Drugs 2004; 64 (24): 2813-2820
0012-6667/04/0024-2813/$34.00/0

Pregabalin

In the Treatment of Painful Diabetic Peripheral Neuropathy

James E. Frampton and *Lesley J. Scott*

Adis International Limited, Auckland, New Zealand

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Abstract

▲ Pregabalin, the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, has a similar pharmacological profile to that of its developmental predecessor gabapentin, but showed greater analgesic activity in rodent models of neuropathic pain.

▲ The exact mechanism of action of pregabalin is unclear, although it may reduce excitatory neurotransmitter release by binding to the α_2-δ protein subunit of voltage-gated calcium channels.

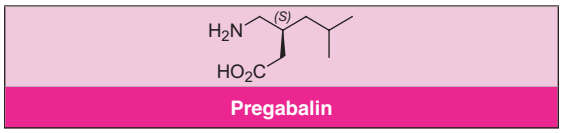
▲ Oral pregabalin at fixed dosages of 300 and 600 mg/day, administered three times daily, was superior to placebo in relieving pain and improving pain-related sleep interference in three randomised, double-blind, multicentre studies of 5–8 weeks' duration in a total of 724 evaluable patients with painful diabetic peripheral neuropathy (DPN).

▲ Significant reductions in weekly mean pain scores (primary endpoint) and sleep interference scores were observed at 1 week and sustained thereafter. A significant reduction in pain was apparent on the first day of treatment with pregabalin 300 mg/day.

▲ Twice daily fixed (600 mg/day) or flexible (150–600 mg/day) pregabalin was also effective in reducing pain and sleep interference in two 12-week placebo-controlled trials in a total of 733 randomised DPN patients.

▲ Pregabalin was well tolerated in DPN patients; mild-to-moderate dizziness, somnolence and peripheral oedema were the most common adverse events.

Features and properties of pregabalin (Lyrica®, CI-1008)	
Indication	
Painful diabetic peripheral neuropathy	
Putative mechanism of action	
Binds to the α_2-δ protein subunit of voltage-gated calcium channels and reduces excitatory neurotransmitter release	
Dosage and administration	
Recommended dosage	150–600 mg/day
Route of administration	Oral
Frequency of administration	2 or 3 times daily
Mean pharmacokinetic parameters (1–300mg single oral dose in healthy volunteers)	
Bioavailability	≈90% (no plasma protein binding)
Peak plasma concentration	0.04–9.46 mg/L
Time to peak plasma concentration	1.3h
Area under the plasma concentration-time curve	0.2–66.3 mg • h/L
Metabolism and elimination	Negligible hepatic metabolism, with primarily renal elimination (98% as unchanged drug)
Elimination half-life	4.6–6.8h
Adverse events	
Most frequent	Dizziness, somnolence and peripheral oedema



Painful diabetic peripheral neuropathy (DPN) is estimated to affect 20–24% of the US diabetic population or ≈3 million people.[1] Chronic DPN symptoms, predominantly to the lower limbs and feet, can persist for many years and substantially reduce patients' health-related quality of life through interference with general, social and recreational activities, as well as with work, mobility, mood and sleep.[1] The pathophysiology of DPN is still unclear;[2] however, duration of diabetes mellitus and poor glycaemic control appear to be important risk factors for the development of this condition.[1]

Treatment of DPN, like that of neuropathic pain associated with other specific syndromes, is challenging.[2] In the absence of a curative therapy, management relies mainly on pharmacological control of pain symptoms in conjunction with good glycaemic control and other appropriate diet and lifestyle interventions.[2] Prior to duloxetine, a dual serotonin and noradrenaline (norepinephrine) reuptake inhibitor, becoming the first agent to be specifically approved for use in this indication by the US FDA,[3] suggested first-line medications included tricyclic antidepressants (TCAs; e.g. nortryptyline, imipramine) and topical treatments (e.g. capsaicin) for patients with mild-to-moderate DPN; the anticonvulsant gabapentin for patients with moderate to severe pain; and opioid analgesics (e.g. codeine, tramadol, oxycodone) for intermittent/severe/breakthrough pain only.[2,4] However, drawbacks with some of these agents include a slow onset of analgesic action (TCAs, capsaicin), a potentially limiting adverse effect profile (TCAs; to a lesser extent opioids) and possible dependency related to long-term use (opioids).[2,5] Moreover, most patients require a combination of these drugs for adequate pain relief,[4] which increases the risk of drug-related adverse events.[5] Additional rapidly acting, effective and safe treatments are therefore desirable.

