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Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial

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Abstract

This study was designed to assess the efficacy and safety of pregabalin—a novel α_2-δ ligand with analgesic, anxiolytic, and anticonvulsant activity—for treating neuropathic pain in patients with post-herpetic neuralgia (PHN). Two hundred and thirty-eight patients were randomised into this multicentre, doubleblind, placebo-controlled trial to receive 150 ($n = 81$), 300 mg/day ($n = 76$) pregabalin, or placebo ($n = 81$) for 8 weeks. Among the exclusion criteria was failure to respond to previous treatment for PHN with gabapentin at doses ≥ 1200 mg/day. Endpoint mean pain scores were significantly reduced in patients receiving 150 or 300 mg/day pregabalin compared with placebo. Efficacy was observed as early as week 1 and was maintained throughout the study. Significantly more patients in both pregabalin groups (150 mg, 26%; 300 mg, 28%) were responders ($\geq 50\%$ decrease in mean pain score from baseline to endpoint) than in the placebo group (10%). Additionally, by week 1 and for the study's duration, 150 and 300 mg/day pregabalin significantly reduced weekly mean sleep interference scores. More pregabalin-treated patients than placebo-treated patients reported that they were 'much improved' or 'very much improved'. Health-related quality-of-life (HRQoL) measurements using the SF-36 Health Survey demonstrated improvement in the mental health domain for both pregabalin dosages, and bodily pain and vitality domains were improved in the 300 mg/day group. The most frequent adverse events were dizziness, somnolence, peripheral oedema, headache, and dry mouth. Pregabalin efficaciously treated the neuropathic pain of PHN. Additionally, pregabalin was associated with decreased sleep interference and significant improvements in HRQoL measures.
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1. Introduction

Post-herpetic neuralgia (PHN) has been variously defined as pain lasting as little as 1 month after rash onset to as many as 6 months beyond the crusting of the skin lesions after an acute attack of herpes zoster (HZ); (Dworkin and Portenoy, 1996). Depending on the definition used, 10–15% of patients will develop PHN following an attack of HZ (Bowsher, 1994; Goh and Khoo, 1997; Kost and Straus, 1996; Lee and Gauci, 1994; Schmader, 1998). Prognostic factors for PHN are age, concomitant diseases (e.g. malignancies or diabetes), the extension or localisation of the primary lesion or the number of lesions, permanent sensory loss in the affected area, and the severity of the acute herpetic pain (Goh and Khoo, 1997; Helgason et al., 2000; Meister et al., 1998; Schmader, 1998). PHN is characterised by burning, lancinating, or stabbing pain. Allodynia and/or hyperaesthesia of the affected dermatome

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is common (Engberg et al., 1995; Dworkin and Portenoy, 1996; Gershon, 1996; Helgason et al., 2000). More than half of the patients with PHN have sleep disturbances and decreased daily activity, and social life is affected in about one quarter (Engberg et al., 1995).

Tricyclic antidepressants and opioid analgesics, such as slow-release morphine or oxycodone, have been shown to be effective in controlling pain in PHN (Max et al., 1988; Rowbotham, 1994; Watson, 2000; Watson and Babul, 1998; Watson et al., 1998). However, their use may be limited by side effects. Gabapentin is effective in the treatment of PHN, but its intersubject variability and nonlinear pharmacokinetics make it difficult to predict the appropriate dose or which patients are likely to achieve a meaningful clinical response (Filadora et al., 1999; Rice and Maton, 2001; Rowbotham et al., 1998; Segal and Rordorf, 1996).

Pregabalin is an alpha$_2$-delta (α_2-δ) ligand that has analgesic, anxiolytic, and anticonvulsant activity. α_2-δ is an auxiliary protein associated with voltage-gated calcium channels. Pregabalin binds potently to the α_2-δ subunit (Gee et al., 1996). Potent binding at this site reduces calcium influx at nerve terminals and, thereby, reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P (Dooley, et al., 2000a,b; Fink et al., 2002; Maneuf et al., 2001). These activities and effects result in the analgesic, anxiolytic, and anticonvulsant activity exhibited by pregabalin. Pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors, it is not converted metabolically into GABA or a GABA antagonist, and it does not alter GABA uptake or degradation (Bialer et al., 1999; Welty et al., 1997).

