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Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study

Thomas Tölle [a,*], Rainer Freynhagen [b], Mark Versavel [c], Uwe Trostmann [d], James P. Young Jr. [e]

[a] *Neurologic Clinic, Technical University of Münich, Germany*
[b] *Universitätsklinikum Düsseldorf, Klinik für Anaesthesiologie, Moorenstr. 5, 40225 Düsseldorf, Germany*
[c] *Pfizer Global R&D, Eastern Point Road 8260/1522, Groton, CT 06340, USA*
[d] *Muehlenweg 14, D-79232 March, Germany*
[e] *Pfizer Global R & D, 2800 Plymouth Road, Ann Arbor, MI 48105 USA*

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Abstract

Seven published, randomized, placebo-controlled clinical trials with pregabalin have shown robust efficacy for relief of neuropathic pain from DPN and PHN. An investigation of the efficacy and safety of twice daily pregabalin enrolled 395 adults with painful DPN for $\geqslant$1 year in a 12-week, double-blind, placebo-controlled trial. Patients were randomized to placebo, 150, 300, or 600 mg/day pregabalin ($n = 96$, 99, 99, and 101). Primary efficacy measure was change from baseline in endpoint mean pain score from patients' daily pain diaries. Secondary efficacy measures included pain-related sleep-interference scores, Patient and Clinical Global Impressions of Change (PGIC, CGIC), and the EuroQOL Health Utilities Index (EQ-5D). Statistically significant reduction in pain was observed in patients receiving pregabalin 600 mg/day, and 46% of patients treated with 600 mg/day pregabalin reported $\geqslant$50% improvement in mean pain scores from baseline (vs 30% of placebo patients, $p = 0.036$). Number needed to treat to achieve such response was 6.3. Pregabalin 600 mg/day was significantly superior to placebo in improving pain-related sleep-interference scores ($p = 0.003$), PGIC ($p = 0.021$), and CGIC ($p = 0.009$). (Neither pregabalin 150 nor 300 mg/day separated from placebo on these measures, largely because of an atypically large placebo response in one country representing 42% of patients.) All pregabalin dosages were superior to placebo in improving EQ-5D utility scores (all $p \geqslant 0.0263$ vs placebo). Pregabalin was well tolerated at all dosages; adverse events were generally mild to moderate. Number needed to harm (discontinuation because of adverse events) was 10.3 for pregabalin 600 mg/day.

Keywords: Diabetes; Neuropathic pain; Pregabalin; Quality of life; Sleep

1. Introduction

The number of persons worldwide with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030 (Wild et al., 2004). Diabetic peripheral neuropathy (DPN) is a frequent complication, occurring in 20–24% of all persons with diabetes (Schmader, 2002)

* Corresponding author. Present address: Geschäftsführender Oberarzt, der Klinik Leiter der interdisziplinären Schmerzambulanz, Neurologische Klinik, Technische Universitaet Muenchen, Moehlstraße 28, 81675 Muenchen, Germany. Tel.: +49 89 4140 4658/4606; fax: +49 89 4140 4659.
E-mail address: toelle@lrz.tu-muenchen.de (T. Tölle).

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and in about 50% of patients with long-standing (⩾25 years) diabetes (Wright, 1994). Pain ranging from mild tingling to deep lancinating or severe unremitting pain is a common symptom of DPN (Schmader, 2002). This pain can be very distressing to patients and may have significant negative effects on psychologic and social well-being and quality of life (QoL; Quattrini and Tesfaye, 2003; Benbow et al., 1998).

Drugs from many different classes have been used to treat painful DPN, including tricyclic antidepressants (TCAs), selective serotonin–norepinephrine reuptake inhibitors (SNRIs), opioids, and antiepileptic drugs (AEDs). Each of these classes has demonstrated some degree of efficacy, but each has important limitations that often require the use of multidrug regimens. However, even multidrug regimens do not achieve complete relief for many patients (Bonezzi and Demartini, 1999; Harden and Cohen, 2003). Further, their use may be associated with increased risk for drug–drug interactions (DDI; Harden and Cohen, 2003), a problem particularly relevant to older patients who often receive multiple medications for chronic conditions (AGS Panel, 2002).

Pregabalin has demonstrated rapid onset of robust efficacy in relieving neuropathic pain associated with DPN (Rosenstock et al., 2004; Lesser et al., 2004; Richter et al., 2005; Freynhagen et al., 2005a), postherpetic neuralgia (PHN; Dworkin et al., 2003; Sabatowski et al., 2004; Freynhagen et al., 2005a; van Seventer et al., 2006), and spinal cord injury (SCI; Siddall et al., 2006) as well as pain associated with fibromyalgia (Crofford et al., 2005). Recently issued guidelines from the European Federation of Neurological Societies (Attal et al., 2006) identify pregabalin as a recommended first-line treatment for painful polyneuropathy, which includes painful DPN as "the most classical example."

Pregabalin has been shown to significantly improve pain-related sleep disturbance in all chronic pain models studied, including PHN, painful DPN, and chronic central neuropathic pain from SCI. Pregabalin has also improved the quality of sleep in conditions, such as osteoarthritis, for which it is not used as a treatment for pain (Pfizer data on file). Improvements also have been observed in comorbid symptoms of anxiety and depression in patients with PHN, painful DPN, SCI, and fibromyalgia (Sabatowski et al., 2004; Rosenstock et al., 2004; Richter et al., 2005; Crofford et al., 2005; Siddall et al., 2006). If criteria for efficacy include both pain relief and QoL measures, pregabalin and gabapentin are drugs of first choice, as described in a recent meta-analysis of published randomized clinical trials of drugs used as treatments for neuropathic pain (Finnerup et al., 2005).

The objective of this randomized, double-blind, placebo-controlled study was to evaluate the efficacy and safety of pregabalin – administered twice daily across its full dosing range (150–600 mg/day) – as treatment of painful DPN for a period of 12 weeks.

