	DPN or PHN	Feb 2006 to Sep 2007	8 weeks
A0081037[34]	NCT00141219	DPN, PHN, or PT/PS	Dec 2005 to Dec 2007	8 weeks

Not all historical trials are recorded at ClinicalTrials.gov. DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia; PT/PS, post-traumatic or postsurgical pain.
*Only the first period of the crossover studies were included in the analysis.

analysis was to confirm whether these patients responded similarly to the full population.

Patients were separated into pain duration categories based on duration of neuropathic pain, time since diagnosis of DPN, or time since onset of symptoms for patients with DPN; duration of PHN for patients with PHN; and duration of PT/PS neuropathic pain for patients with PT/PS. The 5 pain duration categories, selected to provide an even distribution of patients in each group, were < 6 months, 6 months to < 1 year, 1 year to < 2 years, 2 years to < 5 years, and ≥ 5 years.

Studies in Patients with Central Neuropathic Pain

All Pfizer-sponsored studies of pregabalin for the treatment of central neuropathic pain associated with SCI were also assessed. They included 2 studies: 1008-000-125, a 12-week study with 70 patients receiving pregabalin and 67 placebo,[36] and A0081107 (NCT00407745), a 17-week study with 112 patients receiving pregabalin and 107 placebo.[37] Assigning patients into the designated pain duration categories revealed that the majority of patients (65.7%) had a pain duration of ≥ 5 years (median 8.2 years with pregabalin; 8.6 years with placebo). Given the lack of patients in the shorter pain duration categories, along with the clinical differences between patients with peripheral and central neuropathic pain, this patient population was not included in the analysis.

Efficacy Outcomes

Pooled patient data were assessed for the change in mean pain score at endpoint compared with placebo. Mean pain score was the mean score over the past 7 days as recorded by patients in a daily pain diary and measured using an 11-point numeric rating scale scored from 0 (no pain) to 10 (worst possible pain). Also assessed at endpoint was the Patient Global Impression of Change (PGIC), a patient-rated measure of change in overall status on a scale of 1 (very much improved) to 7 (very much worse). PGIC responders were those whose condition was "very much improved" or "much improved" at the end of treatment. Other efficacy outcomes included the change in Medical Outcomes Study (MOS) Sleep Scale,[38] a 12-item patient-completed questionnaire with the subscale of sleep adequacy, together with the overall 9-item sleep problems index, included in this analysis. Each measure in the MOS Sleep Scale is scored from 0 to 100, with higher scores indicating improved sleep adequacy but worse sleep by the sleep problems index. Finally, the Hospital Anxiety and Depression Scale—Anxiety (HADS-A) and Hospital Anxiety and Depression Scale—Depression (HADS-D)[39], which measure the presence and severity of

symptoms of anxiety and depression, scored from 0 to 21, with higher scores indicating greater presence of the mood disorder.

Statistical Analysis

The change in mean pain score at endpoint from baseline was assessed using a mixed model of repeated measures method with terms such as *baseline pain score, protocol, treatment, indication, duration of pain,* and *study week* and interaction terms such as *treatment by duration of pain*. PGIC responses were assessed by logistical regression, with odds ratio and 95% confidence interval (CI) as well as calculated by exponentiating the log odds ratio and 95% CI corresponding to the treatment which is in contrast with the logistic regression model with treatment, indication, study, duration of pain and interaction terms of treatment and duration of pain as the categorical covariates with missing data imputation by last observation carried forward (LOCF). MOS and HADS were assessed by analysis of variance, with baseline score, study, indication, treatment, and duration of pain as categories and interaction terms of treatment by pain duration categories with missing data imputation by LOCF.

RESULTS

Patient Population

A total of 5,783 patients with peripheral neuropathic pain (3,619 treated with pregabalin, 2,164 with placebo) were included in the analysis. This included 3,319 patients with DPN, 2,136 with PHN and 328 with PT/PS. The median duration of pain was shorter in patients with PHN (1.6 years for pregabalin and 1.5 years for placebo) than with DPN (3.0 years for pregabalin and 3.0 years for placebo) or PT/PS (2.3 years for pregabalin and 2.3 years for placebo). Demographic characteristics of patients were broadly similar across the 5 pain duration categories, with the exception of a trend toward a higher body mass index (BMI) and a lower proportion of Asian patients in patients with a longer duration of pain (Table 2). The mean baseline pain scores of patients were broadly similar across the 5 pain duration categories (Table 3). However, there was a trend toward poorer sleep and more severe baseline HADS-A and HADS-D scores in patients with a longer duration of pain.