Although it is structurally and mechanistically related to gabapentin, pregabalin has linear pharmacokinetics with low intersubject variability, and its binding affinity for the α_2-δ subunit is six times more potent than that of gabapentin (Jones and Sorkin, 1998). The randomised, doubleblind, placebo-controlled trial described in this article examined the efficacy and safety of pregabalin at doses of 150 and 300 mg/day in patients with PHN.

2. Methods

This study was conducted at 53 sites in Europe and Australia. The first patient visit was on 17 February 1999, and the last patient observation was recorded on 19 June 2000. It adhered to the Declaration of Helsinki and to Good Clinical Practice guidelines, and this report has been prepared in accordance with CONSORT guidelines. The protocol and informed consent document were reviewed and approved by the appropriate Institutional Review Board or Ethics Committee for each respective site. All patients provided written informed consent at study screening before receiving any study medication.

The study was comprised of two phases: a 1-week baseline and an 8-week, doubleblind treatment phase (1-week forced titration period followed by 7-week, fixed-dose period). All medications were blinded and taken orally. Placebo capsules were identical in appearance to capsules containing active drug. Study medication was packaged and labeled with sequential randomisation numbers according to a randomisation schedule generated with a block size of 6 and according to a computer-generated code.

During baseline and treatment phases, patients recorded daily pain scores and sleep interference scores in daily diaries. On awakening, patients evaluated their pain for the previous 24 h by circling numbers that best described their pain on an 11 point Numerical Rating Scale (NRS), where 0 indicates no pain or sleep interference and 10 is the worst possible pain or sleep interference. Patients who met all inclusion criteria were randomised to receive 150 [50 mg, three times a day (TID)], 300 mg/day pregabalin (100 mg, TID), or placebo. Patients were evaluated at clinic visits that took place at 1–3-week intervals throughout the study. Following completion of the study, patients at most sites were eligible to continue open-label treatment with pregabalin.

Patients with pain present for more than 6 months after healing of the HZ rash were eligible to participate in the study. Patients were men or women 18 years of age or older. Female patients were required to be non-pregnant, non-lactating, and either post-menopausal, surgically sterilised, or using an appropriate method of contraception. Patients needed to have completed at least four daily pain diaries during the 7 day baseline phase, with an average daily pain score ≥ 4. Patients were also required to score ≥ 40 mm on the 100 mm visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire (SFMPQ) at the baseline and randomisation visits.

Patients were excluded if they suffered from active malignancy or any clinically significant respiratory, haematologic, hepatic, or cardiovascular disease. Patients were excluded if they had failed to respond to previous treatment for PHN with gabapentin at doses ≥ 1200 mg/day or if they had undergone neurolytic or neurosurgical therapy for PHN. Patients with a skin condition or severe non-PHN pain that might compromise evaluation of pain caused by PHN were excluded. Patients with creatinine clearance ≤ 30 ml/min (estimated from serum creatinine using the Cockcroft–Gault formula) were excluded. Patients were allowed to continue a stable treatment regimen of acetaminophen (up to 3 g/day), non-steroidal anti-inflammatory drugs, opioid or non-opioid analgesics, or antidepressants. No new analgesic therapies were to be initiated at any time during the trial. Benzodiazepines and anticonvulsants were to be discontinued at least 14 days before receiving study medication.

The primary efficacy parameter was the endpoint mean pain score, defined as the mean of the last seven pain NRS diary entries while on study medication, including the entry made on the day after the last dose (Farrar et al., 2001). If fewer than seven scores were recorded post-baseline, the available scores (after day 1 on treatment) were used to

determine a mean. Least squares weekly mean pain scores were also computed for each week in the study. Secondary efficacy parameters included:

- Mean Sleep Interference Scores (how pain interfered with sleep) computed for each week and at the last visit, as described for the weekly mean pain score.
- Patient, and Clinical, Global Impression of Change [global change from baseline according to patient (PGIC) or clinician (CGIC)] on a 7-point, Likert scale: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse.
- SF-36 Health Survey (SF-36); (Ware and Sherbourne, 1992), measuring eight health domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception.
- Zung Self-Rating Depression Scale (Zung, 1965), a self-administered questionnaire that measures physical and psychologic symptoms of depression. Patients provided information on how frequently each of 20 statements about their feelings or psychologic states were true. Individual item scores were summed to yield a total score.
- The VAS of the SFMPQ (Melzack, 1987) provided a rating of pain over the past week on a 100-mm line.