2. Methods

2.1. Study design

This randomized, double-blind, placebo-controlled, multicenter study recruited patients from 58 centers in Europe (Germany, Hungary, Poland, and the United Kingdom), Australia, and South Africa. The institutional review board or ethical committee of each research center approved the study protocol, and all patients provided informed written consent. Eleven patients (3% of those randomized) were withdrawn because of a decision by the Ethics Committee of the European Community Ministry of Health (ECMH) after the US Food and Drug Administration issued a partial clinical hold 12 February 2001 on pregabalin. The study consisted of a 1-week baseline period, followed by a 1-week double-blind, dosage-escalation period and an 11-week double-blind fixed-dosage phase.

2.2. Inclusion and exclusion criteria

Eligible patients were men or women ⩾18 years of age with type 1 or 2 diabetes mellitus for ⩾1 year, glycosylated hemoglobin (HbA_{1c}) ⩽11%, and painful, distal, symmetrical sensorimotor polyneuropathy due to diabetes for ⩾1 year. All patients had scores ⩾40 mm on the visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at baseline and at randomization and an average daily pain score ⩾4 on an 11-point numeric rating scale (NRS) during the 1-week baseline period.

Patients were excluded from the study if they had creatinine clearance (CL_{cr}) ⩽ 30 mL/min. Other standard exclusion criteria were similar to those described by Rosenstock et al. (2004), Lesser et al. (2004), and Richter et al. (2005) in reports of earlier trials of pregabalin in patients with painful DPN.

2.3. Washout of prohibited medications

The washout period was ⩾7 days for patients taking medications and miscellaneous supplements commonly used for relief of neuropathic pain, including benzodiazepines (other than stable bedtime doses for sleep), skeletal muscle relaxants, capsaicin, α-lipoic acid, local anesthetics, opioids, tramadol, memantine, AEDs, or antidepressants (other than selective serotonin-reuptake inhibitors for depression or anxiety given in a stable dose for >30 days). The washout period for analgesics, such as nonsteroidal anti-inflammatory drugs and dextromethorphan, was ⩾1 day.

2.4. Randomization, treatment, and assessment of compliance

Patients were randomized to one of four treatment groups: placebo, 150, 300, or 300/600 mg/day pregabalin, all administered by twice daily dosing. Patients randomized to 300/600 mg/day received either 300 mg/day or 600 mg/day depending on their CL_{cr}: patients with a normal CL_{cr} (>60 mL/min) received 600 mg/day of pregabalin, while those with CL_{cr} below normal (i.e., $CL_{cr} > 30$ but $\leqslant 60$ mL/min; referred to as low) received a maximum dosage of 300 mg/day.[1] This dosage adjustment in patients with low CL_{cr} was based on results of pharmacokinetic studies and was expected to produce pregabalin plasma levels equivalent to those obtained with 600 mg/day pregabalin in patients with normal CL_{cr} (Randinitis et al., 2003). (Creatinine clearance was estimated from serum creatinine, body weight, age, and sex using the Cockroft and Gault equation.) For patients in the 300- and 600-mg/day groups, daily dosage was escalated from 150 mg/day over a 7-day period; those not able to attain the target dosage were withdrawn from the study. Medication was reviewed at each study visit, and all study drugs were carefully inventoried throughout the duration of the trial.

2.5. Efficacy evaluations

The primary efficacy measure was the change from baseline of the mean pain score at endpoint generated from patients' daily pain dairy (i.e., mean of the last 7 diary entries while on study medication, including the entry on the day after the last dose). Pain scores were based on an 11-point NRS that ranged from 0 (no pain) to 10 (worst pain possible) during the past 24 h, completed on awakening. Differences among groups for mean pain scores were assessed at endpoint, weekly, and after 8 weeks (in patients who recorded fewer than 7 diary entries) of treatment. Patients who achieved $\geqslant 50\%$ reduction in pain scores from baseline to endpoint were considered treatment responders. Study results were considered positive if efficacy was demonstrated for at least one pregabalin treatment group for the primary efficacy parameter.

Secondary efficacy parameters included pain-related sleep-interference score from patients' daily sleep diaries, the Patient Global Impression of Change (PGIC; Guy, 1976), the Clinical Global Impression of Change (CGIC), and the EuroQoL Health Utilities Index (EQ-5D). Daily pain-related sleep-interference scores were based on an 11-point NRS (0 = no sleep interference; 10 = pain completely interfered with sleep). Both the PGIC and CGIC were administered at weeks 6 and 12 (termination). The EQ-5D assesses the impact of a health condition on a patient's QoL across five domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – using a single combined index. The EQ-5D also contains a VAS that allows patients to rate their current health state using values from 0 to 100 (0 = the worst imaginable health state; 100 = the best imaginable health state). The entire EQ-5D was administered at randomization and week 12 (termination), while the VAS only component was administered at weeks 1, 4, and 8.

2.6. Safety

Safety was assessed by recording adverse events (AEs), clinical laboratory evaluations, vital signs, physical examinations, 12-lead ECGs, and neurologic assessments. Serious AEs were defined as any adverse event that resulted in death, was life threatening, required inpatient hospitalization or prolonged current hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, and was medically significant (including laboratory abnormalities).

2.7. Statistical analyses

Study populations included the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study medication; the modified intent-to-treat (MITT) population, defined as all randomized patients who received at least one dose of study medication and were not withdrawn as a result of ECMH or ethics committee decisions; and the per-protocol population, defined as all patients in the MITT population without major protocol violations. The population for efficacy assessments was the MITT population and that for safety assessments was the ITT population.

