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Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens

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Abstract

Pregabalin binds with high affinity to the alpha$_2$-delta subunit protein of voltage-gated calcium channels and, thereby, reduces release of excitatory neurotransmitters. This 12-week randomised, double-blind, multicentre, placebo-controlled, parallel-group study evaluated the efficacy and safety of pregabalin in patients with chronic postherpetic neuralgia (PHN) or painful diabetic peripheral neuropathy (DPN). Patients were randomised to placebo ($n=65$) or to one of two pregabalin regimens: a flexible schedule of 150, 300, 450, and 600 mg/day with weekly dose escalation based on patients' individual responses and tolerability ($n=141$) or a fixed schedule of 300 mg/day for 1 week followed by 600 mg/day for 11 weeks ($n=132$). Both flexible- and fixed-dose pregabalin significantly reduced endpoint mean pain score (primary outcome) versus placebo ($P=0.002$, $P<0.001$) and were significantly superior to placebo in improving pain-related sleep interference ($P<0.001$). The most common adverse events (AEs) for pregabalin-treated patients were dizziness, peripheral oedema, weight gain (not affecting diabetes control), and somnolence. These results are consistent with previous studies' demonstrating pregabalin's efficacy, tolerability, and safety for treatment of chronic neuropathic pain associated with DPN or PHN. Pregabalin dosing aimed at optimal balance of efficacy and tolerability provides significant pain relief and may reduce risks for AEs and therapy discontinuation.

Keywords: Diabetic neuropathy; Dosing; Neuropathic pain; Postherpetic neuralgia; Pregabalin; Sleep

1. Introduction

Painful diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are among the more common types of neuropathic pain. Diabetic neuropathy occurs in about 15% of patients with long-standing diabetes (Calcutt, 2002; Nash, 1999; Schmader, 2002; Wright, 1994), and its symptoms range from mild tingling to deep lancinating or severe unremitting pain. These symptoms can be profoundly distressing and negatively impact patient well-being (Quattrini and Tesfaye, 2000).

Postherpetic neuralgia is variably defined as pain persisting after onset of herpes zoster rash to pain present 3 months after rash healing. Its symptoms include constant or burning pain, intermittent, sharp, shooting pain, and allodynia (Bowsher, 1997; Choo et al., 1997; Kost and Straus, 1996). The prevalence of PHN is about 11% among herpes zoster patients, and it is most common among elderly patients (Choo et al., 1997; Dworkin and Portenoy, 1996; Kanazi et al., 2000; Kost and Straus, 1996; Schmader, 2002). Like DPN, PHN is typically chronic, the pain can be intense and unremitting, and it may profoundly impact health-related quality of life and functional status (Dworkin and Portenoy, 1996; Rowbotham, 1994).

It is widely acknowledged that a large percentage of patients with these common neuropathic pain syndromes are

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partially or totally refractory to even the best therapies available. Clinicians are in need of safe, efficacious medications that are generally well tolerated and provide meaningful pain relief and improved quality of life. Drugs that reduce excessive, pathologic neuronal discharge would appear to hold promise for the management of these conditions.

Pregabalin is a selective, high-affinity ligand for the α_2-δ subunit of voltage-gated calcium channels (Fink et al., 2002), which are thought to play an important role in modulating neuropathic pain (Luo et al., 2001; Woolf and Mannion, 1999). By binding to the α_2-δ subunit, pregabalin reduces influx of calcium into nerve terminals and decreases neurotransmitter release (Dooley et al., 2002; Maneuf et al., 2001). Pregabalin is effective in animal models of neuropathic pain (Chen et al., 2001; Diop et al., 2002; Eutamene et al., 2000; Field et al., 1999; Wallin et al., 2002) and in patients with painful DPN or PHN (Dworkin et al., 2003; Lesser et al., 2004; Richter et al., in press; Rosenstock et al., 2004; Sabatowski et al., 2004).

This study evaluated the efficacy, safety, and tolerability of two pregabalin regimens–150 to 600 mg/day flexibly dosed and 600 mg/day fixed-dose compared with placebo for pain relief in patients with neuropathic pain. This comparison was performed to determine whether a flexible-dose regimen, which better reflects clinical practice, might improve tolerability without compromising pain relief.

2. Methods

2.1. Design

This 12-week study used a randomised, double-blind, multicentre, placebo-controlled, parallel-group design to evaluate the efficacy and safety of twice-daily (BID) flexible- (150–600 mg/day) or fixed-dose (600 mg/day) pregabalin in patients with chronic neuropathic pain. The study was conducted in 60 centres in nine European countries. Individual centres randomised between 1 and 45 patients. Interested centres were recruited in order to achieve representation of typical populations within each country and to accommodate different enrolment rates and characteristics. Countries that had total enrolment <5 were pooled with neighbouring countries; countries with total enrolment of 5–20 were treated as a single centre; individual centres with enrolment <15 were pooled within the same country according to geographic proximity; and centres with total enrolment ≥ 15 were not pooled with other centres. The study adhered to the ethical principles originating from the Declaration of Helsinki and subsequent revisions and was in compliance with Good Clinical Practice. The study protocol and consent forms were reviewed and approved by the Independent Ethics Committee (IEC) responsible for each study centre. All patients provided written, informed consent.