Safety was assessed using adverse events (AEs) data, clinical laboratory data, and the results of physical examinations, neurologic examinations, and 12-lead electrocardiograms (ECG). Intensity of AEs was rated as follows: *mild*, subject/patient is aware of the sign or symptom but finds it easily tolerated; *moderate*, subject/patient has discomfort enough to cause interference with or change in usual activities; *severe*, subject/patient is incapacitated and unable to work or participate in many or all usual activities.

Efficacy analyses and safety evaluations were based on data from the Intent-to-Treat population (ITT population), defined as all randomised patients who received at least one dose of study medication. A supplemental analysis was performed using data from the per protocol population, defined as the population of randomised patients who had no major protocol violations that would be likely to affect pain assessment. The selection criteria for the per protocol population were defined during the blinded review of patient data.

The targeted sample size was estimated from treatment differences previously reported in similar studies in neuropathic pain (Backonja et al., 1998; Rowbotham et al., 1998). This sample size would provide 90% power to detect a difference of 1.3 on endpoint mean pain score at the 0.025 level. This type I error level was used in accordance with the Hochberg procedure to guarantee an experiment-wise type I error rate of 0.05 in the presence of two principal comparisons (150 mg/day pregabalin vs. placebo and 300 mg/day pregabalin vs. placebo).

Mean pain scores, mean sleep interference scores, SFMPQ VAS scores, Zung Index score, and SF36 domains were analysed using an analysis of covariance (ANCOVA) main effects model, with treatment and cluster (group of centres) as fixed effects and with the baseline scores as covariate.

Study medication was packaged and labelled with sequential randomisation numbers according to a randomisation schedule generated with a block size of 6 and according to a computer generated code. All capsules were identical in size and appearance. An investigator could break the randomisation code and, thus, the blind for a patient if a medical emergency occurred.

2.1. Role of the funding source

The sponsors of the study helped develop and approved the study design, managed the study, performed the biostatistical analysis, and provided editorial assistance for the preparation of the paper.

3. Results

A total of 307 patients were screened, and 238 patients were randomised and received study medication. Fifty-four screened patients were excluded for failing to meet study criteria, and 15 were excluded for administrative or other reasons. Eighty-one patients received 150 mg/day pregabalin, 76 patients received 300 mg/day pregabalin, and 81 patients received placebo (Fig. 1, Table 1).

3.1. Efficacy

In the ITT population, the endpoint mean pain scores for both the pregabalin 150 mg/day group and the pregabalin 300 mg/day group were significantly lower than scores in the placebo group (Table 2). In the observed-cases analysis of the weekly scores, both the 150 and 300 mg/day pregabalin groups were significantly improved compared with placebo as early as week 1, and the improvement was sustained throughout the study (Fig. 2). Per protocol analysis confirmed these results (Table 2).

The study design employed a rigorous definition of response: patients who had a decrease in mean pain score of at least 50% from baseline to endpoint were defined as responders. Based on a Cochran–Mantel–Haenszel analysis adjusting for cluster, there were statistically significantly greater proportions of responders among the ITT population in the 150 (21/81, 26%, $P = 0.006$) and 300 mg/day (21/76, 28%, $P = 0.003$) pregabalin groups than in the placebo group (8/81, 10%). At endpoint both the 150 (52.03, $P = 0.006$) and the 300 (48.41,