Endpoint mean pain scores, endpoint mean pain-related sleep interference scores, and EQ-5D were analyzed using analysis of covariance (ANCOVA) main effects model with treatment, cluster, and CL_{cr} stratum (>60 mL/min or >30 to 60 mL/min) represented in the model and the respective baseline score as a covariate. Repeated measures analyses were performed for the weekly mean pain scores and the weekly mean pain-related sleep-interference scores. In each case, adjusted least-squares means were obtained from the model, and 95% confidence intervals (CI) on the difference between means for each pregabalin treatment group and placebo were constructed. Proportions of responders in each group were analyzed using the Cochran–Mantel–Haenszel (CMH) test. Patient Global Impression of Change and CGIC were also analyzed using the CMH test with

[1] This dosing group is referred to as 600 mg/day pregabalin in the remainder of the paper.

modified ridit scores adjusting for cluster and CL_{cr} strata. All statistical testing was two-sided. The Hochberg procedure was used to correct the significance level of $p < 0.05$ for multiple comparisons.

2.8. Post hoc by-country analysis

Additional by-country analysis of endpoint mean pain scores and proportion of responders for the MITT population by country were performed post hoc after the primary and secondary analyses were completed. Statistical analysis of by-country results were performed for these endpoints as described above for the entire MITT population.

3. Results

3.1. Patient disposition and baseline characteristics

A total of 512 patients were screened, 396 were randomized, and 395 received at least 1 dose of study medication (96 for placebo, 99 for 150 mg/day pregabalin, 99 for 300 mg/day pregabalin, and 101 for 600 mg/day pregabalin) (Fig. 1). Based on the estimated CL_{cr} of each patient, 47 patients were in the low and 348 patients were in the normal CL_{cr} groups. The majority of the 116 patients not randomized did not meet study criteria. Of the 395 patients who received study medication, 77 (20%) were withdrawn from the study due to: adverse events (32 patients [8%]), lack of efficacy (27 patients [7%]), or ECMH decision (11 patients [3%]). Of the patients withdrawn due to lack of efficacy, 11 (11.5%) were given placebo and 8 (8.1%) were in the pregabalin 150 mg/day, 5 (5.1%) in the 300 mg/day, and 3 (3.0%) in the 600 mg/day groups. Seventy-nine patients who received placebo, as well as 82, 79, and 78 patients treated with 150, 300, or 600 mg/day pregabalin, respectively, completed the study. Baseline characteristics for the ITT population are summarized in Table 1. Assessment of medical history and baseline clinical characteristics for the MITT population indicated that the four study groups were well matched. Approximately 85% of patients in each group had type 2 diabetes, the average duration of diabetes was 12.1–13.1 years, and the duration of DPN ranged from 3.7–4.4 years. Baseline mean pain scores for patients in the placebo and three pregabalin groups were 6.4, 6.2, 6.4, and 6.6, respectively.

3.2. Efficacy

3.2.1. Pain

Endpoint mean pain scores (with mean change from baseline given in parentheses for each treatment group) for patients in the MITT population treated with placebo, 150, 300, or 600 mg/day pregabalin were: 4.5 (−1.9), 4.1 (−2.1), 4.4 (−2.1) and 3.7 (−3.0), respectively. The results of ANCOVA with baseline pain severity as a covariate are shown in Table 2. Results for both the ITT and per-protocol populations were similar to those for the MITT population. In all three analyses, the 600 mg/day pregabalin group was significantly superior to placebo ($p < 0.01$). ANCOVA revealed a significant cluster effect: results from one country, representing 161 of the 384 total MITT patients, were different from those collected in all the other countries in which the study was conducted. In that one country, none of the pregabalin treatment groups achieved statistical significance compared with placebo; rather, treatment differences of endpoint mean pain score were 0.30, 0.47, and 0.05 for pregabalin 150, 300, and 600 mg/day groups relative to placebo (for all pregabalin groups, unadjusted $p \geqslant 0.266$).

Analysis of weekly mean pain scores (Fig. 2) indicated significant superiority of the highest dosage of pregabalin, 600 mg/day, over placebo as early as week 2 ($p = 0.0003$). The significant difference in weekly mean pain scores between these two groups was sustained over weeks 3–12 (Fig. 2).

A statistically significantly greater proportion of patients treated with pregabalin 600 mg/day were responders ($\geqslant$50% reduction in mean pain score from baseline to endpoint) than were patients receiving placebo: 45.9% vs 30.1%, $p = 0.036$ (response rates for 150 and 300 mg/day pregabalin were 34.4% and 33.3%). Of note, the country that demonstrated the cluster effect for mean pain score had a placebo responder rate of 41.9%, which was more than twice as great as the responder rate of patients receiving placebo in the other countries represented in the trial (20.0%) and greater than the responder rate in any of the pregabalin treatment groups in that country (150 mg/day, 35.1%; 300 mg/day, 37.2%; 600 mg/day, 39.5%).

3.2.2. Number needed to treat (NNT) and number needed to harm (NNH)

Among the full MITT population who received pregabalin 600 mg/day, the NNT to achieve response (ie, $\geqslant$50% improvement in endpoint mean pain score) was 6.3 (95% confidence interval 3.4, 44.7). The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42.6). Neither NNT nor NNH was determined for the MITT population excluding the one country that demonstrated the cluster effect.