Pregabalin (Lyrica® [1]; 3-isobutyl GABA) is the pharmacologically active *S*-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid.[6] It was developed as a follow-up compound to gabapentin, and has been shown to be effective in the treatment of several disorders, including neuropathic pain [DPN and postherpetic neuralgia (PHN)], epilepsy (add-on treatment of partial seizures) and generalised anxiety disorder.[6] This profile, however, focuses on the efficacy and tolerability of oral pregabalin in the treatment of DPN.

1. Pharmacodynamic Profile

- Pregabalin has a similar pharmacological profile to that of gabapentin.[7,8] It demonstrated antiallodynic and antihyperalgesic activities in various rodent models of neuropathic pain, including: vincristine-,[9] streptozocin-[10] and nerve injury-induced[11-13] mechanical allodynia; formalin-,[14] carrageenan-,[14,15] substance P-,[16] NMDA-,[16] and thermal injury-[17,18] induced hyperalgesia; and surgically-induced mechanical allodynia.[19] The antiallodynic and antihyperalgesic effects of pregabalin were observed at dosages 2- to 4-fold lower than those of gabapentin.[7]
- The exact mechanism of action of pregabalin is unclear.[6] It is a structural analogue of GABA, like gabapentin, although neither compound interacts with GABA-A or -B receptors, or influences GABA uptake.[8,20]
- Pregabalin (and gabapentin) may, however, modulate the presynaptic release of excitatory neurotransmitters, such as glutamate and noradrenaline (norepinephrine), by selectively binding with high affinity to α_2-δ protein, an auxiliary subunit of voltage-gated calcium channels[21-23] (see also review by Lauria-Horner and Pohl[7]). Recent structure-activity studies as well as results with a mutant mouse model of neuropathic pain indicate that binding to α_2-δ protein is a prerequisite for the analgesic actions of pregabalin.[24]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• Both pregabalin and gabapentin modulated the release of the sensory neuropeptides substance P and calcitonin gene-related peptide from rat spinal tissues, but only under conditions that correspond to significant inflammation-induced sensitisation of the spinal cord.[25]

2. Pharmacokinetic Profile

The pharmacokinetics of pregabalin have been examined in healthy volunteers (data only available as abstracts[26-29]), in otherwise healthy subjects with various degrees of renal function[30] and in patients with end-stage renal failure (ESRF).[30] Additional information is available from earlier reviews of the drug,[6,7] as well as a recent summary of pharmacokinetic studies published as an abstract.[31] Mean pharmacokinetic parameters are reported throughout this section.

• Pregabalin was rapidly absorbed and displayed linear pharmacokinetics after oral administration in a total of 86 healthy volunteers.[27,28] The time to peak plasma concentration (C_{max}), was 1.3 hours.[28] Both C_{max} and the area under the plasma concentration-time curve (AUC) increased in proportion to the dose following single rising (1–300mg) or multiple rising (25–300mg every 8 hours then 300mg every 12 hours) doses.[27] Values for C_{max} and the AUC following a single 1–300mg dose are listed in the Features and Properties table.

• The oral bioavailability of pregabalin was ≈90%.[28] Food delayed the rate, but not extent, of pregabalin absorption.[31] The drug undergoes negligible hepatic metabolism after oral administration in healthy volunteers[6] and does not bind to plasma proteins.[7] The lack of hepatic metabolism (and of pregabalin activity at cytochrome P450 enzymes) was reflected in an absence of pharmacokinetic drug-drug interactions in relevant studies.[31] However, no further details are available.[6,7,31]

• Similarly, no pharmacokinetic drug interactions between pregabalin (dosage unspecified) and oral antidiabetic agents or insulins were observed in a population pharmacokinetic (meta)analysis of 1099 healthy volunteers, subjects with renal impairment and patients with chronic pain.[29]