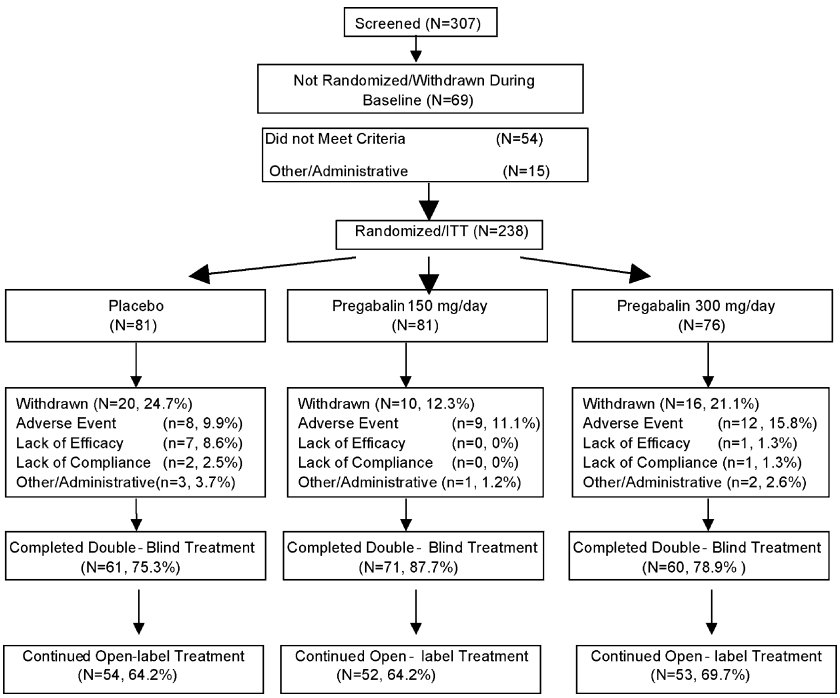


Fig. 1. Summary of patient disposition.

Table 1
Summary of patient characteristics (intent-to-treat population)

Characteristics		Placebo, ($N = 81$)	Pregabalin	
			150 mg/day, ($N = 81$)	300 mg/day, ($N = 76$)
Sex, *N* (%)	Male	37(46)	39(48)	31(41)
	Female	44(54)	42(52)	45(59)
	Pre-menopausal	2(5)	2(5)	1(2)
	Post-menopausal	42(95)	40(95)	44(98)
Race, *N* (%)	White	81(100)	79(98)	76(100)
	Black	0(0)	2(2)	0(0)
Age (years)	Mean (SD)	73.2(10.3)	71.3(10.1)	71.9(10.3)
	Median	74	73	74
	Min/max	36/96	43/88	32/90
Estimated	Mean (SD)	60.5(18.5)	62.9(20.3)	58.9(21.0)
Creatinine	Median	58.0	60.0	54.5
Clearance (ml/min)	Min/max	31.0/104.0	31.0/116.0	23.0/158.0
Duration of PHN (months)	Mean (SD)	44.8(46.3)	40.9(41.8)	40.7(42.1)
	Median	32	29	30.5
	Min/max	0/267	5/243	1/215
Baseline mean pain score	Mean (SD)	6.6(1.6)	6.9(1.7)	7.0(1.6)
	Median	6.7	7.1	7
	Min/max	4/10	4/10	4/10
Concomitant drugs (patients may be taking > 1)	Analgesics[a]	31	46	42
	Anti-inflammatories[b]	12	21	17
	Antidepressants[c]	18	17	22

[a] Includes acetaminophen/paracetamol (62), codeine (1), lidocaine (2), morphine/morphine sulfate (5), oxycodone (1), panadeine (13), and tramadol/tramadol HCl (33).

[b] Includes aspirin (34); celecoxib (1), ibuprofen (11), and naproxen (4).

[c] Includes amitriptyline/amitriptyline HCl (37), citalopram/citalopram HBr (3), clomipramine (2), fluoxetine/fluoxetine HCL (3), imipramine (2), nortriptyline (1), paroxetine/paroxetine HCl (4), and sertraline/sertraline HCl (5).

Table 2
Endpoint mean pain scores: results analysis of covariance

Treatment	*N*	Least-square means	SE	Comparison pregabalin–placebo		
				Difference	95% CI	*P*-value
ITT Population						
Placebo	81	6.33	0.22			
Pregabalin (150 mg/day)	81	5.14	0.22	−1.20	(−1.81, −0.58)	0.0002
Pregabalin (300 mg/day)	76	4.76	0.23	−1.57	(−2.20, −0.95)	0.0001
Per protocol population						
Placebo	73	6.31	0.23			
Pregabalin (150 mg/day)	67	5.10	0.24	−1.21	(−1.88, −0.55)	0.0004
Pregabalin (300 mg/day)	65	4.66	0.25	−1.65	(−2.32, −0.98)	0.0001

SE, standard error; CI, confidence interval. Endpoint: last seven available scores while on study medication, up to and including day after last dose.

$P = 0.0003$) mg/day pregabalin groups had statistically significantly better mean VAS scores than in the placebo treatment group (62.05); (Table 3).

Pregabalin also significantly improved mean sleep-interference scores among the ITT population. At endpoint, 150 (3.13, $P = 0.0003$) and 300 mg/day pregabalin (2.81, $P = 0.0001$) were both significantly superior to placebo (4.24) in reducing patients' pain-associated sleep interference (Table 4). This effect was evident as early as week 1, and it was maintained throughout the study (Fig. 3).