3.2.3. Sleep

Assessment of endpoint, pain-related sleep-interference scores indicated significant superiority of 600 mg/day pregabalin over placebo ($p = 0.003$; Table 3). Weekly pain-related sleep-interference scores (Fig. 3)

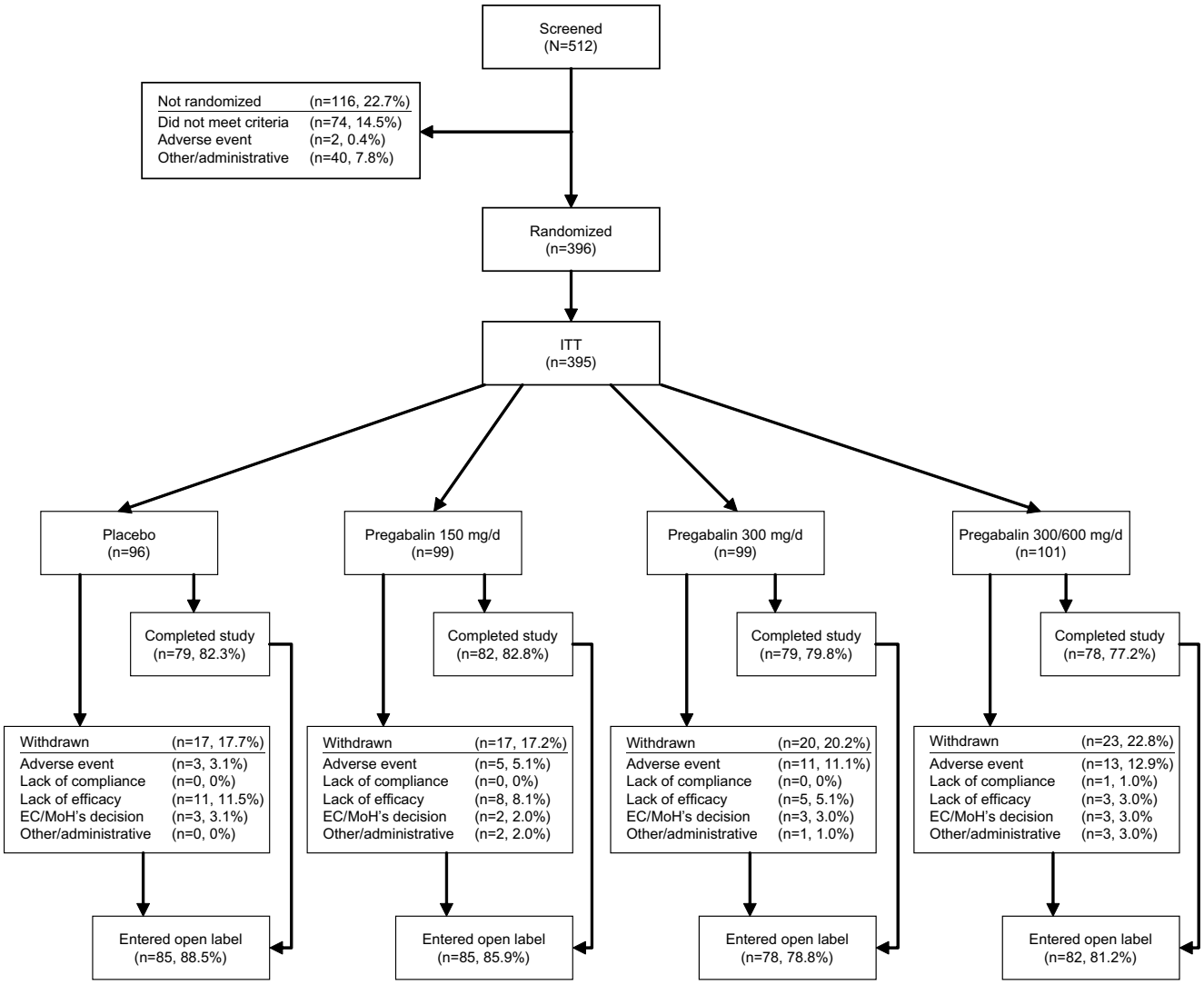

Fig. 1. Patient disposition.

were significantly superior to placebo for 600 mg/day pregabalin beginning at week 1 ($p = 0.0182$) and continuing through endpoint. Pain-related sleep-interference scores for patients in the 300 mg/day pregabalin group were significantly superior to placebo at weeks 1, 2, 3, 6, and 11 (all $p \leqslant 0.05$).

3.2.4. PGIC and CGIC

Evaluation of the PGIC demonstrated that 33.3% of patients who received placebo reported they were "very much" or "much improved" versus 45.8%, 42.5%, and 50.5% of those treated with pregabalin, respectively ($p = 0.021$ for 600 mg/day pregabalin versus placebo; Fig. 4). The CGIC indicated significant superiority of pregabalin 600 mg/day over placebo ($p = 0.009$). The percentages of patients reported as "very much" or "much improved" were 34.5% for placebo versus 47.9%, 40.4%, and 53.7% for the three pregabalin groups, respectively (Table 3).

3.2.5. EQ-5D utility score

At endpoint, all three pregabalin dose groups had significantly better mean EQ-5D utility scores than the placebo group (all $p \leqslant 0.0263$; Table 3).

3.3. Safety

3.3.1. Adverse events

All pregabalin dosages were generally well tolerated. The number of patients who discontinued due to AEs were 3 (3.1%) for placebo and 5 (5.1%), 11 (11.1%), and 13 (12.9%) for pregabalin 150, 300, and 600 mg/day. The respective rates for discontinuation due to treatment-associated AEs were 2.1%, 3.0%, 10.1%, and 10.9%. The most commonly reported treatment-associated AEs, occurring in $\geqslant 5\%$ of patients, were dizziness, peripheral edema, and somnolence (Table 4). The vast majority of AEs (see Table 1 both treatment associated and all causality) were mild to moderate in intensity.