• Renal excretion is the primary route of elimination of pregabalin; 98% of the administered dose is eliminated as unchanged drug in the urine.[31] Urinary recovery of pregabalin was independent of the dose, although it was slightly higher after multiple- than single-dose administration.[27] The elimination half-life ($t_{1/2}$) was ≈6 hours (range, 4.6–6.8 hours following a single 1–300mg dose[28]), and was independent of the dose.[27]

The pharmacokinetics of a single 50mg oral dose of pregabalin have been investigated in 26 otherwise healthy subjects aged 18–75 years with various degrees of renal function.[30] For the purposes of making pregabalin dosage recommendations, subjects were stratified according to the following creatinine clearance (CL_{CR}) groups: >60 mL/min (n = 11); 30–60 mL/min (n = 7); 15–29 mL/min (n = 7); and <15 mL/min (n = 1). An additional 12 patients with ESRF (urinary output ≤200 mL/24h) who required three times weekly haemodialysis were also studied; pregabalin was administered ≈24 hours before the next scheduled dialysis session.[30]

• Pregabalin oral clearance was directly proportional to CL_{CR} in patients not on dialysis; it was 56.5, 30.6, 16.7 and 8.3 mL/min in the >60, 30–60, 15–29 and <15 mL/min CL_{CR} groups, respectively. In line with this, $t_{1/2}$ was prolonged and $AUC_{0-\infty}$ was increased. Pregabalin was effectively cleared in patients with ESRF undergoing dialysis, with each 4-hour haemodialysis session removing ≈50–60% of the amount of drug initially present in the circulation.[30]

3. Therapeutic Trials

The efficacy of pregabalin in treating neuropathic pain due to DPN has been evaluated in five randomised, double-blind, placebo-controlled, multicentre studies (n = 146–395).[32-36] Four trials enrolled exclusively DPN patients and evaluated fixed dosages of pregabalin administered twice daily for 12 weeks[36] or three times daily for 5–8 weeks (studies 1008-014,[33] 1008-029[34] and 1008-131[32]). The fifth trial (hereafter referred to as the 'fixed-flexible dosage study') assessed both fixed and flexible dosages of the drug administered twice daily for 12

weeks in predominantly DPN patients.[35] Two of these studies have been published in full (1008-131[32]) or are in press (1008-029[34]); the remaining three studies are only available as abstracts.[33,35,36] Also reported in abstracts are additional data from two[33,34,37] or all three[32-34] of the fixed-dosage three times daily trials,[38-40] and an analysis of six follow-on, open-label extensions of controlled trials in patients with neuropathic pain (DPN or PHN).[41]

Patients aged ≥18 years with a diagnosis of DPN for ≥6 months[35] or 1–5 years[32-34,36] were considered eligible if: (i) they had completed at least four daily pain diaries and had a minimum daily score of ≥4 on an 11-point numerical pain rating scale[42] (0 = no pain to 10 = worst possible pain) during the baseline week preceeding randomisation; and (ii) they had pain equivalent to ≥40mm on the 100mm visual analogue scale (VAS) of the Short-form McGill Pain Questionnaire (SF-MPQ) at baseline and randomisation visits. Exclusion criteria included CL_{CR} <30[36] or ≤60[32-35] mL/min and failure to respond to previous treatment with gabapentin ≥1200 mg/day.[32]

The primary efficacy measure was the endpoint weekly mean pain score on the 11-point pain rating scale[42] from patients' daily pain diaries.[32-36] A supplementary analysis of the primary efficacy parameter was the responder rate (i.e. proportion of patients with a ≥50% reduction in mean pain score from baseline to endpoint).[32,35,36,38]

Secondary measures included: SF-MPQ;[32-34,36] daily/weekly sleep interference score;[32-36] Short-form (SF)-36 questionnaire;[32-34] and patient/clinician global impression of change (PGIC/CGIC).[32-35]

All efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all patients who received at least one dose of study medication.[32,35,38] For the fixed-dosage three times daily trials, the ITT populations consisted of the following: 79, 82 and 82 patients randomised to pregabalin 150 mg/day, 600 mg/day and placebo in study 1008-014;[33] 77, 81, 82 and 97 patients randomised to pregabalin 75 mg/day, 300 mg/day, 600 mg/day and placebo in study 1008-029;[34] and 75 and 69 patients randomised to pregabalin 300 mg/day and placebo in study 1008-131.[32]

In the fixed-dosage twice daily trial,[36] 99, 99, 101 and 96 patients were randomised to pregabalin 150 mg/day, 300 mg/day, 600 mg/day and placebo; the corresponding ITT populations are not, however, available. Patients assigned to the 600 mg/day dosage group received pregabalin 600 mg/day only if their CL_{CR} was normal (>60 mL/min; n = 88); those with a low CL_{CR} (>30–≤60 mL/min; n = 13) received a clinically equivalent dosage of pregabalin 300 mg/day.[36]

In the fixed-dosage three times daily trials, pregabalin dosages of 150 and/or 600 mg/day were force-titrated over the first 6 days[34] or 2 weeks[33] in studies 1008-014[33] and 1008-029,[34] whereas dosages of 75 and/or 300 mg/day in studies 1008-029[34] and 1008-131[32] were not titrated. In the fixed-dosage twice daily trial,[36] pregabalin dosages of 150, 300 or 600 mg/day were titrated over 1 week; no other details are available.

DPN patients (n = 96) in the fixed-dosage arm of the fixed-flexible dosage study[35] received pregabalin 300 mg/day for the first week followed by 600 mg/day for the remainder of the study. DPN patients (n = 105) in the flexible-dosage arm had their dosage optimised between 150 and 600 mg/day during an initial 4-week dosage adjustment period before continuing on that dosage for the remainder of the study. There were 48 DPN patients in the placebo group. This study also included 89 (26%) patients with PHN; however, separate results for the DPN and PHN populations are not available.[35]

- In the three fixed-dosage three times daily trials, pregabalin 300 and 600 mg/day, but not 75 and 150 mg/day, were effective in reducing pain associated with DPN.[32,38] The endpoint least squares (LS) mean pain scores were 4.29 with pregabalin 600 mg/day in study 1008-014 ($p = 0.0002$ vs placebo [5.55]),[33] 3.80 and 3.60 with pregabalin 300 and 600 mg/day in study 1008-029 ($p \leq 0.0002$ vs placebo [5.06])[34] and 3.99 with pregabalin 300 mg/day in study 1008-131 ($p = 0.0001$ vs placebo [5.46]).[32] Baseline LS mean pain scores were between ≈6 and 7 for all treatment groups in all three studies.[32-34]

• The proportion of responders among patients treated with pregabalin 300 or 600 mg/day three times daily (39–48%) was more than double that for placebo-treated patients (15–18%) [figure 1].[32,37]

• Patients receiving pregabalin 300 or 600 mg/day three times daily also experienced significantly less sleep disturbance than placebo recipients. The endpoint LS mean sleep interference scores were 2.90 with pregabalin 600 mg/day in study 1008-014 ($p = 0.0004$ vs placebo [4.05]),[39] 2.86 and 2.62 with pregabalin 300 and 600 mg/day in study 1008-029 ($p = 0.0001$ vs placebo [4.17])[39] and 2.78 with pregabalin 300 mg/day in study 1008-131 ($p < 0.0001$ vs placebo [4.32]).[32] Baseline LS mean sleep interference scores were between ≈4.5 and 6 for all treatment groups in all three studies.

• Both weekly mean pain and sleep interference scores were significantly ($p < 0.05$) improved with pregabalin 300 or 600 mg/day three times daily versus placebo at 1 week (i.e. at the first clinical assessment) in all three studies; the improvement was sustained during treatment for 5–8 weeks.[32,38,39] Of note, daily mean pain scores were significantly improved compared with placebo beginning on the first day of treatment in the untitrated pregabalin 300 mg/day dosage groups in studies 1008-029 and 1008-131 ($p \leq 0.0004$), and beginning on the second and seventh day of treatment in the titrated pregabalin 600 mg/day dosage groups in studies 1008-029 ($p = 0.004$; initial dosage 75 mg/day) and 1008-014 ($p = 0.006$; initial dosage 100 mg/day), respectively.[40]