2.2. Subjects

Eligible patients were men and non-pregnant, non-lactating women ≥ 18 years of age with a primary diagnosis of painful DPN (type 1 or 2 diabetes mellitus with glycosylated haemoglobin [HbA_{1c}] $\leq 11\%$ and painful, distal, symmetrical, sensorimotor polyneuropathy for ≥ 6 months) or PHN (pain present for ≥ 3 months after healing of the herpes zoster skin rash). Patients were also required to have a score ≥ 40 mm (0 mm = 'no pain' and 100 mm = 'worst possible pain') on the Visual Analogue Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at baseline and randomisation.

Patients were excluded if they had any clinically significant or unstable medical or psychiatric condition. Patients who had a malignancy within the past 2 years (with the exception of basal cell carcinoma) or an anticipated need for surgery during the study were also excluded, as were patients with an abnormal electrocardiogram (ECG), creatinine clearance <60 mL/min, or abnormal haematology. Patients who had abused illicit drugs or alcohol within the last 2 years were excluded. Those who had participated in a previous clinical trial for pregabalin or had taken any investigational drug or agent within 30 days prior to screening were also excluded. Medications prohibited for use during the study, and which were required to be washed out at least 7 days prior to baseline visit, included the following: drugs commonly used to treat neuropathic pain (e.g. benzodiazepines, skeletal muscle relaxants, capsaicin, local anaesthetics, opioids, memantine), antiepileptic drugs (e.g. carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, gabapentin), non-SSRI antidepressants (e.g. tricyclics, venlafaxine), and potential retinotoxins (e.g. hydroxychloroquine, deferoxamine, thioridazine, vigabatrin). Patients with DPN were also prohibited from taking NSAIDS (including COX-2 inhibitors) and dextromethorphan without a washout of at least 1 day.

Patients who had been exposed previously to gabapentin, regardless of dose and treatment duration, were permitted to enter the study. SSRIs for treatment of depression, aspirin for myocardial infarction and stroke prophylaxis, short-acting benzodiazepines for insomnia, and paracetamol as rescue medication were allowable medications during the study period.

Patients were also excluded if they had a history of hepatitis B or C or HIV infection, neurologic disorders, severe pain unrelated to their primary diagnosis of DPN or PHN, or any potentially sensation-altering skin conditions in the affected dermatome or area of neuropathic involvement that could confound their assessment of neuropathic pain. Finally, patients with DPN and a history of pernicious anaemia, untreated hypothyroidism, or amputations other than toes were also excluded, as were patients with PHN who had undergone neurolytic or neurosurgical therapy for their condition.

2.3. Treatments

The study had two phases: a 1-week observation phase to establish baseline pain scores and a 12-week double-blind treatment phase in which a blinded adaptation in response to patients' needs was applied in one of the treatment arms. Patients were randomised in 1:2:2 ratio to placebo, flexible-dose pregabalin (150–600 mg/day), or fixed-dose pregabalin (600 mg/day). Patients randomised to the pregabalin flexible-dose group received escalating doses (150, 300, 450 and 600 mg/day) titrated at weekly intervals based on response and tolerability (Fig. 1). A single downward dose titration, after Week 1 or at or after Week 2, 3, or 4, was allowed. If this occurred, the patient remained on this dosage

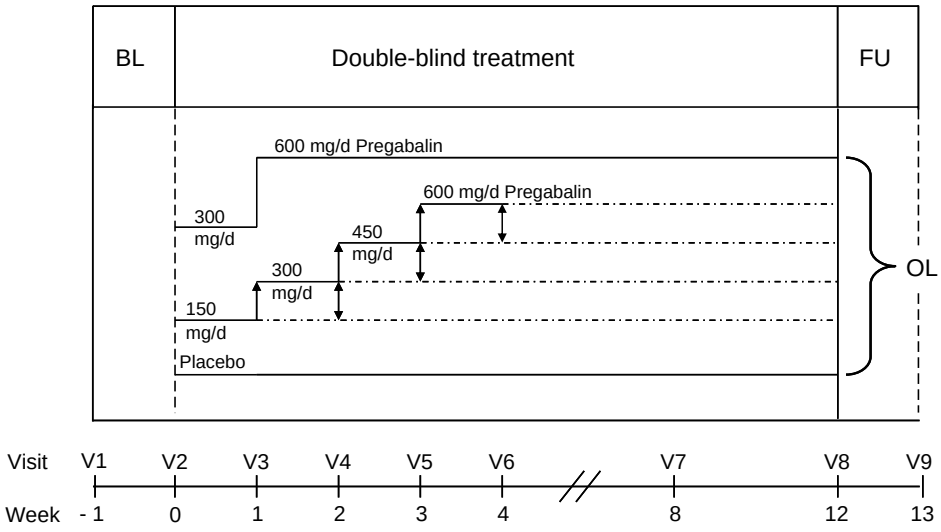

Fig. 1. Study design and dosing schedule.

for the rest of the study. The advantage of this new study design is that it more closely approximates the treatment routine in which doctors tailor the dosage of prescribed drugs based on individual patients' responses. Patients randomised to the pregabalin 600 mg/day fixed-dose group started with pregabalin 300 mg/day for 1 week and then followed with 600 mg/day for the remaining 11 weeks of double-blind treatment. All patients received active medication or matching placebo capsules and followed the same BID oral dosing schedule (daily dosages were split into two equivalent doses, one administered in the morning and one in the evening). Adherence was assessed by medication inventory control and review of dosing procedure at each study visit. At any time during the double-blind trial, patients were free to discontinue it and enter the open-label extension.