Table 1
Summary of patient characteristics at baseline (ITT population)

	Placebo ($N = 96$)	Pregabalin (mg/day)				All patients ($N = 395$)
		150 ($N = 99$)	300 ($N = 99$)	600 ($N = 101$)	Any[a] ($N = 299$)	
Gender						
Male, *n* (%)	51 (53.1)	54 (54.5)	53 (53.5)	61 (60.4)	168 (56.2)	219 (55.4)
Female, *n* (%)	45 (46.9)	45 (45.5)	46 (46.5)	40 (39.6)	131 (43.8)	176 (44.6)
Race						
White, *n* (%)	95 (99.0)	95 (96.0)	95 (96.0)	95 (94.1)	285 (95.3)	380 (96.2)
Black, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (0.7)	2 (0.5)
Asian or Pacific Islander, *n* (%)	0 (0.0)	2 (2.0)	2 (2.0)	3 (3.0)	7 (2.3)	7 (1.8)
Other, *n* (%)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	5 (1.7)	6 (1.5)
Age (years)						
Mean (SD)	58.93 (11.7)	58.51 (12.4)	57.28 (10.5)	59.70 (11.3)	58.51(11.4)	58.61 (11.5)
Age categories						
18–64 years, *n* (%)	63 (65.6)	68 (68.7)	73 (73.7)	71 (70.3)	212 (70.9)	275 (69.6)
⩾65, *n* (%)	33 (34.4)	31 (31.3)	26 (26.3)	30 (29.7)	87 (29.1)	120 (30.4)
Weight (kg)						
Mean (SD)	82.96 (12.9)	85.44 (15.4)	87.66 (16.7)	86.83 (15.7)	86.65 (15.9)	85.75 (15.3)
Estimated baseline CL_{cr} (mL/min)						
Mean	91.72 (27.1)	95.34 (31.6)	95.07 (28.9)	91.75 (28.4)	94.04 (29.6)	93.48 (29.0)
CL_{cr} status						
Normal (>60 mL/min), *n* (%)	84 (87.5)	87 (87.9)	89 (89.9)	88 (87.1)	264 (88.3)	348 (88.1)
Low (30–60 mL/min), *n* (%)	12 (12.5)	12 (12.1)	10 (10.1)	13 (12.9)	35 (11.7)	47 (11.9)

[a] Any pregabalin treatment group.

Table 2
Endpoint mean pain scores: analysis of covariance (MITT, ITT, and per protocol populations)

	Placebo	Treatment comparisons (Placebo:Pregabalin)		
		150 mg/day	300 mg/day	600 mg/day
MITT population				
N	93	96	96	98
Difference (95% CI)		−0.33 (−0.94, 0.28)	−0.18 (−0.79, 0.43)	−0.97 (−1.58, −0.36)
p-value[a]		.5580	.5580	.0054
ITT population				
N	96	98	99	101
Difference (95% CI)		−0.27 (−0.87, 0.34)	−0.10 (−0.70, 0.50)	−0.91 (−1.51, −0.31)
p-value[a]		0.7481	0.7481	0.0093
Per protocol population				
N	87	87	89	85
Difference (95% CI)		−0.40 (−1.04, 0.24)	−0.15 (−0.79, 0.48)	−1.03 (−1.68, −0.38)
p-value[a]		0.4480	0.6364	0.006

CI = Confidence interval.
[a] *p*-Values are based on Hochberg's procedure for the three pair-wise comparisons versus placebo.

Severe treatment-associated AEs were reported for 1%, 2%, 4%, and 4% of patients in the placebo and pregabalin groups, respectively. There were two deaths during the study (one patient assigned to 150 mg/day and one to 300 mg/day pregabalin). Both were due to cardiovascular events, and neither was considered to be associated with study medication. Serious nonfatal AEs (all causality and as defined above) were reported for 2.1%, 4.0%, 3.0%, and 5.9% of patients in the placebo and 150, 300, and 600 mg/day pregabalin treatment groups. The respective values for treatment-associated nonfatal, serious AEs were 0%, 1%, 2%, and 0%.

Weight change was reported as an AE by 0%, 7.1%, 8.1%, and 9.9% of patients in the placebo and 150, 300, and 600 mg/day pregabalin treatment groups. A change in weight ⩾7% from baseline to endpoint was reported for 1.0%, 4.1%, 7.1%, and 13.9% of patients in the placebo and three pregabalin groups (see Table 1 for baseline mean weights). Only one patient (treated with 300 mg/day pregabalin) discontinued the trial due

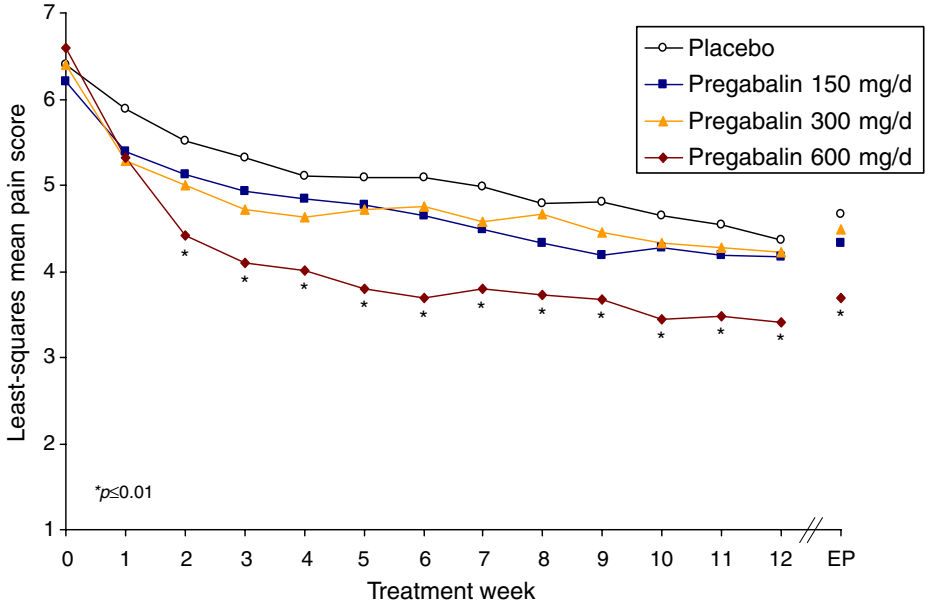

Fig. 2. Weekly mean pain scores from baseline to week 12 and endpoint: least-squares means from analysis of covariance (MITT population).