The mean (median) maintenance dose of pregabalin in patients treated with flexible-dose pregabalin was similar in each pain duration category: < 6 months, 481.5 (600.0) mg/day; 6 months to < 1 year, 443.2 (450.0) mg/day; 1 year to < 2 years, 458.8 (450.0) mg/day; 2 years to < 5 years, 437.5 (450.0) mg/day; and ≥ 5 years, 446.1 (450.0) mg/day.

Change in Pain Score

Pregabalin significantly improved pain score at endpoint, compared with placebo, in all patients regardless of duration of pain (Figure 1A). There were small, insignificant differences between patients with pain duration of < 6 months or > 5 years; however, these differences were not indicative of any preferential treatment response in patients with a short or long pain duration (Figure 2A).

Those patients treated with flexible-dose pregabalin (150 to 600 mg/day) were also assessed separately ($n = 986$) and compared with the placebo-treated patients in those studies ($n = 584$). The change in pain score with flexible-dose pregabalin was also significantly

Table 2. Baseline Demographic Characteristics by Duration of Pain

	< 6 Months		6 Months to < 1 Year		1 to < 2 Years		2 to < 5 Years		≥ 5 Years	
	PGB	PBO	PGB	PBO	PGB	PBO	PGB	PBO	PGB	PBO
n	329	218	360	210	805	457	1375	871	750	408
Female, *n* (%)	165 (50.2)	118 (54.1)	178 (49.4)	94 (44.8)	382 (47.5)	208 (45.5)	675 (49.1)	440 (50.5)	343 (45.7)	161 (39.5)
Male, *n* (%)	164 (49.8)	100 (45.9)	182 (50.6)	116 (55.2)	423 (52.5)	249 (54.5)	700 (50.9)	431 (49.5)	407 (54.3)	247 (60.5)
Race, *n* (%)										
White	145 (44.1)	91 (41.7)	187 (51.9)	109 (51.9)	391 (48.6)	210 (46.0)	715 (52.0)	406 (46.6)	550 (73.3)	284 (69.6)
Asian	168 (51.1)	116 (53.2)	159 (44.2)	93 (44.3)	356 (44.2)	213 (46.6)	556 (40.4)	399 (45.8)	153 (20.4)	85 (20.8)
Black	5 (1.5)	6 (2.8)	9 (2.5)	5 (2.4)	19 (2.4)	16 (3.5)	53 (3.9)	33 (3.8)	25 (3.3)	24 (5.9)
Other	11 (3.3)	5 (2.3)	5 (1.4)	3 (1.4)	39 (4.8)	18 (3.9)	51 (3.7)	33 (3.8)	22 (2.9)	15 (3.7)
Age, mean years (SD)	65.1 (10.9)	63.2 (10.9)	63.8 (12.8)	63.7 (12.1)	60.8 (12.7)	60.5 (12.1)	62.1 (11.1)	61.6 (11.6)	64.2 (11.4)	63.5 (11.3)
BMI, mean kg/m^2 (SD)	26.1 (5.0)	26.5 (6.0)	26.5 (6.4)	26.6 (6.0)	27.1 (5.7)	27.3 (6.3)	28.1 (6.2)	28.0 (6.4)	29.4 (6.5)	29.7 (7.0)

PGB, pregabalin (all doses); PBO, placebo; SD, standard deviation; BMI, body mass index.