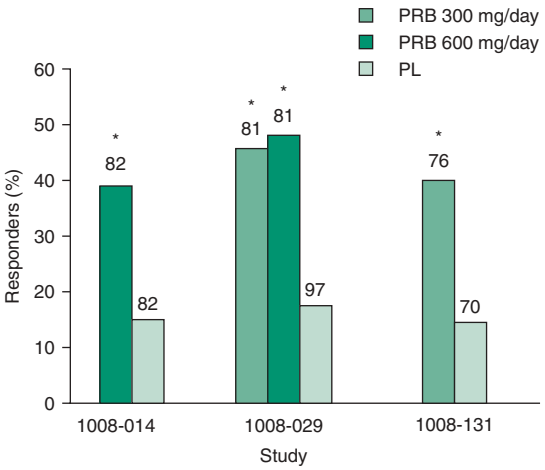


Fig. 1. Efficacy of pregabalin (PRB) in the treatment of painful diabetic peripheral neuropathy (DPN). The proportion of responders (i.e. those experiencing a ≥50% reduction in pain from baseline to endpoint, based on endpoint change in weekly mean pain score [primary endpoint]) among patients with DPN receiving fixed dosages of PRB 300 or 600 mg/day, or placebo (PL), administered three times daily, for 5–8 weeks in three, double-blind, multicentre trials.[32,37] Number of evaluable patients is shown above the bars. Data for patients receiving PRB dosages of 75 mg/day in study 1008-029 and 150 mg/day in study 1008-014 that were ineffective based on endpoint change in weekly mean pain score are not shown. * $p = 0.001$ vs PL.

• Other secondary endpoints significantly improved with pregabalin 300 or 600 mg/day three times daily compared with placebo included the SF-MPQ (in all three studies[32-34]), PGIC and CGIC scores (in all three studies[32-34]) and bodily pain domain of the SF-36 (in studies 1008-014[33] and 1008-131[32]) [$p \leq 0.036$[32] or not reported[33,34]].

• Twice daily administration of pregabalin was also effective in reducing pain and sleep interference associated with DPN or PHN.[35,36] Significant reductions in pain levels were observed at 1 week and sustained during treatment for 12 weeks in the 600 mg/day dosage group in the fixed-dosage twice daily trial (endpoint LS mean pain scores and p-values vs placebo not available).[36] The treatment response rate with pregabalin 600 mg/day was also higher than that with placebo (46% vs 30%; $p = 0.036$). Pregabalin (all dosages) significantly improved sleep interference scores (p-values vs placebo not available).[36]

• The endpoint LS mean pain scores were 3.81 and 3.60 with fixed and flexible pregabalin dosages in the fixed-flexible dosage study ($p \leq 0.002$ vs placebo [4.98]).[35] Baseline LS mean pain scores were between 6.50 and 7.00 for all three treatment groups. Treatment response rates with fixed (52%) and flexible (48%) dosages of pregabalin were at least double that with placebo (24%) [$p < 0.001$ for both comparisons].[35] Significant ($p < 0.05$) improvements in weekly mean pain scores versus placebo were seen at 1 week (fixed-dosage arm) or 2 weeks (flexible-dosage arm); sleep interference scores were significantly ($p \leq 0.01$) improved at 1 week in both treatment arms.[35]

• Pregabalin 150–600 mg/day (dosage frequency not specified) appeared to be an effective long-term maintenance therapy based on an *ad hoc* analysis of a subset of 217 DPN or PHN patients (relative proportions not specified) who received the drug for ≥420 days in open-label extensions of six randomised clinical trials.[41] Moreover, tolerance to flexible dosages of pregabalin (range 75–600 mg/day; dosage frequency not specified) did not develop based on another *ad hoc* analysis of all 517 DPN or PHN patients (relative proportions not specified) who received the drug for ≥420 days in open-label studies.[41]

4. Tolerability

Unless otherwise indicated, the following preliminary tolerability profile of pregabalin is based on 728 patients with painful DPN who were evaluated for safety in three randomised, placebo-controlled fixed dosage-only trials of pregabalin 150–600 mg/day administered three times daily for 5–8 weeks[32-34] (section 3).