Table 3
Endpoint results for secondary efficacy parameters (MITT population)

	Placebo	Pregabalin (mg/day)		
		150	300	600
Mean pain-related sleep interference				
N	93	96	96	98
Difference (95% CI)		−0.45 (−1.05, 0.15)	−0.62 (−1.22, −0.02)	−1.01 (−1.60, −0.41)
p-value[a]		0.1444	0.0844	0.003
CGIC (*n*, %)				
N	93	96	94	95
Very much improved	2 (2.2)	9 (9.4)	11 (11.7)	10 (10.5)
Much improved	30 (32.3)	37 (38.5)	27 (28.7)	41 (43.2)
Minimally improved	31 (33.3)	23 (24.0)	31 (33.0)	27 (28.4)
No change	26 (28.0)	23 (24.0)	19 (20.2)	15 (15.8)
Minimally worse	2 (2.2)	4 (4.2)	5 (5.3)	2 (2.1)
Much worse	2 (2.2)	0 (0.0)	1 (1.1)	0 (0.0)
Very much worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value[a]		0.101	0.101	0.009
EQ-5D utility				
N	90	92	92	90
Difference (95% CI)		0.10 (0.03, 0.16)	0.08 (0.01, 0.14)	0.14 (0.07, 0.20)
p-value[a]		0.0092	0.0263	0.0003

[a] *p*-Values are based on Hochberg's procedure for the three pair-wise comparisons versus placebo.

to weight change; dyspnea was also cited as a reason for discontinuation of this patient. Peripheral edema was reported for 3.1%, 7.1%, 11.1%, and 11.9% of patients treated with placebo or pregabalin 150, 300, and 600 mg/day. Most cases of peripheral edema were considered mild or moderate in severity and were not considered to be associated with weight change or cardiovascular events; no case of peripheral edema was reported as a serious AE. Study results indicated no correlation between weight change or edema and changes in blood pressure or glycemic control. No more than 2% of patients in any pregabalin group reported hypertension, hyperglycemia, or hypoglycemia, and the only pregabalin-treated patients who withdrew from the study because of peripheral edema were 3 (3%) patients in the 300 mg/day group.

The median times to onset of any AEs were shorter for the pregabalin groups (8.5, 7, and 4 days, respectively)

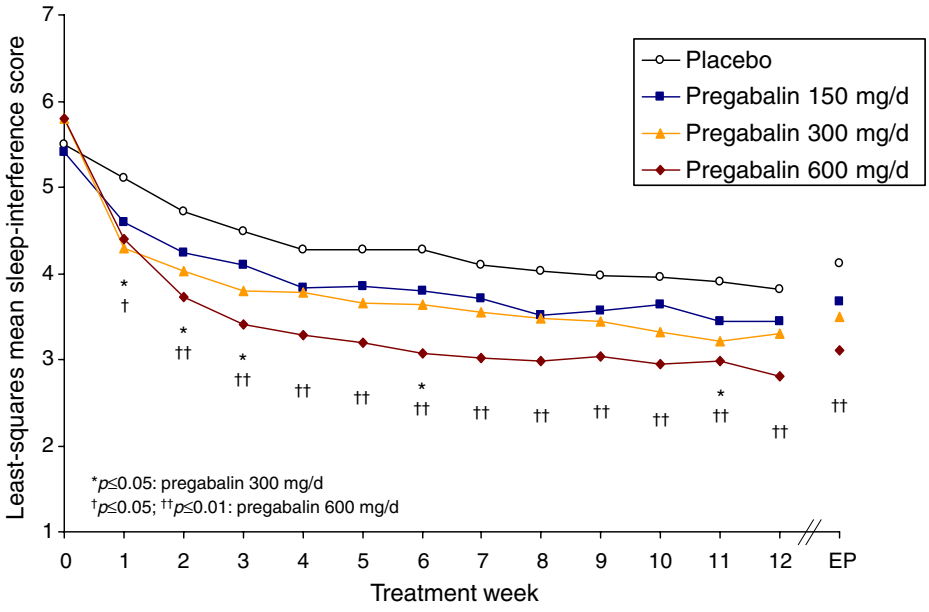

Fig. 3. Weekly pain-related sleep-interference scores from baseline to week 12 and endpoint: least-squares means from analysis of covariance (MITT population).

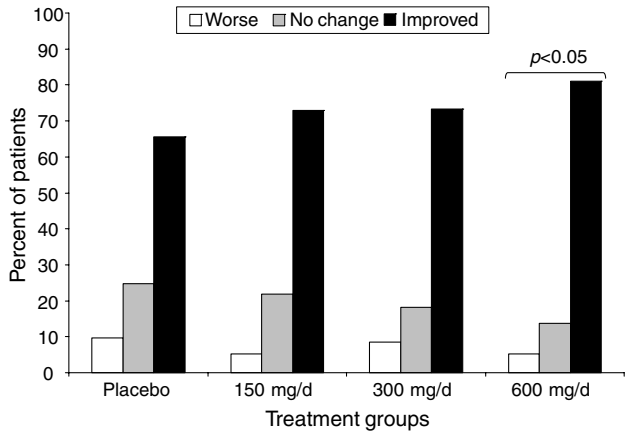

Fig. 4. Patient global impression of change at endpoint (MITT population) "Worse" category includes "minimally", "much", and "very much" worse. "Improved" category includes "very much", "much", and "minimally" improved.