2.4. Evaluations and endpoints

During the baseline phase (no active treatment), patients made daily diary entries of pain and pain-related sleep interference using 11-point numerical (0 = 'no pain' to 10 = 'worst possible pain'; 0 = 'pain does not interfere with sleep' to 10 = 'pain completely interferes with sleep') rating scales (NRS). Patients who continued to meet all inclusion/exclusion criteria at the end of this phase were randomised to double-blind study medication and evaluated at six post-randomisation visits.

The primary efficacy parameter was endpoint mean pain score based on patients' NRS scores as recorded in their daily pain diaries. On awakening each morning, patients recorded their neuropathic pain intensity during the previous 24 h in their diaries, using the NRS. Secondary efficacy parameters included the Daily Sleep Interference Diary (similar to the pain diary) and the Medical Outcomes Study (MOS)-Sleep Scale (Hays and Stewart, 1992), and the Patient Global Impression of Change (PGIC). The MOS-Sleep Scale is a validated, 12-item, patient-completed questionnaire used to measure the influence of sleep on health-related quality of life. Additional secondary measures were included in the protocol and analysed, and these will be reported in a subsequent article.

2.5. Safety

Safety assessments included summary of adverse events (AEs, occurrence, nature, intensity, and relationship to study drug), clinical laboratory test results, and the results of physical and neurologic examinations and 12-lead ECGs. Owing to clinical experience with gabapentin and to findings from previous clinical trials of pregabalin in which a minority of patients experienced weight gain or oedema of unknown pathophysiology, the study protocol called for specific assessment of weight gain and oedema using multiple measures, including, for weight gain, patients' reports of weight gain as an AE, occurrence of investigator-verified weight gain of $\geq 7\%$ from baseline, ratio of waist to hip measurements, and, for oedema, investigator assessment of peripheral, facial, and generalised oedema.

2.6. Statistics

The sample size calculation was based on the means and standard deviations (SD) observed for pain scores in previous trials of pregabalin versus placebo in painful DPN. Assuming two-sided testing at the 0.025 significance level, 130 patients per pregabalin treatment group and 65 patients in the placebo treatment group were determined to provide 95% power to detect a difference of 1.26 (SD = 2.12) between each pregabalin treatment group and placebo.

The primary and secondary efficacy analyses were performed on the intent-to-treat (ITT) population defined as patients who received at least one dose of randomised study medication and had at least one post-baseline efficacy evaluation. All statistical testing was two-sided and adjusted for the multiple comparisons of the two pregabalin arms versus placebo using the Hochberg procedure.

The endpoint mean pain score was analysed using an analysis of covariance (ANCOVA) with effects for treatment, centre, pain type, and baseline mean pain score as covariates. Additionally, data from all weeks were analysed using repeated-measures models that included treatment, centre, pain type, baseline mean pain score, week, and week-by-treatment interaction as covariates. Planned analyses also included the analysis of weekly mean pain scores and the proportion of responders, defined as patients with

≥30 or ≥50% reduction in mean pain score from baseline to endpoint. Mean pain score, mean sleep interference scores, and MOS-Sleep Scale (except Optimal Sleep Scores) were analysed using the ANCOVA main-effects model with baseline mean score as a covariate. The PGIC was analysed using the Cochran–Mantel–Haenszel (CMH) test, and the proportion of responders and MOS-Sleep Scale Optimal Sleep score were analysed using logistic regression.

All randomised patients who received ≥1 dose of study medication were evaluated for safety. Summaries documented the number and percent of patients in each treatment group who experienced each type of AE.

3. Results

3.1. Patients

Patient disposition, including discontinuations and reasons for them, is summarized by treatment group in Fig. 2. All randomised patients received study drug and were evaluated for safety. All but two had post-treatment efficacy data and constituted the ITT population for efficacy evaluations. Demographic and baseline clinical characteristics are summarized in Table 1. Treatment groups were well matched at baseline for all clinical characteristics.

3.2. Pregabalin dosing

Overall, 63.7% ($n=174$) of patients randomised to active treatment with either dosing regimen completed all 12 weeks versus 53.8% ($n=35$) of those assigned to placebo (Fig. 2). For the full 12-week treatment period (including titration), the average pregabalin dosage was 372.2 mg/day (range = 148.7–535.7 mg/day) for patients in the flexible-dose treatment group and 481.5 mg/day (range = 26.5–585.7 mg/day) for patients in the fixed-dose group. Over the last 8 weeks of treatment—by which time most patients had reached a stable dosage—the average pregabalin dosage for patients in the flexible-dose treatment group was 457.0 mg/day compared with 554.8 mg/day for patients in the fixed-dose group. Among the flexible-dose treatment group, 11.4% of patients were taking 150 mg/day pregabalin, 22.6% were taking 300 mg/day, 33.3% were taking 450 mg/day, and 32.6% were taking 600 mg/day at either endpoint or the point at which they discontinued.

3.3. Efficacy

3.3.1. Pain relief

Compared with placebo, treatment with either pregabalin regimen resulted in statistically significant improvement in pain symptoms (Fig. 3). Subgroup analysis showed that improvements of similar magnitude were achieved in patients with either PHN or painful DPN.