• Pregabalin was well tolerated;[32] double-blind treatment completion rates ranged from 85–94% with dosages of 300 or 600 mg/day (vs 85–92% with placebo).[32-34]

• The most commonly reported treatment-emergent adverse events included dizziness, somnolence, peripheral oedema, headache, blurred vision and constipation. The majority (85%) of these (and other) adverse events were of mild-to-moderate intensity in study 1008-131.[32]

• The three most frequently occurring treatment-related adverse events appeared to be dose-dependent. The incidence of dizziness ranged from 27–39% with pregabalin dosages of 300 or 600 mg/day (three studies[32-34]) versus 10% with pregabalin 150 mg/day (one study[33]); the incidence of dizziness with placebo ranged from 2–11% (three studies[32-34]). The respective results for somnolence and peripheral oedema were 20–27% and 7–17% with pregabalin 300 and 600 mg/day versus 5% and 4% with pregabalin 150 mg/day; the respective incidences of somnolence and peripheral oedema with placebo ranged from 3–4% and 1–5%.[32-34]

• Discontinuation rates due to adverse events appeared to be dose-dependent; they were 3% and 9% with pregabalin 150 and 600 mg/day in study 1008-014;[33] 3% and 12% with pregabalin 75 and 600 mg/day in study 1008-029;[34] and 11% with pregabalin 300 mg/day in study 1008-131.[32] Discontinuation rates due to adverse events with placebo ranged from 3–5% across all three studies.[32-34]

• No cardiovascular, ophthalmological, renal or hepatic concerns were noted in studies 1008-014 and 1008-029; no neurological concerns were noted in study 1008-131.[32]

• Regarding diabetes control, pregabalin had no effect on glycosylated haemoglobin A_{1c} levels in study 1008-131[32] (relevant data for studies 1008-014 and 1008-029 not available). Three pregabalin 300 mg/day recipients (4.3%) versus one placebo recipient (1.4%) in study 1008-131 experienced a weight gain of ≥7% from baseline to study end; however, mild weight gain as an adverse event was only reported by one pregabalin recipient (who did not withdraw from treatment).[32]

• Twice daily administration of fixed (600 mg/day)[35,36] or flexible (150–600 mg/day)[35] pregabalin dosages for 12 weeks was generally well tolerated in populations of exclusively[36] or predominantly[35] DPN patients. Most adverse events were of mild-to-moderate intensity;[35,36] no new safety concerns were noted.[35]

5. Dosage and Administration

Based on EU approval (see section 6), the recommended pregabalin dosage range for the treatment of neuropathic pain, which includes that associated with DPN and PHN, is 150–600 mg/day administered in two or three divided doses (with or without food).[43] An initial dosage of 150 mg/day may be increased to 300 mg/day after 3–7 days, based on individual patient response and tolerability; if necessary, the dosage can be increased to 600 mg/day after an additional 7 days.[43] Pregabalin dosage adjustment should be considered in cases of renal impairment (section 2).[30]

6. Pregabalin: Current Status in Painful Diabetic Peripheral Neuropathy

Pregabalin 300 or 600 mg/day three times daily was an effective, rapid and well tolerated therapy for painful DPN in three randomised clinical trials. Fixed (600 mg/day) or flexible (150–600 mg/day) pregabalin dosages administered twice daily were also effective in the treatment of neuropathic pain (and related sleep interference) due to DPN.