Among patients receiving pregabalin 150 mg/day, 25/81 (31%)—compared with 11/81 (14%) on placebo—rated themselves 'much improved' or 'very much improved' on the PGIC at endpoint [($P = 0.064$); (a total of 44/81 (55%) were at least minimally improved)]. Among patients receiving 300 mg/day pregabalin, 29/76 (40%) rated themselves 'much improved' or 'very much improved' [($P = 0.002$); (a total of 44/76 (60%) were at least minimally improved)] (Fig. 4).

Health-related quality of life (HRQoL) was assessed using the SF-36 Health Survey. Each of the eight domains of the SF-36 was analysed separately. The 150 and 300 mg/day pregabalin groups were significantly superior to placebo in the Mental Health domain [least-square (LS) means difference from placebo 5.72 and 6.05 for 150 and 300 mg/day pregabalin groups, respectively; $P = 0.043$ for each]. The 300 mg/day pregabalin group showed significant improvement over placebo in the Bodily Pain domain (LS means difference 9.58; $P = 0.005$) and in the Vitality domain (LS means difference from placebo 7.11; $P = 0.044$). While the 150 mg/day pregabalin group showed numerically greater improvement than placebo ($P = 0.056$) on the Zung Self-Rating Depression Scale index, the 300 mg/day pregabalin group showed statistically significant improvement (LS means difference from placebo 4.01, $P = 0.024$); (Table 5).

3.2. Safety

Pregabalin was well tolerated at both dosages. The most frequently (in ≥10% of patients in either PGB group) occurring AEs were dizziness, somnolence, peripheral oedema, headache, and dry mouth (Table 6). The occurrence of AEs appeared to be dose-related. Although most patients (83%) receiving pregabalin 300 mg/day reported one or more AEs, the events were most often mild (37%) or moderate (34%) in intensity. Severe AEs were similarly distributed among the three treatment groups. Eighty-eight and 79% of patients treated with pregabalin 150 and 300 mg/day, respectively, completed the study, while 75% of patients treated with placebo completed it (Fig. 1). Few patients withdrew from the trial because of AEs: 9 from the 150 mg/day pregabalin group, 12 from the 300 mg/day group, and 8 from the placebo group (Fig. 1).

The median duration of the most frequently occurring events was examined in patients who completed the study. Among those patients, the median duration of dizziness was approximately 9 days for the 150 mg/day pregabalin group, 21 days for the 300 mg/day pregabalin group, and 18 days for the placebo group. The median duration of somnolence was 32–35 days among all three treatment groups.

The proportion of patients with possibly clinically important changes in laboratory values was similar among the treatment groups, and no clinically relevant trends were observed. Three patients in the 150 mg/day group, two in

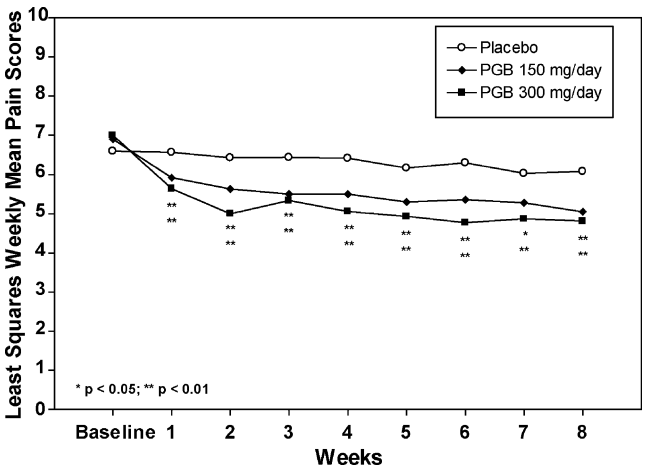


Fig. 2. Weekly least-square mean pain scores.

Table 3
Endpoint shortform McGill Pain Questionnaire visual analogue scale: results of analysis of covariance

Treatment	*N*	Least-square means	SE	Comparison pregabalin–placebo		
				Difference	95% CI	*P*-value
ITT population						
Placebo	80	62.05	2.56			
Pregabalin (150 mg/day)	80	52.03	2.56	−10.02	(−17.15, 2.90)	0.0060
Pregabalin (300 mg/day)	76	48.41	2.63	−13.64	(−20.87, −6.40)	0.0003

SE, standard error; CI, confidence interval. Endpoint: last seven available scores while on study medication, up to and including day after last dose.

Table 4
Endpoint mean sleep interference score: results of analysis of covariance

Treatment	*N*	Least-square means	SE	Comparison pregabalin–placebo		
				Difference	95% CI	*P*-value
ITT population						
Placebo	81	4.24	0.21			
Pregabalin (150 mg/day)	81	3.13	0.21	−1.11	(−1.71, −0.51)	0.0003
Pregabalin (300 mg/day)	76	2.81	0.22	−1.43	(−2.04, −0.82)	0.0001

SE, standard error; CI, confidence interval. Endpoint: last seven available scores while on study medication, up to and including the day after last dose.

the 300 mg/day group, and four in the placebo group had significant new ECG findings during the study. These changes were unlikely to be related to study drug, and there was no dose-related trend. There were no clinically significant changes in physical examination parameters in any of the treatment groups. More patients in the 300 mg/day pregabalin group (14%) experienced weight gain >7% from baseline to termination than in the 150 mg/day pregabalin group (4%) or the placebo group (4%). Three patients reported weight gain as an AE, and no patients discontinued the study because of weight gain.

In the placebo group, one patient, a 74-year-old man, died of myocardial infarction. Eight patients (4 in the pregabalin 150 mg/day group, 1 in the pregabalin 300 mg/day group, and 3 in the placebo group) experienced serious AEs during the study. Two patients receiving pregabalin 150 mg/day and one patient receiving placebo experienced ventricular extrasystoles that were considered serious and possibly or probably related to study medication. No other specific, serious AE was reported by more than one patient in any treatment group. One CNS-related serious AE was reported: a patient receiving pregabalin 150 mg/day reported confusion beginning on study day 7 and lasting for 2 days. The subject discontinued study drug, and the confusion resolved.

4. Discussion

In this PHN trial, patients receiving 150 or 300 mg/day pregabalin (given TID) showed statistically and clinically

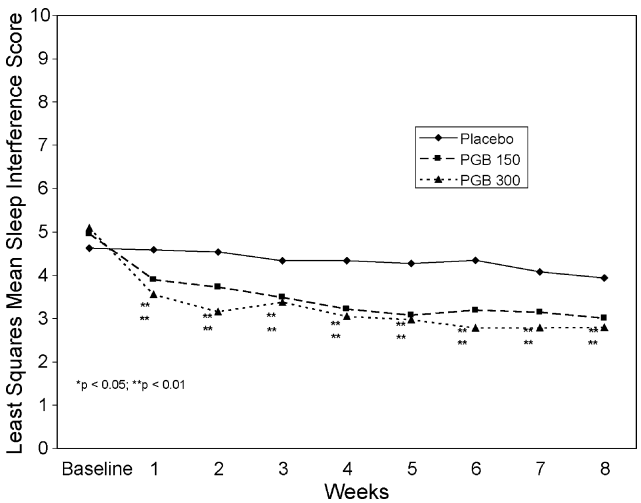


Fig. 3. Weekly least-square mean sleep interference scores.

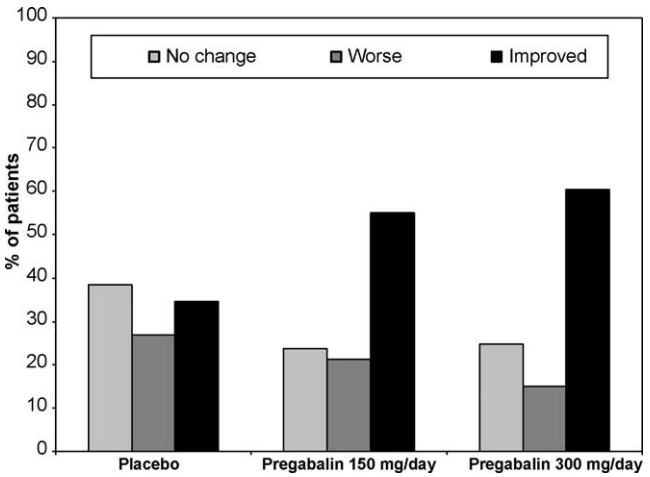


Fig. 4. Patient global impression of change.

Table 5
Zung Self-Rating Scale Index Scores: results of analysis of covariance

Treatment	N	Least-square means	SE	Comparison pregabalin–placebo			
				Difference	95% CI	Unadjusted *P*-value	Adjusted[a] *P*-value
Placebo	77	50.64	1.10				
Pregabalin (150 mg/day)	78	47.66	1.10	−2.97	(−6.03, 0.08)	0.0560	0.0560
Pregabalin (300 mg/day)	73	46.62	1.13	−4.01	(−7.13, −0.89)	0.0120	0.0240

SE, Standard error; CI, confidence interval.
[a] Adjustment based on Hochberg's procedure for the two pairwise comparisons vs. PBO.

significant improvement in endpoint mean pain score compared with placebo patients. Pain relief occurred as early as the first week of treatment, and it was sustained throughout the 8-week study. The effect on the pain score was consistent with improvements on secondary measures of analgesic efficacy and of sleep disturbance—both of which improved by week 1 and remained improved throughout the study period. Patient and clinician global impressions of change and mood and HRQoL measures were also improved at each timepoint measured.

The significantly higher percentage of responders in the 150 and 300 mg/day pregabalin groups (26 and 28%, respectively) than in the placebo group (10%) strongly supports pregabalin's efficacy for a substantial proportion of patients. This result was based on a stringent definition of responders as those who had a ≥50% reduction in endpoint mean pain score from baseline. Farrar has argued that a lesser, 30% reduction in pain score represents a clinically important improvement (Farrar et al., 2001). Were this definition used, the percentages of responders in the study would increase to 37% in the 150 mg/day, 50% in the 300 mg/day, and 19% in the placebo groups. Thus, both pregabalin doses provided clinically meaningful pain relief.

Two methodologic aspects of this study require comment. In this study, approximately two-thirds of patients took concomitant medication for analgesia, and the proportion of patients taking concomitant medication was well balanced across treatment groups (Table 1). After adjusting for concomitant use of other pain medication (stable use of antidepressants, anticonvulsants, opioids, and/or other pain medications), analysis indicates that the treatment effect is similar regardless of whether patients used any concomitant pain medications. Given that a majority of patients took concomitant medication(s), that the mean pain score at baseline was 6.6, 6.9, and 7.0 in the placebo, 150 mg/day, and 300 mg/day pregabalin groups, respectively, and that mean duration of PHN was >40 months, one might reasonably conclude that the patients included in this study were largely refractory to previous treatment.

Failure to respond to previous treatment for PHN with gabapentin at doses of ≥1200 mg/day was an exclusion criterion in this study. This criterion was added to the protocol, in part, because at the time of the study's design, there were experimental indications that pregabalin and gabapentin might act via similar mechanisms. Principles of rational therapy suggested that patients failing high-dose gabapentin should not be included in this randomised, placebo-controlled trial.

Among the more intriguing findings of this study are the salubrious effects associated with pregabalin on comorbid symptomatology and on HRQoL. Both pregabalin dosages produced statistically significant improvements in the CGIC and in the SF-36 Mental Health domain. The 300 mg/day dose also showed significant improvements in the PGIC, the SF36 Bodily Pain and Vitality domains, and the Zung Index score.

Sleep disturbance and neuropathic pain are significant comorbidities in PHN: each can exacerbate the other. Thus, improvement of a comorbid sleep disturbance should be among the goals of clinical management of patients with neuropathic pain. Treatment with pregabalin substantially improved patients' sleep from the first few days of the forced titration period through the remainder of the study, with very little sleep interference reported.

This reduction in sleep disturbance may be interpreted as an indirect effect of pregabalin, owing to reduction of neuropathic pain intensity or to improvement of sleep quality. Pregabalin has been shown to be effective in increasing the duration of non-rapid eye movement sleep (NREMS) along with decreasing rapid eye movement sleep (REMS) in rats (Kubota et al., 2001). Furthermore, an increase in slow-wave sleep has been demonstrated during

Table 6
Most frequently occurring AEs, number (% of patients)

Adverse event preferred term	Placebo (*N* = 81)	Pregabalin	
		150 mg/day, (*N* = 81)	300 mg/day, (*N* = 76)
Dizziness	12 (15)	10 (12)	21 (28)
Somnolence	6 (77)	12 (15)	18 (24)
Peripheral oedema	0 (0)	2 (3)	10 (13)
Headache	3 (4)	9 (11)	8 (11)
Dry mouth	3 (4)	9 (11)	5 (7)
Infection	0 (0)	2 (3)	5 (7)
Diarrhoea	4 (5)	4 (5)	4 (5)
Asthenia	4 (5)	5 (6)	2 (3)

AEs reported by at least 5% of patients in any pregabalin treatment group.

polysomnography study in healthy volunteers (Hindmarch et al., 2001). Slow-wave sleep has been correlated with the restorative aspects of sleep. These findings suggest pregabalin may have a direct effect on sleep architecture. Additional polysomnography studies are underway to investigate this hypothesis.

PHN has a substantial, deleterious effect on mood. In this study, the Zung Self-Rating Depression Scale was used to assess depression. At the beginning of the trial, the mean index scores by treatment group fell into the minimal to mild depression category. Patients treated with pregabalin 300 mg/day improved their Zung Index scores significantly vs. placebo. Given the relatively short duration of this study, these improvements in HRQoL measures are promising.

Among the general population, anxiety disorders are common, with a lifetime prevalence of 25% (Kessler et al., 1994), and patients suffering from chronic pain are more than four times as likely to have an anxiety disorder than are persons who do not have chronic pain (Gureje et al., 1998). Pregabalin has shown anxiolytic efficacy in several controlled studies of anxiety disorders (Feltner et al., 2000; Pande et al., 2000). Its dual effect of efficacy for pain and for symptoms of anxiety (independent of pain relief) may prove to be highly beneficial clinically.

No significant safety concerns were noted. The most frequently occurring AEs, dizziness and somnolence, were mild to moderate in intensity. The duration of these AEs was often shorter than the study duration, meaning they often resolved with continued treatment. A dose-dependent increase in weight—although not considered important by the patients—was evident in some of the pregabalin-treated patients. Another potential dose-dependent effect was peripheral oedema, which was without clinical significance, was not related to underlying cardiac failure, and did not lead to cardiovascular complications. More patients in the pregabalin-treatment groups completed the study than did patients in the placebo group. This suggests that AEs associated with pregabalin may have been of less importance to the majority of treated patients than was the clinically meaningful pain relief they derived from therapy.

Results from this study confirm those reported by Dworkin et al., (2003), in which mean pain score, with a pregabalin dosage of 600 mg/day, was significantly decreased at endpoint. In the present study, endpoint mean pain scores in the 300 mg/day pregabalin group decreased by 1.57 ($P = 0.0001$) and in the 150 mg/day group by 1.20 ($P = 0.0002$).

Comparisons between pregabalin and other drugs used to treat PHN are, as yet, somewhat difficult to make, as direct comparator trials in PHN have not yet been undertaken. However, although Watson has reported that many patients achieve satisfactory pain relief (as assessed by 100-mm VAS) with amitriptyline or nortriptyline, he cautions that the well-documented TCA AE profile limits TCAs' effectiveness in the long term—particularly in the elderly—and that pain relief is rarely complete (Watson, 2000; Watson et al., 1982, 1998). Further, the American Geriatrics Society has issued therapeutic guidelines suggesting that TCAs 'often demonstrate unacceptable side effects in elderly persons' (AGS, 2002). Pregabalin's benign side-effects in this trial of mostly elderly patients suggest it offers advantages in terms of tolerability to TCAs. And although no clinical trials comparing pregabalin with gabapentin have yet been conducted, it appears that pregabalin has a more rapid onset of action than does gabapentin.

In summary, pregabalin produced clinically significant reductions in pain, as well as improvement of sleep, mood disturbances, and HRQoL in subjects suffering from PHN. Clinically meaningful pain relief was evident by the first week of treatment, and it was maintained for the duration of the study. As expected, owing to pregabalin's linear PK, the 300 mg/day dose provided additional therapeutic benefit beyond that provided by 150 mg/day. Both dosages were well tolerated, and 64% of patients treated with 150 mg/day and 70% of patients treated with 300 mg/day pregabalin elected to continue study medication in the open-label phase. Based on the results of this trial, pregabalin has substantial promise as therapy for PHN and could be a welcome addition to the armamentarium of agents used to treat neuropathic pain syndromes.

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Appendix A

Contributors

R. Sabatowski, R. Galvez, and D. Cherry were investigators and contributed the introduction and discussion of the publication. R. Allen helped design the study while employed by Parke-Davis but has since left the company and did not contribute to this manuscript. F. Jacquot was the study manager and M. Versavel the medical monitor, who reviewed and edited the publication. E. Vincent and P. Maisonobe were the study biostatisticians.

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