Table 3. Baseline Clinical Characteristics by Duration of Pain

	< 6 Months		6 Months to < 1 Year		1 to < 2 Years		2 to < 5 Years		≥ 5 Years	
	PGB	PBO	PGB	PBO	PGB	PBO	PGB	PBO	PGB	PBO
Baseline pain score										
Mean (SD)	6.37 (1.46)	6.33 (1.42)	6.39 (1.48)	6.42 (1.46)	6.42 (1.50)	6.41 (1.54)	6.47 (1.47)	6.54 (1.41)	6.51 (1.53)	6.49 (1.48)
Median	6.29	6.14	6.29	6.31	6.33	6.29	6.43	6.57	6.57	6.43
Baseline MOS score, mean (SD)										
Sleep adequacy	50.75 (29.07)	53.59 (27.43)	47.30 (30.24)	52.79 (29.29)	49.95 (30.42)	49.48 (28.60)	47.83 (28.72)	49.18 (29.67)	46.05 (28.87)	46.68 (29.01)
Sleep problems index	37.45 (19.47)	35.56 (16.51)	40.76 (19.52)	36.26 (19.78)	41.48 (21.23)	41.52 (19.45)	41.98 (20.58)	40.24 (21.11)	44.72 (20.90)	44.23 (20.18)
Baseline HADS score, mean (SD)										
HAD S-A	5.59 (4.80)	5.02 (4.10)	5.63 (4.29)	5.38 (4.50)	7.06 (4.73)	6.45 (4.76)	6.38 (4.65)	6.07 (4.51)	6.64 (4.09)	6.93 (4.36)
HADS-D	5.48 (4.77)	4.46 (3.64)	6.01 (4.31)	5.95 (4.17)	6.71 (4.55)	6.09 (4.28)	6.09 (4.15)	5.80 (4.30)	5.71 (3.77)	6.11 (4.17)

Higher scores indicate better sleep adequacy. Lower scores indicate better sleep by the sleep problems index. MOS, Medical Outcomes Study; PGB, pregabalin (all doses); PBO, placebo; SD, standard deviation; HADS-A, Hospital Anxiety and Depression Scale—Anxiety; HADS-D, Hospital Anxiety and Depression Scale—Depression.

Figure 1. Change in pain score and PGIC responders at endpoint with pregabalin compared with placebo by duration of pain. (A) Change in pain score from baseline compared with placebo for each pain duration category and all patients together. (B) Proportion of Patient Global Impression of Change (PGIC) responders (patients "very much improved" or "much improved" at endpoint) with pregabalin and placebo for each pain duration category and all patients together. $^{**}P < 0.001$, $^{***}P < 0.0001$, for pregabalin compared with placebo. SE, standard error.

improved, compared with placebo, for patients of any pain duration (treatment difference [95% CI] −0.52 [−0.66, −0.38]) and for each pain duration category separately (data not presented). As with all pregabalin doses together, no consistent differences were observed between pain duration categories (data not presented).

Change in Function, Sleep, and Mood

There were significantly more PGIC responders with pregabalin, compared with placebo, for all pain duration categories together and individually (Figure 1B).