Patients randomised to the fixed-dose pregabalin group experienced pain relief significantly superior to that for placebo by the end of the first treatment week ($P=0.007$), and this superiority continued throughout the remaining 11 weeks (Fig. 3) (all subsequent $P<0.001$). Patients randomised to flexible-dose pregabalin exhibited significant superiority

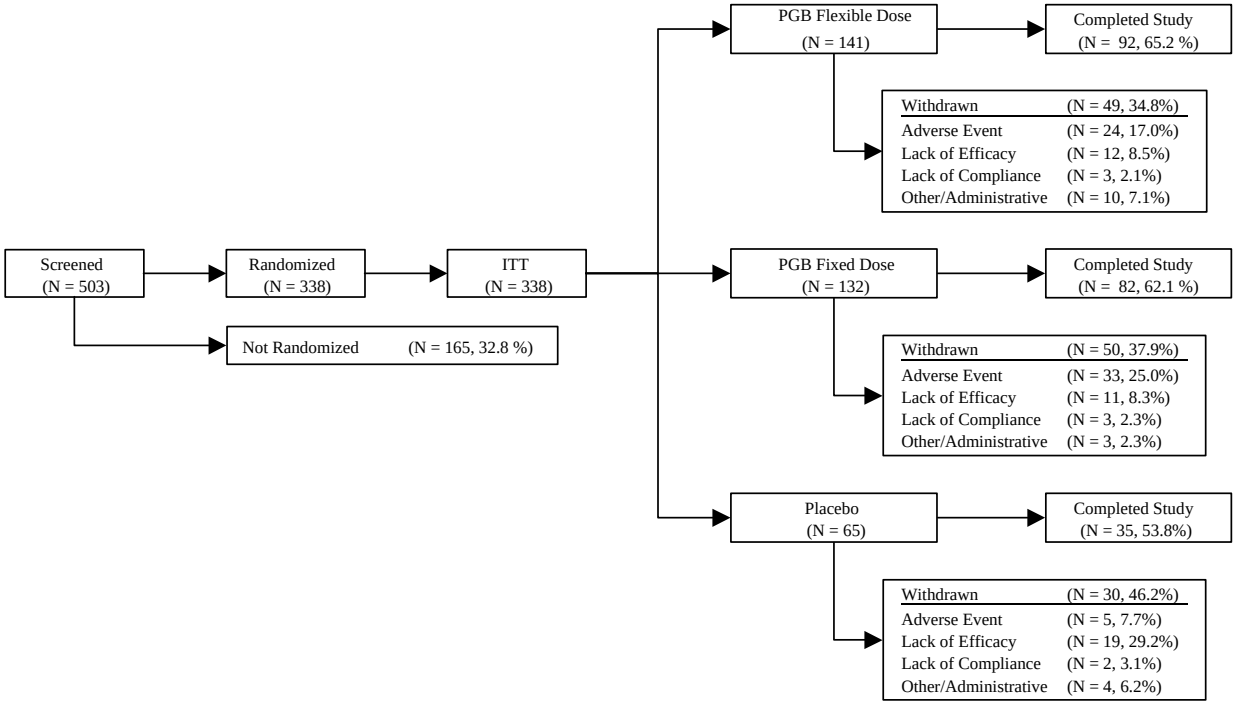

Fig. 2. Disposition of patients. The most common reasons that screened patients were not randomised were failures to meet inclusion criteria (e.g. 90 screened patients had creatinine clearance <60 mL/min, 20 had HbA_{1c} >11%, and 15 had VAS score <40 at baseline).

Table 1
Demographic and baseline clinical characteristics

	Placebo ($N=65$)	Pregabalin		All ($N=338$)
		Flexible-dose ($N=141$)	Fixed-dose ($N=132$)	
Characteristics				
Gender, *N* (%)				
Male	37 (56.9)	74 (52.5)	72 (54.5)	183 (54.1)
Female	28 (43.1)	67 (47.5)	60 (45.5)	155 (45.9)
Race, *N* (%)				
White	63 (96.9)	136 (96.5)	131 (99.2)	330 (97.6)
Black	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.3)
Hispanic	1 (1.5)	3 (2.1)	1 (0.8)	5 (1.5)
Asian or Pacific Islander	1 (1.5)	1 (0.7)	0 (0.0)	2 (0.6)
Age, years				
Mean ± SD	61.7 ± 12.6	62.7 ± 10.6	61.8 ± 11.0	62.2 ± 11.1
Range	28–82	40–87	26–86	26–87
Weight, kg				
Mean ± SD	81.4 ± 15.4	84.8 ± 14.2	83.8 ± 16.1	83.8 ± 15.2
Height, cm				
Mean ± SD	169.8 ± 9.6	168.2 ± 10.2	167.3 ± 9.9	168.1 ± 10.0
Creatinine clearance, mL/min				
Mean ± SD	86.0 ± 25.1	88.6 ± 24.0	88.5 ± 23.5	88.1 ± 24.0
Disease history				
PHN	$N=17$	$N=36$	$N=36$	$N=89$
Duration of PHN months, mean ± SD	38.7 ± 33.9	39.1 ± 52.8	34.7 ± 33.0	37.2 ± 41.9
Baseline pain score, mean ± SD	6.7 ± 1.7	7.0 ± 1.5	7.1 ± 1.7	7.0 ± 1.6
Painful DPN	$N=48$	$N=105$	$N=96$	$N=249$
Diabetes type, *N* (%)				
Type 1	9 (18.8)	16 (15.2)	17 (17.7)	42 (16.9)
Type 2	39 (81.3)	89 (84.8)	79 (82.3)	207 (83.1)
Duration of diabetes, years, mean ± SD	13.6 ± 9.2	13.8 ± 10.1	13.2 ± 8.7	13.5 ± 9.4
Duration of DPN, years, mean ± SD	4.5 ± 3.0	5.0 ± 5.2	4.6 ± 4.1	4.7 ± 4.4
Baseline pain score mean ± SD	6.6 ± 1.7	6.7 ± 1.6	6.7 ± 1.5	6.7 ± 1.5

versus placebo by Week 2 ($P=0.021$) and throughout the study (all $P \leq 0.013$).