Table 4
Treatment-associated adverse events reported for ⩾5% of patients in any treatment group

Adverse event	Placebo, $n = 96$ (n %)	Pregabalin (mg/day)		
		150, $n = 99$ (n, %)	300, $n = 99$ (n, %)	600, $n = 101$ (n %)
Dizziness	2 (2.1)	3 (3.0)	9 (9.1)	14 (13.9)
Peripheral edema	2 (2.1)	5 (5.1)	9 (9.1)	10 (9.9)
Somnolence	1 (1.0)	5 (5.1)	4 (4.0)	8 (7.9)
Dry mouth	0 (0.0)	3 (3.0)	5 (5.1)	7 (6.9)
Weight change	0 (0.0)	6 (6.1)	6 (6.1)	7 (6.9)
Asthenia	0 (0.0)	1 (1.0)	4 (4.0)	5 (5.0)
Vertigo	0 (0.0)	2 (2.0)	6 (6.1)	5 (5.0)
Edema	0 (0.0)	4 (4.0)	12 (12.1)	4 (4.0)
Headache	5 (5.2)	5 (5.1)	3 (3.0)	1 (1.0)

than for the placebo group (14 days). There was no relationship between pregabalin dosage and time to onset of the five most common AEs. The median duration of AEs was 31.5, 31.0, and 48.5 days, respectively, for the pregabalin groups and 20.0 days for the placebo group.

Twenty-six patients experienced AEs that investigators classified as severe in intensity. One severe AE was reported in the placebo group, and 6, 8, and 11 in the 150, 300, and 600 mg/day pregabalin treatment groups. Severe AEs included myocardial infarction (considered to be definitely not related to pregabalin treatment), pain, vomiting, peripheral edema, hypoglycemia, hyperlipidemia, dizziness, and pneumonia. Most of the severe AEs were not related to treatment with pregabalin, and the only severe AE that was probably related to pregabalin was a case of dizziness that resolved upon discontinuation of therapy.

3.3.2. Laboratory assessments

High cholesterol and triglycerides were seen in all treatment groups, which can be expected in a population of diabetic patients. However, there was little change from baseline to endpoint in the mean values, and only one case of hypertriglyceridemia was considered possibly treatment related. The mean change (increase) from baseline to endpoint in the average HbA_{1c} concentration was similar across all treatment groups.

3.3.3. Physical and neurologic examinations

There were no consistent differences among groups with respect to results of physical or neurologic examinations.

3.3.4. ECGs

Two patients had new (or not present at baseline) clinically significant abnormal ECG findings at study termination. These included one patient in the placebo group with arterial flutter and nonspecific ST-changes and one patient receiving pregabalin 150 mg/day who had T-wave abnormality. The ECG results were classified as definitely not treatment related.

4. Discussion

This placebo-controlled study of patients with diabetes and painful DPN for ⩾1 year demonstrates that pregabalin administered twice daily is safe, well tolerated, and significantly superior to placebo in reducing pain and pain-related interference with sleep. Pain scores in patients receiving pregabalin 600 mg/day were significantly lower than those for the placebo group by the second treatment week, while the between-group difference in pain-related sleep-interference scores achieved significance by week 1. Treatment with pregabalin 600 mg/day was found to improve patients' overall health status (PGIC and CGIC), and at all dosages, pregabalin was associated with statistically significantly improved EQ-5D Utility scores, a measure of treatment impact on health-related QoL. All pregabalin dosages were well tolerated, with few discontinuations due to AEs. The most common treatment-associated AEs were dizziness, peripheral edema, and somnolence, all of which increased with pregabalin dosage.

Previously reported trials of pregabalin have consistently demonstrated the efficacy of pregabalin for reducing neuropathic pain when dosed three times daily at fixed dosages of 300 or 600 mg/day in patients with painful DPN (Rosenstock et al., 2004; Lesser et al., 2004; Richter et al., 2005) and dosed two or three times daily at fixed dosages of 150–600 mg/day in patients with PHN (Dworkin et al., 2003; Sabatowski et al., 2004; van Seventer et al., 2006). These trials also demonstrated statistically significant superiority of pregabalin over placebo for decreasing pain-related sleep interference and for improving PGIC, CGIC, and QoL ratings. In a further extension of its treatment spectrum, pregabalin has been shown – in a study designed to resemble clinical practice – to significantly improve pain symptoms in patients with painful DPN or PHN when administered for 12 weeks in flexible- (150–600 mg/day) and fixed-dosage (600 mg/day) twice daily regimens (Freynhagen et al., 2005a). Under fixed-dosage treatment, a decrease of one full point on the 11-point NRS was reached on day 1, two full points on day 13, and three full points on day 23 (under flexible-dosage pregabalin, similar improvements were observed on days 6, 17, and 30), demonstrating a rapid time to onset (Freynhagen et al., 2005b).

Results of the present trial with regard to the efficacy of 300 mg/day pregabalin differ from effects of this dosage in the trials reported by Rosenstock et al. (2004) and Lesser et al. (2004). Unlike the current trial, both these earlier trials demonstrated statistically significant superiority of 300 mg/day pregabalin (in three divided doses) over placebo for relieving pain and improving sleep interference in patients with normal renal function. The disparity of these results is most likely explained by an unusually high placebo response in this trial, particularly in one of the participating countries.

Placebo response in the current study was substantially greater than in previous studies of pregabalin in painful DPN. The endpoint least-squares mean pain score for patients randomized to placebo was 4.66 (a–1.74 change from baseline), and 30.1% of all patients assigned to placebo had ⩾50% reductions in pain scores from baseline to endpoint. In contrast, Rosenstock et al. reported that patients in the placebo group had an endpoint mean pain score of 5.46, with only 14.5% attaining ⩾50% reduction in pain score. Those numbers were 5.06 and 18% as reported by Lesser et al. and 5.6 and 15% by Richter et al.

A significant cluster effect was evident in one country representing 161 of the 384 MITT patients. ANCOVA of the MITT population from that one country showed nonsignificant treatment differences in mean pain scores at endpoint of 0.30, 0.47, and 0.05 for the three pregabalin treatment groups (150, 300, 600 mg/day) relative to placebo. That one country had an atypically high placebo responder rate of 41.9%, which is well over two times as great as that reported in previous trials in patients with DPN (placebo responder rates reported by Rosenstock et al., 14.5%, Lesser et al., 18%, Richter et al., 15%). In contrast, ANCOVA of the MITT population for all other countries, excluding that one, found treatment differences in mean pain scores at endpoint of −0.92, −0.77, and −1.85 for the pregabalin groups relative to placebo (unadjusted p-values: 150 mg/day, $p = 0.0318$; 300 mg/day, $p = 0.0779$; 600 mg/day, $p = 0.0001$), and the placebo responder rate of 20.0% was less than half that of the anomalous country and similar to that of previously published trials.

Reasons for the anomalous results in the one country are unclear. Baseline pain scores and other patient characteristics, including presence of comorbidities, were similar to that of the patients from other participating countries. However, far fewer patients from this country were receiving any medication for their neuropathic pain prior to enrollment, so it is possible that the very fact of receiving any treatment contributed to the atypically large placebo response.

The safety-tolerability profile emerging from this study is consistent with that of previous trials of pregabalin in peripheral neuropathic pain in terms of which AEs were most common. However, the incidence rates

of the most common AEs are lower than those previously reported by Rosenstock et al. (2004), Lesser et al. (2004), and Richter et al. (2005). This can be explained, at least in part, by the country that demonstrated the significant cluster effect for efficacy measures. In this country, across treatment groups, far fewer patients reported AEs than did patients from other participating countries (pregabalin 150 mg/day, 38.5% vs 58.3%; pregabalin 300 mg/day, 54.5% vs 70.9%; pregabalin 600 mg/day, 48.7% vs 79.0%; placebo, 25.0% vs 53.8%). Excluding this one country, rates of the most common AEs would be more consistent with those reported from earlier trials.

Weight change and peripheral edema have been noted in patients treated with pregabalin, and both were carefully monitored per protocol in this trial. Results from this study indicated dosage-related weight change in patients treated with pregabalin. However, weight change did not affect glycemic control, and only one patient withdrew because of weight change.

Peripheral edema was reported for 9.9% of patients treated with 600 mg/day pregabalin in this trial. The peripheral edema observed in pregabalin-treated patients is not of cardiovascular, renal, or hepatic origin and was not associated with significant changes in blood pressure (Rosenstock et al., 2004; Lesser et al., 2004).

Results from this 12-week, randomized, double-blind, placebo-controlled study add to the growing body of evidence demonstrating the safety and rapid, robust efficacy of pregabalin as treatment of chronic neuropathic pain. Specifically, the present results show that pregabalin 600 mg/day (administered in two divided doses) was well tolerated by these patients with painful DPN and was significantly superior to placebo in reducing pain and pain-related sleep interference and in improving overall patient health status and quality of life.

Declaration of interests

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Australia: Dennis K. Yue, MD, Camperdown; Stephen Colagiuri, MD, Randwick; Richard Walter Simpson, MD, Victoria; John James Graham, MD, Ashford; Anthony Philip Roberts, MD, Kent Town; Paul Zimmet, MD, Victoria; Deborah Jane Holmes-Walker, MD, NEW; Richard Charles O'Brien, MD, VICT.

Germany: Peter Brommer, MD, Rhoen; Michael Dietrich, MD, Bayern; Andreas Hamann, MD, Heidelberg; Juergen Schmidt, MD, Floersheim; Andrea Sprogies, MD, Tostedt; Michael Simonsohn, MD, Frankfurt; Herbert Mauersberger, MD, Ehrenberg/Rhoen; Ulrich M. Aigner, MD, Sulzbach-Rosenberg; Erika-Maria Oerter, MD, Wurzburg; Joachim Springub, MD, Westerstede; Jan Andre Schmidt-Lucke, MD, Leipzig; Manfred Dreyer, MD, Hamburg; Martin Anders, MD, Berlin; Bernhard Rathay, MD, Karlsruhe; Monika Kiper, MD, Berlin; Bertold Schrank, MD, Wiesbaden; Ulrich Alfons Muller, MD, Jena; Helmut Anderten, MD, Hildesheim; Claudia Sommer, MD, Wurzburg.

Hungary: Gyozo Vandorfi, MD, Veszprem; Tamas Oroszlan, MD, Zalaegerszeg; Zsolt Haffner, MD, Gyor; Erzsebet Doemoetoer, MD, Budapest; Peter Kempler, MD, Budapest.

Poland: Bogna Wierusz-Wysocka, MD, Plewiska; Dr. Jerzy Wladyslaw Andrzej Lopatynski, MD, Lublin; Zbigniew Szybinski, MD, Krakow; Elizbieta Bandurska-Stankiewicz, MD, Ul. Pszenna; Katarzyna Cypryk, MD, Lodz; Marcin Regulski, MD, Warsaw; Maria Gorska, MD, Bialystok; Ewa Semetkowska-Jurkiewicz, MD, Gdansk; Anna Mikolajczyk-Swatko, MD, Lodz; Ida Kinalska, MD, Bialystok; Janina Kijanska, MD, Warszawska; Marek Grzywa, MD, Rzeszow; Ewa Jarosz-Skokowska, MD, Lublin; Arleta Zardzewialy Kuczynska, MD, Warsaw.

South Africa: Gerrit C. Burger, MD, Port Elizabeth; Jonathan Carr, MD, Parow; Wilma Lourens, MD, Muckleneuk; Ray Moore, MD, Umghlanga Rocks; Hendrik F.M. Nortje, MD, Goodwood; Leslie Ivan Robertson, MD, Overport (Durban).

United Kingdom: John Phillip David Reckless, MD, Bath; Beverley Ann Millward, MD, Plymouth; Alan Rees, MD, Heath Park; Joseph Paul O'Hare, MD, Rugby; John Martin Gibson, MD, Salford; Giancarlo Francesco Viberti, MD, London; Paul Edward Jennings, MD, York; Thomas Hugh Jones, MD, Barnsley; Stephen Charles Langford Gough, MD, Birmingham; David Michael Levy, MD, London; Andrew F. MacLeod, MD, Shrewsbury; Ian Lawrence, MD, Leicester; Michael Edwin Edmonds, MD, London; Gerrard Rayman, MD, Suffolk.

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