In July 2004, pregabalin received EU approval for the treatment of peripheral neuropathic pain, which includes DPN and PHN, and as adjunctive therapy for partial seizures in patients with epilepsy.[44] In September 2004, the US manufacturer announced that pregabalin had received approvable letters from the US FDA for DPN, PHN and as adjunctive therapy in the treatment of partial seizures in adults.[45]

References

1. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002 Nov-2002 31; 18 (6): 350-4
2. Spruce MC, Potter J, Coppini DV. The pathogenesis and management of painful diabetic neuropathy: a review. Diabet Med 2003; 20 (2): 88-98
3. US Food and Drug Administration. FDA approves drug for neuropathic pain associated with diabetes [online]. Available from URL: http://www.fda.gov/bbs/topics/news/2004/NEW01113.html [Accessed 2004 Sep 7]
4. Backonja M. Managing painful diabetic neuropathy. Hosp Pract (Off Ed) 1999 Oct 15; 34 (11): 79-88
5. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003 Nov; 60 (11): 1524-34
6. Huckle R. Pregabalin (Pfizer). Curr Opin Investig Drugs 2004 Jan; 5 (1): 82-9
7. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs 2003; 12 (4): 663-72
8. Bryans JS, Wustrow DJ. 3-Substituted GABA analogs with central nervous system activity: a review. Med Res Rev 1999; 19: 149-77
9. Nozaki-Taguchi N, Chaplan SR, Higuera ES, et al. Vincristine-induced allodynia in the rat. Pain 2001 Jul; 93 (1): 69-76
10. Field MJ, McCleary S, Hughes J, et al. Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat. Pain 1999 Mar; 80 (1-2): 391-8
11. Field MJ, Bramwell S, Hughes J, et al. Detection of static and dynamic components of mechanical allodynia in rat models of neuropathic pain: are they signalled by distinct primary sensory neurones? Pain 1999 Nov; 83 (2): 303-11
12. Wallin J, Cui JG, Yakhnitsa V, et al. Gabapentin and pregabalin suppress tactile allodynia and potentiate spinal cord stimulation in a model of neuropathy. Eur J Pain 2002; 6 (4): 261-72
13. Chen SR, Xu Z, Pan HL. Stereospecific effect of pregabalin on ectopic afferent discharges and neuropathic pain induced by sciatic nerve ligation in rats. Anesthesiology 2001 Dec; 95 (6): 1473-9
14. Field MJ, Oles RJ, Lewis AS, et al. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol 1997 Aug; 121 (8): 1513-22
15. Hurley RW, Chatterjea D, Rose Feng M, et al. Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. Anesthesiology 2002 Nov; 97 (5): 1263-73
16. Partridge BJ, Chaplan SR, Sakamoto E, et al. Characterisation of the effects of gabapentin and 3-isobutyl-gamma-aminobutyric acid on substance P-induced thermal hyperalgesia. Anesthesiology 1998 Jan; 88 (1): 196-205
17. Jun JH, Yaksh TL. The effect of intrathecal gabapentin and 3-isobutyl gamma-aminobutyric acid on the hyperalgesia observed after thermal injury in the rat. Anesth Analg 1998 Feb; 86 (2): 348-54
18. Jones DL, Sorkin LS. Systemic gabapentin and S(+)-3-isobutyl-gamma-aminobutyric acid block secondary hyperalgesia. Brain Res 1998 Nov 9; 810 (1-2): 93-9
19. Field MJ, Holloman EF, McCleary S, et al. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol Exp Ther 1997 Sep; 282 (3): 1242-6
20. Bialer M, Johannessen SI, Kupferberg HJ, et al. Progress report on new antiepileptic drugs: a summary of the fifth Eilat conference (EILAT V). Epilepsy Res 2001; 43: 11-58
21. Dooley DJ, Donovan CM, Meder WP, et al. Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: inhibition of K+-evoked. Synapse 2002 Sep 1; 45 (3): 171-90
22. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology 2002 Feb; 42 (2): 229-36
23. Dooley DJ, Mieske CA, Borosky SA. Inhibition of K(+)-evoked glutamate release from rat neocortex and hippocampal slices by gabapentin. Neurosci Lett 2001 Feb; 280 (2): 107-10
24. Taylor CP. Meeting report: the biology and pharmacology of calcium channel alpha2-delta proteins. Pfizer satellite symposium to the 2003 Society for Neuroscience Meeting. CNS Drug Rev 2004; 10 (2): 159-64
25. Fehrenbacher JC, Taylor CP, Vasko MR. Pregabalin and gabapentin reduce release of substance P and CGRP from rat spinal tissues only after inflammation or activation of protein kinase C. Pain 2003 Sep; 105 (1-2): 133-41
26. Corrigan BW, Pool WF, Posvar EL, et al. Metabolic disposition of pregabalin in healthy volunteers [abstract no. PI-68]. Clin Pharmacol Ther 2001 Feb; 69: P18
27. Bockbrader HN, Hunt T, Strand J, et al. Pregabalin pharmacokinetics and safety in healthy volunteers: results from two phase 1 studies [abstract no. P06.051]. Neurology 2000 Apr 11; 54 Suppl. 3: A421
28. Busch JA, Strand JC, Posvar EL, et al. Pregabalin (CI-1008) single-dose pharmacokinetics and safety/tolerance in healthy subjects after oral administration of pregabalin solution or capsule doses [abstract no. 2.108]. Epilepsia 1998; 39 Suppl. 6: 58