Two responder analyses were performed: ≥50% decrease in mean pain score from baseline to endpoint, a benchmark typically used in pain trials, and a lesser, yet clinically meaningful, level of ≥30% (Farrar et al., 2001). Based on either criterion, both flexible- and fixed-dose pregabalin were significantly superior to placebo: 48.2% of patients treated with flexible-dose pregabalin, 52.3% of patients treated with fixed-dose pregabalin, and 24.2% of patients on placebo experienced a ≥50% pain score reduction ($P<0.001$ for each pregabalin group versus placebo), and 59.0% of flexible-dose, 66.4% of fixed-dose, and 37.1% of placebo-treated patients had a ≥30% pain score reduction ($P=0.003$ for flexible-dose and $P<0.001$ for fixed-dose versus placebo).

The NNT to obtain one patient with ≥50% reduction of ongoing pain was calculated to be 3.6 (95% CI = 2.4–6.9, $P<0.001$) for patients in the fixed-dose arm, 4.2 (95% CI = 2.7–9.5, $P<0.001$) for patients in the flexible-dose arm, and 3.8 (95% CI = 2.6–7.3, $P<0.001$) for all pregabalin-treated patients. Similarly, the NNT for a ≥30% reduction of ongoing pain at study endpoint was 3.4 (95% CI = 2.3–6.8, $P<0.001$) for patients in the fixed-dose arm, 4.6 (95% CI = 2.7–13.6, $P=0.003$) for patients in the flexible-dose arm, and 3.9 (95% CI = 2.6–8.3, $P<0.001$) for all pregabalin-treated patients. These NNT values are consistent with those reported by Dworkin et al. (2003) in patients with PHN who were treated with pregabalin.

3.3.2. Secondary endpoints

The impact of neuropathic pain on sleep interference was significantly improved at endpoint over placebo for patients in each pregabalin treatment group ($P<0.001$ for each group versus placebo) (Fig. 4). At endpoint, both pregabalin treatments were significantly superior to placebo in improving Sleep Disturbance ($P<0.001$ for both) and Overall Sleep Problem Index ($P<0.05$ for both) on the MOS-Sleep scale.

The percentage of patients reporting improvement at endpoint in PGIC (Fig. 5) was statistically significantly greater in each pregabalin treatment group compared with placebo.

3.4. Safety

Of the 338 patients who received study medication, 224 (66.3%) experienced ≥1 AE, most of which were treatment related. Sixty-two (18.3%) patients discontinued from the study due to any adverse event: 5 (7.7%) placebo-treated patients and 57 (20.9%) pregabalin-treated patients

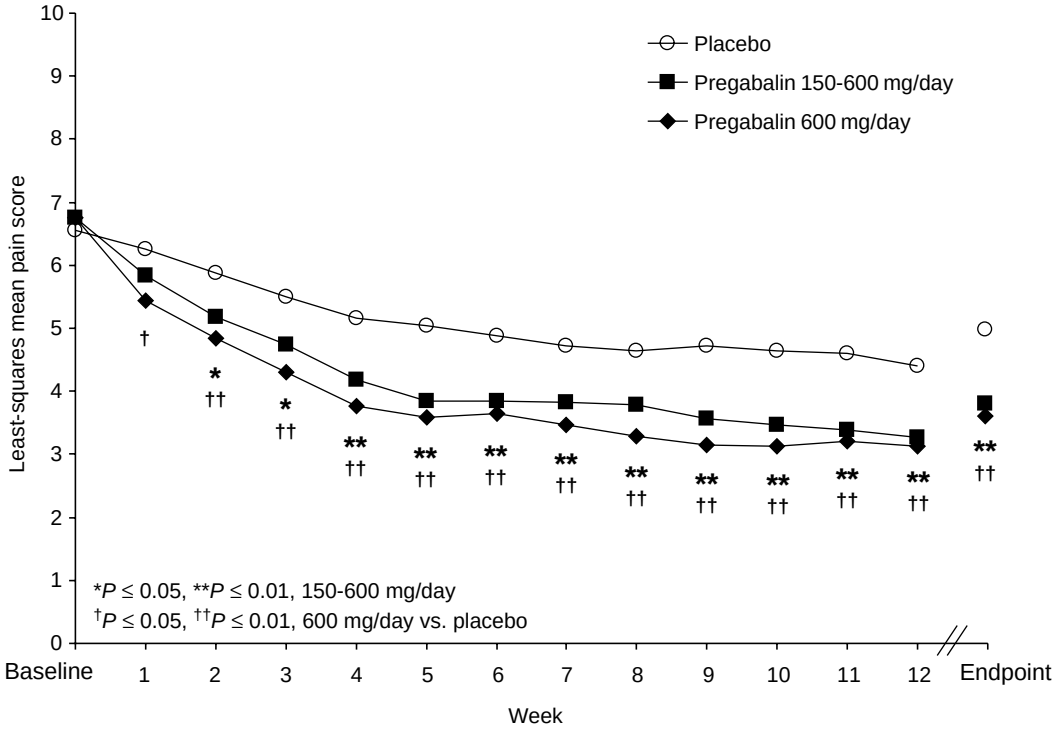

Fig. 3. Weekly mean pain scores (Least squares means from repeated measures ANCOVA) for ITT patients treated with placebo, or pregabalin with flexible or fixed dosing.

(24 [17.0%] in the flexible-dose treatment group and 33 [25.0%] in the fixed-dose treatment group). The AEs that most frequently led to discontinuation in the pregabalin fixed-dose and flexible-dose groups were dizziness (7.6 and 2.1%), nausea (6.1 and 1.4%), vertigo (3.8 and 2.8%), and somnolence (3.8 and 0.0%).

Associated AEs (summarized in Table 2) occurred more frequently in the pregabalin arms (55.3%, $n=78$ for

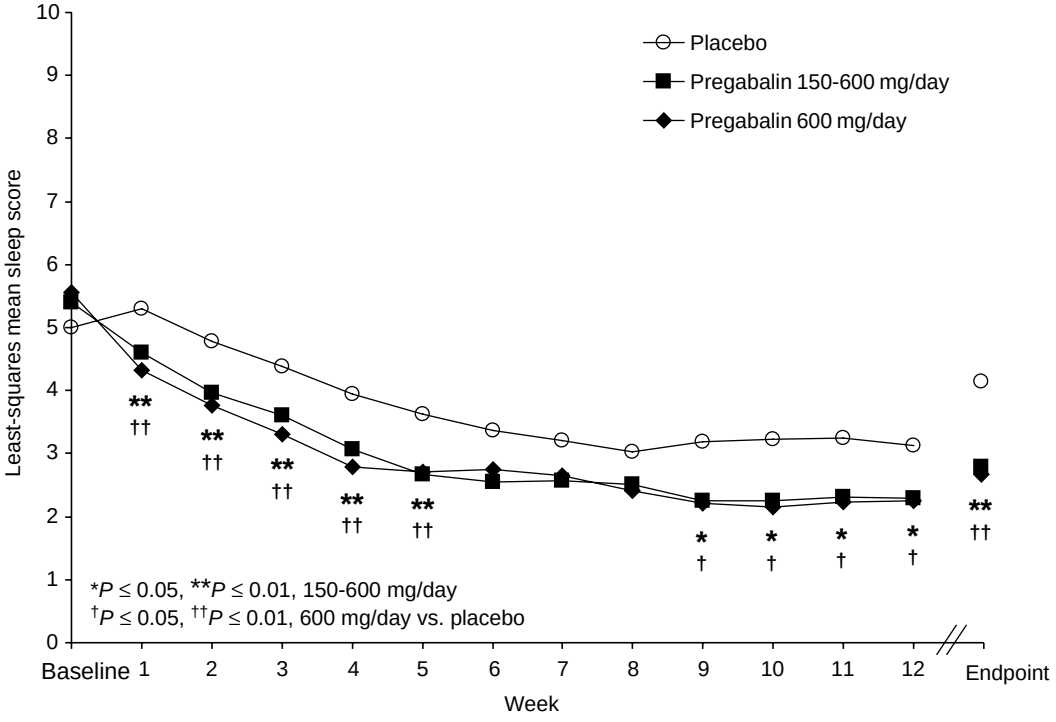

Fig. 4. Weekly mean sleep interference scores (Least squares means from ANCOVA).

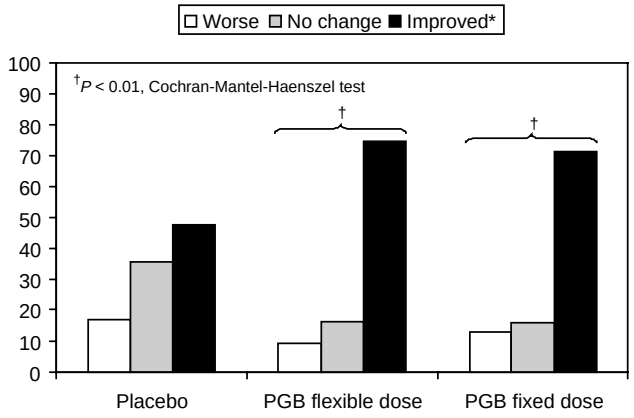

Fig. 5. PGIC evaluation of patients' overall status at endpoint. *Proportion reporting 'very much improved' or 'much improved': 52.0% of flexible-dose group; 53.6% of fixed-dose group; and 30.5% of placebo group.

flexible-dose and 68.9%, $n=91$ for fixed-dose) than in the placebo arm (27.7%, $n=18$). Most were mild or moderate in intensity and generally transient. There were two deaths, both due to cardiac arrest, in patients in the pregabalin fixed-dose treatment group. Neither death was considered to be treatment related.

Numbers needed to harm (for all pregabalin-treated patients) were calculated for the most common ($\geq 10\%$ in any treatment group) AEs: dizziness = 5.2; peripheral oedema = 11.6; weight gain = 10.3; somnolence = 8.5; nausea = 16.2. Dizziness and somnolence were generally transient and appeared to be dose related: median onset of dizziness and somnolence were 6.0 days and 9.0 days in the flexible-dose group and 1.0 day and 4.0 days in the fixed-dose group. Median duration of any AE in the pregabalin treatment groups was 1.0 day. Weight gain was recorded in two ways, as reported by patients as an AE (Table 2) and as measured per protocol by the investigators. No severe AE of weight gain was reported by patients, and only one patient from the flexible-dose group (0.7%) and one from the fixed-dose group (0.8%) discontinued due to this AE (in one of these patients, the relationship of the weight gain to study medication was deemed unknown). Per-protocol measurements of weight showed that 13.9% ($n=19$) of patients in the pregabalin flexible-dose group and 7.0% ($n=9$) in the pregabalin fixed-dose group experienced a $\geq 7\%$ increase from baseline in body weight, while one patient in each pregabalin treatment group experienced a $\geq 7\%$ decrease. At the last study visit, mean change in weight from baseline was 1.9 kg in the flexible-dose, 1.6 kg in the fixed-dose, and 0.2 kg in the placebo groups.

Table 2
Summary of associated AEs occurring in $\geq 5\%$ of patients in any treatment group (safety population)

Adverse event	% of Patients (% discontinued due to AE)			
	Placebo, $n=65$	Pregabalin		
		Flexible-dose, $n=141$	Fixed-dose, $n=132$	All pregabalin, $n=238$
Dizziness	4.6 (1.5)	19.1 (2.1)	28.8 (7.6)	23.8 (4.8)
Peripheral oedema	3.1 (0.0)	15.6 (2.1)	7.6 (0.8)	11.7 (1.5)
Weight gain	3.1 (0.0)	12.1 (0.7)	13.6 (0.8)	12.8 (0.7)
Somnolence	0 (0.0)	10.6 (0.0)	12.9 (3.8)	11.7 (1.8)
Nausea	1.0 (1.5)	5.0 (1.4)	10.6 (6.1)	7.7 (3.7)
Vertigo	1.5 (1.5)	7.8 (2.8)	9.8 (3.8)	8.8 (3.3)
Asthenia	0 (0.0)	6.4 (0.7)	9.1 (2.3)	7.7 (1.5)
Dry mouth	4.6 (0.0)	2.8 (0.0)	6.1 (0.0)	4.4 (0.0)
Headache	3.1 (1.5)	5.0 (2.1)	2.3 (0.0)	3.7 (1.1)

There were modest changes in indices of glycaemic control for patients in all groups. The shifts in laboratory values were generally not correlated with AEs. Only one patient experienced serious hyperglycaemia (not treatment related). ECG abnormalities were reported as AEs in four patients who received pregabalin, but none was considered to be treatment related.

Changes in peripheral (lower leg, lower leg to knee, above knee) oedema based on per-protocol measurements from baseline to termination were observed in 12.4% of the pregabalin-treated patients versus 1.6% of those who received placebo. Treatment-related peripheral oedema was reported as an AE in 15.6% of patients in the pregabalin flexible-dose, 7.6% of patients in the pregabalin fixed-dose, and 3.1% of patients in the placebo groups. Peripheral oedema resulted in discontinuation by 2.1% of patients in the flexible-dose group and by 0.8% in the fixed-dose group. Generalised or abdominal oedema was observed in 0.7% of flexible-dose and 0.8% of fixed-dose pregabalin patients and in no placebo patients, while 2.2% of flexible- and 2.3% of fixed-dose patients and no placebo-treated patients had facial/periorbital oedema. No patients in any treatment group discontinued the study because of either of these non-peripheral types of oedema.

4. Discussion

This randomised, placebo-controlled trial examined flexible- and fixed-dose arms to determine whether individual tailoring of pregabalin dosage might achieve a more optimal balance between tolerability and efficacy.

Pregabalin dosed BID in flexible- and fixed-dose regimens produced statistically significant reductions in mean pain scores. Analysis of weekly pain scores indicated that the flexible-dose pregabalin treatment group achieved statistically significant improvement compared with placebo as early as Week 2, and this improvement was maintained through Week 12. The fixed-dose pregabalin treatment group was statistically significantly superior to placebo as early as Week 1 and throughout Week 12. The apparently more rapid onset of action with fixed-dose pregabalin may reflect the higher dose (300 versus 150 mg/day) during the first week of treatment with this regimen.

Farrar et al. (2001) reported that an approximately 30% reduction in NRS pain score was clinically meaningful.

This change in pain score provides a good surrogate measure of a patient-determined, clinically important response. Other, more conservative, investigators have suggested that a 50% reduction in pain score corresponds to a clinically significant improvement (Forouzanfar et al., 2003). By either criterion, both BID regimens of pregabalin were associated with significantly greater percentages of patients achieving clinically meaningful response.

Flexible- and fixed-dose pregabalin were significantly superior to placebo in improving sleep-interference scores and both Sleep Disturbance and Overall Sleep Problem Index scores on the MOS-Sleep Scale. These findings are clinically important, since sleep interference is common among patients with neuropathic pain (Bajwa and Ho, 2001; Meyer-Rosberg et al., 2001). Significant improvement in PGIC scores, described as the '''gold standard' of clinically significant change'' (Hurst and Bolton, 2004), also supports the similar effectiveness of the two pregabalin regimens for patients with painful DPN or PHN. Finally, the similar effectiveness of both pregabalin treatment regimens over placebo was reflected by the low discontinuation rates due to lack of efficacy for pregabalin versus placebo (8.5 and 8.3% for flexible- and fixed-dose pregabalin versus 29.2% for placebo).

The rate of AEs among patients who were randomised to the fixed-dose group was higher (74.2%) than that for patients who were randomised to flexible-dose pregabalin (68.8%), and more patients from the fixed-dose group (25.0%) withdrew from treatment due to AEs than did patients from the flexible-dose group (17.0%) (placebo group: 7.7%). Patients in the fixed-dose arm were randomly assigned to 600 mg/day pregabalin, the upper end of the dosing range. Such a dose may well have been higher than what individual patients required to achieve meaningful pain relief and acceptable tolerability. These differences between the pregabalin regimens suggest an advantage of the flexible dosing (based on patients' individual response and tolerability) over the fixed dosing at the upper end of pregabalin's dosing range.

The incidence rates of the most commonly reported AEs, with the exception of peripheral oedema and headache, were lower in the flexible-dose group compared with the fixed-dose group. In this study, the incidence of oedema was similar between the two pregabalin groups, but it was higher than that observed in previous clinical trials of pregabalin in similar patient populations. This greater incidence may be attributable to several factors, including the provisions of the study protocol for the investigators to specifically look for oedema and to measure calf circumference.

Administration of pregabalin with flexible dosing did not reduce the prevalence of the most common, clinically relevant CNS-related AEs but did delay their onset. There were no apparent relationships between pregabalin treatment regimen and median duration of common AEs. The overall study completion rate in the flexible-dose group was 65.2 versus 62.1% in the fixed-dose group. Importantly, discontinuations from the pregabalin groups due to the most commonly reported AEs were low: 4.8% for dizziness, 1.5% for peripheral oedema, 0.7% for weight gain, 1.8% for somnolence, and 3.7% for nausea. Additionally, 73.8% of flexible-dose patients, 70.5% of fixed-dose patients, and 76.9% of placebo patients entered the open-label follow-on study. These observations suggest—along with the large percentage of patients reporting improvement on the PGIC, a global measure of status change—a high degree of patient satisfaction with treatment.

In clinical practice, AEs may be managed by a more individualised dosing schedule based on patients' clinical responses. It is important to note that the starting dose of 150 mg/day in the flexible-dose group may be clinically effective in some patients, thus eliminating the need for upward dosing (Rowbotham et al., 2003). Further, because many patients will not require dosing of pregabalin at the upper end of its dosing range to achieve meaningful improvement in their pain, individualised dosing of pregabalin may decrease the incidence of AEs and discontinuation of therapy. This finding is consistent with other results which have shown that individualised dosing can enhance the tolerability of a wide range of drugs, including agents used to treat neuropathic pain (Biton et al., 2001; Egbunike and Chaffee, 1990; Ferrendelli, 2001; Ruoff, 1999).

Five previous randomised, placebo-controlled trials of pregabalin as treatment of DPN (Lesser et al., 2004; Richter et al., in press; Rosenstock et al., 2004) or PHN (Dworkin et al., 2003; Sabatowski et al., 2004) have used fixed, three-times-daily dosing for 5 or 8 weeks. These five trials, which together enrolled over 1100 patients, showed significant, rapid-onset (as early as Week 1) efficacy for reduction of pain and pain-related sleep interference that was sustained throughout the duration of the studies. The present trial—which used BID dosing schedules for a treatment period of 12 weeks—demonstrates rapid, sustained, and robust efficacy, as well as tolerability, similar to that seen in the earlier TID studies.

Although direct comparisons are not possible, as comparator trials with other drugs used to treat neuropathic pain have not been performed, findings from recent trials of pregabalin, including those from the present study, as well as recent recommendations from the American Academy of Neurology (Dubinsky et al., 2004), support the view that pregabalin may be a valuable first-line alternative to current, often poorly effective, pharmacologic treatments for neuropathic pain. For example, tricyclic antidepressants are used to treat neuropathic pain, yet they require lengthy titrations, and they may be limited by safety concerns and adverse effects, especially in the elderly (AGS Panel, 2002; Attal, 2000; McQuay et al., 1996). Opioids, which have demonstrated efficacy for treating neuropathic pain, are often limited in their response rates and carry the risk for significant adverse effects (Attal, 2000). Antiepileptic drugs, such as carbamazepine and lamotrigine, have been

used for treatment of neuropathic pain, but there are few randomised, clinical trial data to support their use, they are not effective in all patients, and they are limited by significant adverse effects and low tolerability (Attal, 2000; Ross, 2000; Seetharam and Pellock, 1991). And though gabapentin is approved for use in PHN and has been reported to demonstrate efficacy in many kinds of neuropathic pain conditions, including DPN, its pharmacokinetics are non-linear, it must be dosed TID, and its dosing typically requires complicated titration to reach the effective dose of 1800 mg/day (Backonja and Glanzman, 2003; Backonja et al., 1998; Rowbotham et al., 1998). The limitations of current therapies for neuropathic pain may require the use of complicated, multidrug treatments in many individuals. Even with such regimens, a large percentage of patients do not achieve complete or even sufficient pain relief (Bonezzi and Demartini, 1999; Vu, 2004). For such patients, pregabalin—owing to its lack of known drug–drug interactions—may also be useful as add-on therapy to a currently used drug or drugs that provide the patient some, but not sufficient, pain relief.

The results of this 12-week study are consistent with previous studies and further support the efficacy, tolerability, and safety of pregabalin as treatment of neuropathic pain syndromes. Twice-daily administration of pregabalin using either a flexible- or fixed-dose regimen was statistically significantly superior to placebo in relieving chronic neuropathic pain associated with either painful DPN or PHN. Pregabalin was safe, effective, and generally well tolerated. Its BID dosing and rapid therapeutic onset of pain relief—without the need for complex titration—suggest that pregabalin will be easy to use in clinical settings, which is an important consideration for the elderly patients who represent a large proportion of the populations with neuropathic pain syndromes. Based on our findings, and general clinical practice, flexible BID dosing of pregabalin, allowing for dosage adjustment to optimize tolerability and efficacy, is recommended.

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