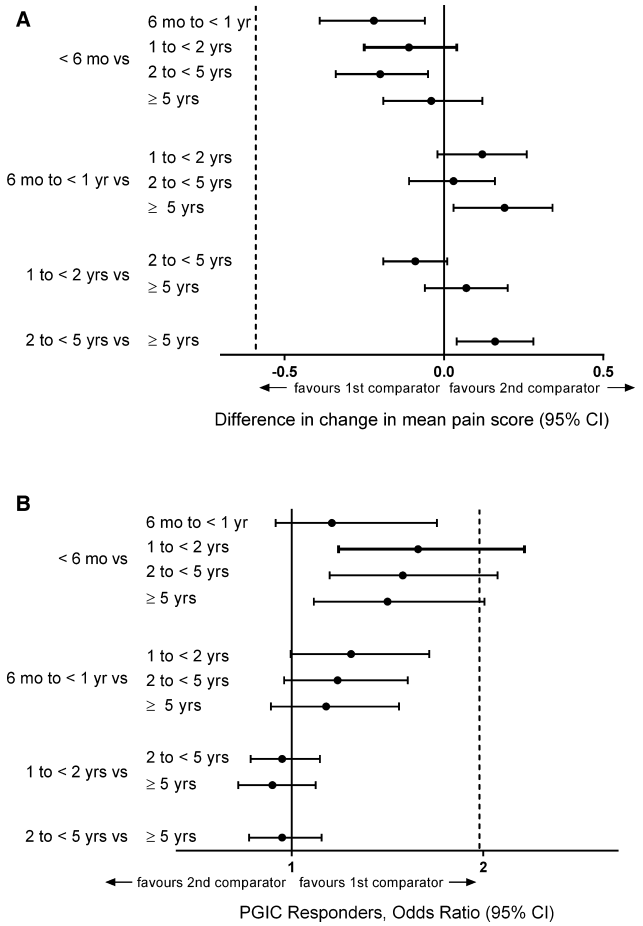

Figure 2. Comparison of treatment effect with pregabalin between each duration of pain category. (A) Difference in the change in mean pain score for pregabalin at a pain duration category vs. pregabalin at every other pain duration category. Dotted line shows treatment difference for pregabalin vs. placebo for all pain durations together (treatment difference [95% confidence interval (CI)], −0.59 [−0.67, −0.52]). (B) Odds ratios for pregabalin at a pain duration category vs. pregabalin at every other pain duration category. Dotted line shows odds ratio of pregabalin vs. placebo for all pain durations together (odds ratio [95% CI], 1.98 [1.72, 2.28]). PGIC, Patient Global Impression of Change.

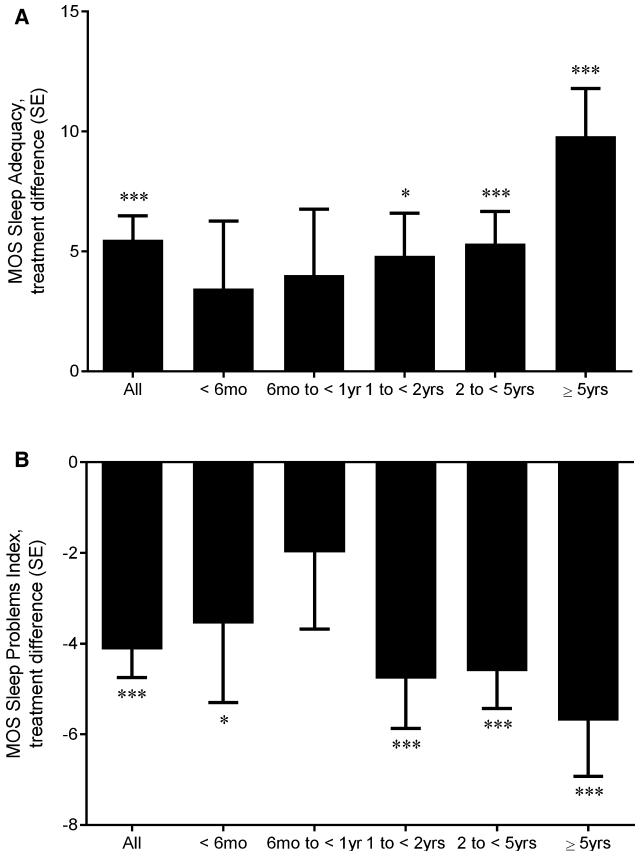

Figure 3. Change in Medical Outcomes Study (MOS) Sleep Scale by duration of pain. Change at endpoint from baseline for pregabalin compared with placebo in the MOS Sleep Scales of (A) sleep adequacy and (B) sleep problems index for each pain duration category and all patients together. Higher scores indicate better sleep adequacy. Lower scores indicate improved sleep by the sleep problems index. *$P < 0.05$, ***$P < 0.0001$, for pregabalin compared with placebo.

There was a slight trend toward a greater proportion of PGIC responders, as shown by odds ratio, in patients with a shorter duration of pain (Figure 2B). Patients with pain duration of < 6 months were statistically significantly more likely to be a PGIC responder than patients with pain duration of 1 year to < 2 years, 2 years to < 5 years, or ≥ 5 years ($P < 0.05$).

All patients together had significantly improved MOS sleep adequacy and sleep problems index scores at endpoint with pregabalin, compared with placebo (Figure 3). As assessed in each individual pain duration category, the improvement in sleep adequacy was significant in the majority of pain duration categories; these were the categories 1 year to < 2 years, 2 years to < 5 years, and ≥ 5 years. The improvement in sleep problems index was also significant in the majority of pain duration categories: < 6 months, 1 year to < 2 years, 2 years to < 5 years, and ≥ 5 years. For both sleep adequacy and sleep problems index, the improvement was the largest in the pain duration category ≥ 5 years.

Pregabalin significantly improved HADS-A and HADS-D scores at endpoint, compared with placebo, in all patients together (Table 4). When assessed by pain duration category, HADS-A scores were significantly improved for categories 1 year to < 2 years and 2 years to < 5 years, and HADS-D scores were significantly improved in the category 1 year to < 2 years. There were no significant differences in MOS or HADS scores

Table 4. Change in Hospital Anxiety and Depression (HADS) Scores at Endpoint by Duration of Pain

	< 6 Months	6 Months to < 1 Year	1 to < 2 Years	2 to < 5 Years	≥ 5 Years	All Durations
HADS-Anxiety						
LS mean treatment difference*	−0.37	0.03	−0.55	−0.50	−0.30	−0.34
95% CI	−1.14, 0.39	−0.71, 0.77	−1.05, −0.05	−0.86, −0.15	−0.83, 0.23	−0.61, −0.07
P value	0.3416	0.9421	0.0305	0.0058	0.2607	0.0133
HADS-Depression						
LS mean treatment difference*	−0.18	−0.58	−0.60	−0.33	−0.02	−0.34
95% CI	−0.94, 0.57	−1.31, 0.15	−1.09, −0.11	−0.68, 0.03	−0.54, 0.50	−0.61, −0.08
P value	0.6374	0.1186	0.0160	0.0692	0.9446	0.0115

LS, least squares; CI, confidence interval.
*Change from baseline at endpoint with pregabalin compared with placebo.

between pain duration categories when compared directly with each other (data not presented).

DISCUSSION

Pathways for the care of patients with neuropathic pain highlight the importance of starting treatment early to reduce the suffering of patients.[8] Determining the response of the patient to early, specific treatments for neuropathic pain, including immediate and frequent review to ensure the patient is quickly treated with the maximum tolerable dose, can also assist with proper diagnosis and reduce comorbidities, disability, and absenteeism.[2,8] Nevertheless, delays in diagnosis and treatment are not uncommon, and treatment is often not in line with current guidelines and recommendations.[7,40–42] There may be concerns, among some physicians, that patients with longer established neuropathic pain may not respond to approved treatment options such as pregabalin. This analysis demonstrates that even patients with a duration of pain of > 5 years respond similarly to treatment with pregabalin, with significant improvements in pain, function, and sleep.

Mean pain severity at baseline was similar in each pain duration category. The mean maintenance dose of flexible-dose pregabalin, escalated based on each patient's individual response and tolerability, was also similar in each pain duration category. Together, these data suggest little progression in pain intensity or need for higher doses of pregabalin over time in this patient population. At the same time, patients in the longer pain duration categories did appear to have poorer baseline sleep and mood, suggestive of some negative effects of prolonged chronic pain.

Trials with flexible dosing more closely resemble real-world clinical practice, where the dose should be tailored to the patient's needs.[12,35] In this analysis, those patients treated with flexible-dose pregabalin were also assessed for the change in pain score in each pain duration category to determine whether these patients responded differently to the full patient population (including patients treated with fixed-dose and flexible-dose pregabalin). The results of these analyses were consistent with results from the full patient population, further supporting the clinical applicability of these findings.

This analysis demonstrates that patients benefit from treatment with pregabalin regardless of their duration of pain. A trend suggested that patients are more satisfied with treatment if it is started earlier after diagnosis. The negative effects of ongoing neuropathic pain, as shown by worse sleep and mood in patients with longer duration of pain, also suggest that patients would benefit from initiating effective treatment earlier.

There appeared to be a trend toward higher BMI in patients with longer duration of pain, and pain could be a contributing factor to increasing BMI, which itself may have further negative health implications. This trend also corresponded to a smaller proportion of Asian patients in the longer pain duration groups. The Asian patients in these studies had a lower mean BMI, and this trend toward an increased BMI reflected the lower proportion of Asian patients in the longer pain duration categories with no such trend in Asian (or non-Asian) patients alone. It is not clear why Asian patients were notably less likely to have a longer duration of pain.

A recent comprehensive analysis reported adverse events and their time to onset and resolution in a broader selection of clinical trials of pregabalin in patients with pain disorders (including most of the studies in this analysis).[43] Analysis of adverse events in

the patient population in this study did not reveal any new safety information.

The results of this analysis contrast with those of an observational study in Spanish primary care, which showed a greater response to pregabalin in patients with shorter disease duration.[17] However, the patients in that study had a notably shorter disease duration (mean 0.9 years) than those in this analysis (where 80.7% of patients had pain duration > 1 year).[17] Furthermore, the observational study included a larger range of neuropathic pain conditions (mostly radiculopathy, a mixed patient group not included in this analysis), and the differences in response could have reflected differences in the distribution of pain conditions across pain duration categories.

There is evidence to suggest that initiating appropriate treatment prior to central sensitization can minimize the likelihood of neuropathic pain developing. For example, the use of preventative analgesia starting in the perioperative period can reduce the incidence of postsurgical pain.[44] However, once a peripheral neuropathic pain condition is established, there is no clear evidence that it becomes more difficult to treat over time. The results of this analysis support this conclusion, with patients responding equally well to treatment regardless of duration of disease.

The specificity of the clinical trial population included here could be viewed as a limitation of this analysis. These trials included only patients with moderate or severe neuropathic pain, with patients with less severe pain (mean pain scores of < 4) excluded and, for the most part, patients had relatively long durations of pain. However, the use of patient-level clinical trial data in this analysis allowed for a more accurate assessment of the treatment effect of pregabalin.

Physicians can be confident that patients with moderate or severe peripheral neuropathic pain respond equally well to treatment with pregabalin regardless of their duration of pain. Nevertheless, physicians should consider patients' associated symptoms and continue to follow treatment guidelines to start treatment as soon as possible to reduce patient suffering and the economic burden of neuropathic pain.

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DISCLOSURES

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REFERENCES

1. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. *Pain* 2014;155:654–662.

2. Haanpaa ML, Backonja MM, Bennett MI, et al. Assessment of neuropathic pain in primary care. *Am J Med* 2009;122:S13–S21.

3. Pérez C, Saldana MT, Navarro A, Vilardaga I, Rejas J. Prevalence and characterization of neuropathic pain in a primary-care setting in Spain: a cross-sectional, multicentre, observational study. *Clin Drug Invest* 2009;29:441–450.

4. Schaefer C, Sadosky A, Mann R, et al. Pain severity and the economic burden of neuropathic pain in the United States: BEAT Neuropathic Pain Observational Study. *Clinicoecon Outcomes Res.* 2014;6:483–496.

5. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain.* 2004;5:143–149.

6. Tolle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. *J Diabetes Complications* 2006;20:26–33.

7. Lynch ME, Campbell F, Clark AJ, et al. A systematic review of the effect of waiting for treatment for chronic pain. *Pain* 2008;136:97–116.

8. Smith BH, Lee J, Price C, Baranowski AP. Neuropathic pain: a pathway for care developed by the British Pain Society. *Br J Anaesth* 2013;111:73–79.

9. Pfizer Ltd. Lyrica® summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000546/WC500046602.pdf (accessed July 23, 2015).

10. Pfizer Inc. LYRICA prescribing information. http://www.pfizer.com/files/products/uspi_lyrica.pdf (accessed July 23, 2015).

11. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Am J Med* 2009;122:S22–S32.

12. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:e1113–e1188.

13. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American

Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758–1765.

14. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;63:959–965.

15. IMS MIDAS™. IMS MIDAS data from quarter ending June 2004 till quarter ending December 2014. Average daily dose based on IMS MIDAS data Q4 2014. Data on file.

16. Pérez C, Navarro A, Saldana MT, Figueras-Balsells M, Munoz-Tuduri M, Rejas J. Cost savings associated with early initiation of pregabalin in the management of peripheral neuropathic pain. *Clin J Pain* 2013;29:471–477.

17. Blanco Tarrio E, Galvez Mateos R, Zamorano Bayarri E, Lopez Gomez V, Perez Paramo M. Effectiveness of pregabalin as monotherapy or combination therapy for neuropathic pain in patients unresponsive to previous treatments in a Spanish primary care setting. *Clin Drug Invest* 2013;33:633–645.

18. Tolle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. *Eur J Pain* 2008;12:203–213.

19. Freeman R, Emir B, Parsons B. Predictors of placebo response in peripheral neuropathic pain: insights from pregabalin clinical trials. *J Pain Res*. 2015;8:257–268.

20. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *BMC Neurol*. 2008;8:33.

21. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med* 2011;28:109–116.

22. Raskin P, Huffman C, Yurkewicz L, et al. Pregabalin in subjects with painful diabetic peripheral neuropathy using an NSAID for other pain conditions: a double-blind crossover study. *Clin J Pain* 2015;32:203–210.

23. Huffman C, Stacey BR, Tuchman M, et al. Efficacy and safety of pregabalin in the treatment of patients with painful diabetic peripheral neuropathy and pain on walking. *Clin J Pain* 2015;31:946–958.

24. Sharma U, Griesing T, Emir B, Young JP Jr. Time to onset of neuropathic pain reduction: a retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. *Am J Ther* 2010;17:577–585.

25. Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004;109:26–35.

26. Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2003;60:1274–1283.

27. van Seventer R, Feister HA, Young JP Jr, Stoker M, Versavel M, Rigaudy L. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin* 2006;22:375–384.

28. Stacey BR, Barrett JA, Whalen E, Phillips KF, Rowbotham MC. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain*. 2008;9:1006–1017.

29. Ogawa S, Suzuki M, Arakawa A, Araki S, Yoshiyama T. Efficacy and tolerability of pregabalin for postherpetic neuralgia: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *J Japan Soc Pain Clinicians*. 2010;17:141–152.

30. Liu Q, Chen H, Xi L, et al. A randomized, double-blind placebo-controlled trial to evaluate the efficacy and safety of pregabalin for postherpetic neuralgia in a population of Chinese patients. *Pain Pract*. 2015;doi: 10.1111/papr.12413. [Epub ahead of print].

31. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain* 2005;115:254–263.

32. Guan Y, Ding X, Cheng Y, et al. Efficacy of pregabalin for peripheral neuropathic pain: results of an 8-week, flexible-dose, double-blind, placebo-controlled study conducted in China. *Clin Ther* 2011;33:159–166.

33. van Seventer R, Bach FW, Toth CC, et al. Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. *Eur J Neurol* 2010;17:1082–1089.

34. Moon DE, Lee DI, Lee SC, et al. Efficacy and tolerability of pregabalin using a flexible, optimized dose schedule in Korean patients with peripheral neuropathic pain: a 10-week, randomized, double-blind, placebo-controlled, multicenter study. *Clin Ther* 2010;32:2370–2385.

35. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care* 2008;31:1448–1454.

36. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology* 2006;67:1792–1800.

37. Cardenas DD, Nieshoff EC, Suda K, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. *Neurology* 2013;80:533–539.

38. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE Jr, eds. *Measuring Functioning and Well-Being*. Durham, NC, USA: Duke University Press; 1992:235–239.

39. Snaith RP, Zigmond AS. *The Hospital Anxiety and Depression Scale Manual*. London: NFER Nelson; 1994.

40. Choiniere M, Dion D, Peng P, et al. The Canadian STOP-PAIN project—part 1: who are the patients on the waitlists of multidisciplinary pain treatment facilities? *Can J Anaesth* 2010;57:539–548.

41. Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Fam Pract*. 2013;14:28.

42. Mafi JN, McCarthy EP, Davis RB, Landon BE. Worsening trends in the management and treatment of back pain. *JAMA Intern Med* 2013;173:1573–1581.

43. Freynhagen R, Serpell M, Emir B, et al. A comprehensive drug safety evaluation of pregabalin in peripheral neuropathic pain. *Pain Pract*. 2015;15:47–57.

44. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. *Local Reg Anesth*. 2014;7:17–22.