29. Corrigan B, Burger P, Bockbrader H. Population pharmacokinetics of pregabalin in healthy volunteers, renally impaired patients, and patients with chronic pain [abstract no. 786]. J Pain 2002 Apr; 3 Suppl. 1: 47

30. Randinitis EJ, Posvar EL, Alvey CW, et al. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. J Clin Pharmacol 2003 Mar; 43 (3): 277-83

31. Bockbrader HN, Wesche D. Pharmacokinetic profile of pregabalin: results of a series of studies [abstract no. NR378]. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, 140

32. Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004; 110: 628-38

33. Sharma U, Allen R, Glessner C, et al. Pregabalin effectively relieves pain in patients with diabetic peripheral neuropathy: study 1008-014 [abstract no. 686-P]. Diabetes 2000 May; 49 Suppl. 1: 167

34. Lesser H, Sharma U, Lamoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004

35. Strojek K, Floter T, Balkenohl M, et al. Pregabalin in the management of chronic neuropathic pain (NeP): a novel evaluation of flexible and fixed dosing [abstract no. 804]. Diabetes 2004; 53 Suppl. 2: 59

36. Toelle T, Versavel M, Glessner C, et al. A novel treatment for diabetic peripheral neuropathy: pregabalin dose and pain relief [abstract]. Anaesthesiology 2004 Oct 23; 101: A967

37. Sharma U, Glessner C, Moore J, et al. Two studies show pregabalin effectively relieves pain in patients with painful diabetic peripheral neuropathy (studies 1008-14/-29) [poster no. NP05]. 2nd World Congress of World Institute of Pain; 2004 Jun 27-30; Istanbul

38. Sharma U, Young J, Lamoreaux L, et al. Pregabalin effectively relieves pain in patients with painful diabetic peripheral neuropathy [abstract no. 322-OR]. Diabetes 2002 Jun; 51 Suppl. 2: 79-80

39. Sharma U, Iacobellis D, Glessner C, et al. Pregabalin improves sleep in neuropathic pain patients [abstract no. NR531 plus poster]. 153rd American Psychiatric Association Annual Meeting; 2000 May 13-18; Chicago, 201

40. Rowbotham M, Young J, Sharma U, et al. Pregabalin shows reduction in pain by day three of treatment [abstract no. 846]. J Pain 2003 Mar; 4 Suppl. 1: 63 plus poster presented the 22nd Annual Scientific Meeting of the American Pain Society; 2003 Mar 20-23; Chicago

41. Portenoy R, Sharma U, Young J, et al. Pregabalin sustains its efficacy as long-term maintenance therapy for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia [abstract no. 599-P]. Diabetes 2004 Jun; 53 Suppl. 2: 142

42. Farrar JT, Young Jr JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001 Nov; 94 (2): 149-58

43. Data on file, Pfizer, 2004

44. Pfizer Inc. Pfizer receives approval to market Lyrica for neuropathic pain and add-on epilepsy in Europe [online]. Available from URL: http://www.pfizer.com/are/news_releases/2004pr/mn_2004_0706.html [Accessed 2004 Sep 28]

45. Pfizer Inc. Pfizer statement on regulatory status of Lyrica [online]. Available from URL: http://www.pfizer.com/are/news_releases/2004pr/mn_2004_0902.html [Accessed 2004 Sep 28]

Correspondence: *James E. Frampton,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz