REVIEW ARTICLE

Drug Saf 2012; 35 (10): 793-806
0114-5916/12/0010-0793/$49.95/0

Pregabalin Treatment for Peripheral Neuropathic Pain

A Review of Safety Data from Randomized Controlled Trials Conducted in Japan and in the West

Setsuro Ogawa,[1] *Jo Satoh*,[2] *Akio Arakawa*,[3] *Tamotsu Yoshiyama*[3] and *Makoto Suzuki*[3]

1 Department of Anesthesiology, Nihon University School of Medicine/Surugadai Nihon University Hospital, Tokyo, Japan
2 Division of Diabetes and Metabolism, Department of Internal Medicine, Iwate Medical University School of Medicine, Iwate, Japan
3 Pfizer Japan Inc., Tokyo, Japan

Contents

Abstract

Two well-studied conditions of peripheral neuropathic pain are postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN). Several pregabalin trials for peripheral neuropathic pain have been conducted in the West, but limited data are available for Japan. As ethnicity may influence health risks, differences may be evident in safety data from pregabalin trials in Japan and in the West.

The objectives of this review were to compare large pooled safety data from randomized controlled trials evaluating pregabalin for the treatment of PHN or DPN in the West with data from two (one PHN, N = 371; one DPN, N = 314) similar trials in Japan. Longer-term safety data from Japanese open-label extension studies were also reviewed in these neuropathic pain populations. Published and unpublished Pfizer-supported pregabalin trials were identified and sourced from internal Pfizer records.

A PubMed search to check for inclusiveness was conducted on 2 November 2011 using the following criteria: 'diabetic peripheral neuropathy' OR 'postherpetic neuralgia' OR 'neuropathic pain' AND 'pregabalin', with limits set for clinical and randomized controlled trials published in English. Five PHN trials (N = 1250) and nine DPN trials (N = 2554) were identified as suitable for inclusion based on methodological comparability. Descriptive safety data from the original trials were reviewed and the most commonly reported adverse events (AEs; dizziness, somnolence, peripheral oedema and weight gain) were identified to be of primary interest. The majority of AEs were of mild to moderate severity in Japanese and Western populations. The most commonly reported AE data (all-causality) with pregabalin (regardless of dose) in Japan (dizziness: PHN = 31.1%; DPN = 24.6%, and somnolence: PHN = 28.6%; DPN = 25.7%) were compared with pooled data from the Western trials (dizziness: PHN = 24.9%; DPN = 23.0%, and somnolence: PHN = 15.1%; DPN = 13.4%). Further assessment of these pooled AE (all-causality) data showed that dizziness and somnolence appeared early in the course of pregabalin treatment, but resolved before the end of the treatment in the majority of PHN and DPN patients (maximum duration of trials was 13 weeks).

The slightly higher incidence of dizziness and somnolence in the two Japanese trials than that seen in the Western trials may reflect an increased exposure to pregabalin per fixed dose due to the lower mean bodyweight of the Japanese versus Western populations (on a mg/kg basis). However, of the participants who experienced these AEs (all-causality), the proportion who withdrew from the trials in Japan (dizziness: PHN = 23.5%; DPN = 18.2%, and somnolence: PHN = 10.3%; DPN = 10.9%) were comparable with the proportion who withdrew from trials in the West (dizziness: PHN = 16.0%; DPN = 29.3%, and somnolence: PHN = 19.4%; DPN = 34.2%). In Japan, 12.5% (PHN) and 15.1% (DPN) of patients experienced peripheral oedema as an AE (all-causality) compared with 8.8% (PHN) and 10.3% (DPN) in the West. Weight gain as an AE (all-causality) was experienced in 11.7% (PHN) and 13.4% (DPN) of patients in Japan compared with 3.8% (PHN) and 7.0% (DPN) in the West, but stabilized with continued treatment. Despite the lower mean bodyweight in Japanese versus Western patients, the PHN and DPN patients in Japan had stable blood glucose and HbA_{1c} levels throughout the trials.

The results of this review indicate safety outcomes in pregabalin trials are comparable between patients in Japan and those in the West. While managing peripheral neuropathic pain with pregabalin treatment, all patients should be observed closely for the incidence of dizziness and somnolence, especially at the beginning of treatment. These patients should also be monitored for evidence of peripheral oedema and weight gain during stable treatment, regardless of the source of neuropathic pain.

Pregabalin (Lyrica®; Pfizer Inc.) binds to the α_2-δ subunit of voltage-gated calcium channels in the central nervous system and has potent anticonvulsant, analgesic and anxiolytic effects.[1]

Pregabalin has been approved in over 100 countries and is indicated for the treatment of central and peripheral neuropathic pain, fibromyalgia and generalized anxiety disorder, and as adjunctive therapy in adults with partial seizures with or without secondary generalization.[2,3] It has been shown to demonstrate predictable pharmacokinetic properties. Pregabalin is rapidly absorbed

via oral administration with approximately 90% bioavailability.[1] It has an elimination half-life of approximately 6 hours, with steady state achieved within 1–2 days of regular administration.[1] There are no known pharmacokinetic drug interactions with pregabalin use, but because pregabalin is eliminated largely renally unchanged, renal function affects its pharmacokinetics.[4,5] Pregabalin demonstrated a similar pharmacokinetic profile in Japanese populations to that in Western populations.[6,7] In Japan, pregabalin was approved for the treatment of postherpetic neuralgia (PHN) in April 2010 and expanded to peripheral neuropathic pain in October 2010.[8]

PHN and painful diabetic peripheral neuropathy (DPN) are two typical forms of chronic neuropathic pain. PHN can redevelop following a herpes zoster (HZ) rash, and the risk of PHN increases with age.[9] In the West, PHN is estimated to affect approximately 10–50% of HZ patients >50 years of age.[10-12] In Japan, there are fewer epidemiology data, but approximately 10–15% of patients have PHN 6 months after the onset of HZ.[13] Approximately 16–26% of patients with diabetes mellitus in the West develop DPN.[12,14] According to one study, the percentage of Japanese patients with diabetes who develop DPN may be as high as 43%.[15]

The efficacy and safety of pregabalin versus placebo was evaluated for pain relief of peripheral neuropathy in patients with PHN[16] and DPN[7] in Japan. The designs of these two Japanese trials[7,16] were similar to the 13-week, fixed-dose pivotal PHN[17] and DPN[18] trials that were conducted in the West and used for new drug application filing.

As with efficacy data, the safety outcomes of the Japanese trials were similar to those reported in the West and the incidence of adverse events (AEs) associated with pregabalin (e.g. dizziness, somnolence, peripheral oedema) increased with increased dose.[7,16] The sample size of each trial was powered to meet the primary efficacy endpoints of the trials. Therefore, a comprehensive evaluation of safety data from a large pooled database of PHN and DPN patients was considered warranted.

A recent review of 38 randomized controlled trials of pregabalin for the treatment of neuropathic pain and other indications (epilepsy, fibromyalgia and generalized anxiety disorder), identified several other AEs associated with pregabalin, including vertigo, ataxia, constipation, dry mouth, blurred vision and attention/concentration difficulties.[19] However, the specific focus of this article is peripheral neuropathic pain.

As some physiological differences have been reported between Asian and Western populations that may or may not impact health outcomes,[20,21] the objective of this manuscript was to review the safety profile of pregabalin in PHN and DPN patients in Japan compared with the safety profile of those in the West. To this end, safety data from Western trials (published and unpublished PHN and DPN trials) that were identified to have similar study design (with the exception of duration), major inclusion and exclusion criteria, titration, schedule of administration, etc., were compared with safety data from the PHN and DPN trials conducted in Japan.

1. Methodology

1.1 Selection of Trials

In Japan, only one pregabalin double-blind, randomized controlled trial has been published in patients with PHN (A0081120)[16] and one in patients with DPN (A0081163).[7] Data from these two trials were selected for comparison with pooled data from trials conducted in the West.

Fourteen Pfizer-supported pregabalin trials, five with PHN patients and nine with DPN patients, with comparable methodology to enable pooling of the data, were identified and sourced from internal records. A PubMed search was then conducted on 2 November 2011 to check for inclusiveness using the following search criteria: 'diabetic peripheral neuropathy' OR 'postherpetic neuralgia' OR 'neuropathic pain' AND 'pregabalin', with limits set for clinical and randomized controlled trials published in English. A total of 64 published articles were identified in this search. Thirty-eight of these articles were not randomized, placebo-controlled trials and a further 17 included pain models not specific to DPN or PHN, or were not conducted in the West. Of the

remaining nine articles,[17,18,22-28] one article[22] reported results from a pregabalin flexible-dose study that included patients with DPN and patients with PHN within the same treatment arm and was therefore also excluded from the pooled analysis. The study design, major inclusion and exclusion criteria, titration, and schedule of administration of the remaining eight articles were all comparable (with the exception of duration) and were included in the selected trials from the Pfizer internal records; no other relevant trials were identified.

1.2 Methodology of the Selected Trials

The designs of the two Japanese trials[7,16] were similar to the 13-week, fixed-dose pivotal PHN[17] and DPN[18] trials conducted in the West. Both Japanese trials were randomized, double-blind, placebo-controlled, parallel-group, multicentre trials and consisted of 1-week baseline, 13-week treatment and 1-week follow-up/taper phases.[7,16] Participants in the PHN trial were randomized to receive pregabalin 150 mg/day (n = 87), 300 mg/day (n = 89) or 600 mg/day (n = 97), or placebo (n = 98), administered by twice-daily dosing for the 12-week, fixed-dose period following a 1-week titration phase. Participants in the DPN trial were randomized to receive pregabalin 300 mg/day (n = 134) or 600 mg/day (n = 45) or placebo (n = 135), also administered twice daily for 12 weeks following 1-week titration. As pregabalin is mainly excreted in urine in a non-metabolized form, the plasma concentration of pregabalin may become greater in patients with renal impairment with a possible increased likelihood of adverse reactions to the drug. Therefore, pregabalin dosage was adjusted according to the creatinine clearance (CLcr) of the patient. Patients assigned to pregabalin 600 mg/day who had low CLcr (defined as $30 < CLcr \leq 60$ mL/min; estimated with Cockcroft and Gault equations) received 300 mg/day. The dosage complied with the Japanese package insert for pregabalin, which advises that adult oral dosage should begin at 150 mg/day administered twice daily and increase to 300 mg/day administered twice daily over ≥1 week, with the daily dose not exceeding 600 mg/day twice daily.

The primary efficacy outcome was the mean pain score at the end of treatment using the numerical rating scale (NRS; 0 = no pain to 10 = pain as bad as you can imagine). Efficacy outcomes of the two Japanese trials[7,16] were consistent with similar trials conducted in the West.[17,18] Significant reductions in pain were observed in patients with pregabalin 300 and 600 mg/day versus placebo.

In all trials, safety was primarily assessed using reported AEs. An AE was defined as any untoward medical occurrence in a participant randomized to pregabalin or placebo (not necessarily with a causal relationship between the occurrence and treatment). AEs were ranked, according to the site investigator's opinion, for severity ('mild'

Table I. Japanese and Western postherpetic neuralgia studies

Region	Study no.	Treatment period (wk)	Administration	Daily dose (mg)	No. of participants		
					Placebo	Pregabalin	Total
Japan	A0081120[16]	13	BID	150, 300, 600[a]	98	273	371
West	1008-030[29,30]	5	TID	75, 150	88	167	255
	1008-045[23]	8	TID	150, 300	81	157	238
	1008-127[24]	8	TID	300, 600[a]	84	89	173
	1008-132[b]	12	BID	150, 300, 600[a]	52	164	216
	1008-196[17]	13	BID	150, 300, 600[a]	93	275	368
	Total[c]	NA	NA	NA	398	852	1250

a Patients assigned to pregabalin 600 mg/day who had low CLcr (defined as $30 < CLcr \leq 60$ mL/min) received 300 mg/day.

b Data on file.

c Pooled data from these trials were also included in the Japan new drug application documents for peripheral neuropathic pain indication.

BID = twice daily; **CLcr** = creatinine clearance; **NA** = not applicable; **TID** = three times daily.

Table II. Japanese and Western diabetic peripheral neuropathy studies

Region	Study no.	Treatment period (wk)	Administration	Daily dose (mg)	No. of participants		
					Placebo	Pregabalin	Total
Japan	A0081163[7]	13	BID	300, 600[a]	135	179	314
West	1008-014[25]	6	TID	150, 600	85	161	246
	1008-029[26]	5	TID	75, 300, 600	97	240	337
	1008-131[27]	8	TID	300	70	76	146
	1008-040[29-31]	8	TID	600	81	86	254[b]
	1008-149[18]	12	BID	150, 300, 600[a]	96	299	395
	1008-173[c]	12	BID	150, 300, 600[a]	30	117	147
	A0081071[32]	13	BID	300, 600	151	305	456
	A0081030[33]	12	BID	150–600	135	271	406
	A0081060[28]	13	BID	600	85	82	167
	Total[d]	NA	NA	NA	830	1637	2554

a Patients assigned to pregabalin 600 mg/day who had low CLcr (defined as 30 < CLcr ≤ 60 mL/min) received 300 mg/day.

b Including 87 patients who were assigned to the amitriptyline group (75 mg/day).

c Data on file.

d Pooled data from these trials were also included in the Japan new drug application documents for peripheral neuropathic pain indication.

BID = twice daily; **CLcr** = creatinine clearance; **NA** = not applicable; **TID** = three times daily.

[does not interfere with usual function], 'moderate' [interferes to some extent with usual function], 'severe' [interferes significantly with usual function]). The study investigator also indicated whether he/she considered any relationship to study treatment.

1.3 Postherpetic Neuralgia and Diabetic Peripheral Neuropathy Populations in the Selected Trials

Inclusion and exclusion criteria of both Japanese trials were similar to those in the Western trials.[7,16-18] Participants were all aged ≥18 years. Entry criteria for PHN patients was pain persisting for at least 3 months after the healing of the HZ rash, a score of ≥40 mm on the Visual Analogue Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at baseline and a mean score of ≥4 on the NRS over the 7-day baseline period. DPN patients were all diagnosed with type 1 or 2 diabetes at least 1 year before the start of the trial and were diagnosed with painful, distal, symmetrical, sensorimotor polyneuropathy due to diabetes at baseline, having had the disease for at least 1 year. They were also required to score ≥40 mm on the VAS of the SF-MPQ at baseline and ≥4 on the NRS over the baseline period.

Patients who experienced pain, or other skin conditions (other than PHN or DPN) that might impair the assessment of pain, or those with a diagnosis of malignant tumour within the past 2 years, or an estimated CLcr of ≤30 mL/min (Cockroft and Gault equation) were excluded from the trials.

1.4 Pooled Analyses

PHN data were pooled from five trials (table I) and DPN data were pooled from nine trials (table II). AE data (all-causality) from each of the pregabalin arms (regardless of dose) were pooled within each population (Japan PHN, Japan DPN, Western PHN, Western DPN) to compare patient demographics and to confirm comparability of the most common AEs within each pain model (PHN/DPN) in Japan and the West. AEs considered related to treatment in the opinion of the study investigator were also pooled within each population group to allow comparison of pregabalin data between pain models (PHN and DPN) with the exclusion of AEs caused by the primary disease. The number of days to onset of the most common AEs (all-causality) and the proportion of participants who withdrew from the trials as a result of experiencing these common AEs were also summarized.

Table III. Demographic characteristics[a]

	PHN				DPN			
	Japanese trial (A0081120)[16]		Pooled data from Western trials		Japanese trial (A0081163)[7]		Pooled data from Western trials	
	Placebo (N = 98)	Pregabalin (N = 273)	Placebo (N = 398)	Pregabalin (N = 852)	Placebo (N = 135)	Pregabalin (N = 179)	Placebo (N = 830)	Pregabalin (N = 1637)
Sex, male [n (%)]	57 (58.2)	141 (51.6)	198 (49.7)	401 (47.1)	103 (76.3)	134 (74.9)	444 (53.5)	908 (55.5)
Age [y; n (%)]								
18–64	14 (14.3)	61 (22.3)	74 (18.6)	191 (22.4)	83 (61.5)	112 (62.6)	571 (68.8)	1137 (69.5)
65–74	52 (53.1)	112 (41.0)	153 (38.4)	282 (33.1)	44 (32.6)	46 (25.7)	203 (24.5)	385 (23.5)
≥75	32 (32.7)	100 (36.6)	171 (43.0)	379 (44.5)	8 (5.9)	21 (11.7)	56 (6.7)	115 (7.0)
Age [y; mean (SD)]	71.1 (8.6)	69.8 (10.7)	71.5 (10.2)	71.4 (10.6)	61.3 (9.6)	61.5 (10.3)	58.8 (10.8)	59.0 (10.7)
Age [y; range]	29–88	24–92	31–96	18–100	35–85	35–85	26–86	20–89
Height [N]	98	273	396	846	135	179	829	1636
Mean [cm (SD)]	158.2 (8.2)	157.6 (9.2)	166.8 (10.0)	166.3 (10.7)	163.4 (9.1)	163.9 (8.8)	169.4 (11.1)	169.8 (10.9)
Range [cm]	142.1–177.0	128.0–180.0	137.2–198.1	127.0–195.6	139.0–182.3	130.0–182.2	132.0–207.5	132.7–200.7
Weight [N]	98	273	397	850	135	179	830	1637
Mean [kg (SD)]	57.4 (10.7)	57.4 (10.9)	75.2 (15.8)	74.6 (16.0)	64.9 (12.8)	65.7 (12.8)	91.4 (22.3)	91.8 (21.7)
Range [kg]	33.2–100.5	34.0–98.3	29.1–154.0	41.0–140.9	40.6–104.4	30.9–113.2	43.0–187.4	41.0–194.4
CLcr [N]	98	273	398	852	135	179	828	1628
Mean [mL/min (SD)]	74.2 (23.5)	73.9 (24.4)	69.7 (26.7)	69.7 (26.2)	97.3 (37.1)	97.6 (33.0)	101.8 (39.3)	100.7 (36.5)
Median [mL/min (range)]	70.5 (34.0–183.0)	70.0 (31.0–159.0)	64.3 (21.0–229.0)	65.0 (23.0–201.0)	91.0 (33.0–258.0)	96.0 (31.0–240.0)	95.3 (31.0–313.0)	94.7 (17.0–388.0)
HbA_{1c}[b] [N]	NA	NA	NA	NA	135	179	829	1634
Mean [% (SD)]	NA	NA	NA	NA	7.6 (1.1)	7.4 (1.1)	7.8 (1.4)	7.8 (1.4)
Median [% (range)]	NA	NA	NA	NA	7.5 (5.3–10.6)	7.3 (5.0–10.5)	7.5 (4.1–12.6)	7.7 (4.7–15.1)

a The n-values given reflect available data for the specified characteristic.

b HbA_{1c} values (%) in the Japanese trial were measured using the standard substance by the JDS, which are 0.4% lower than those measured by the NGSP. The value of HbA_{1c} (%) is estimated as an NGSP equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) [%] + 0.4%, considering the relational expression of HbA_{1c} (JDS) [%] measured by the previous Japanese standard substance and measurement methods for HbA_{1c} (NGSP).[34]

CLcr = creatinine clearance; **DPN** = diabetic peripheral neuropathy; **JDS** = Japan Diabetes Society; **NA** = not applicable; **NGSP** = National Glycohemoglobin Standardization Program; **PHN** = postherpetic neuralgia.

Table IV. Summary of all-causality and treatment-related adverse events for postherpetic neuralgia and diabetic peripheral neuropathy pregabalin trials conducted in Japan vs the West [n (%)]

		PHN				DPN			
		Japanese trial (A0081120)[16]		Pooled data from Western trials		Japanese trial (A0081163)[7]		Pooled data from Western trials	
		Placebo (N = 98)	Pregabalin [pooled treatment groups] (N = 273)	Placebo (N = 398)	Pregabalin [pooled treatment groups] (N = 852)	Placebo (N = 135)	Pregabalin [pooled treatment groups] (N = 179)	Placebo (N = 830)	Pregabalin [pooled treatment groups] (N = 1637)
Patients with any AE	AC	62 (63.3)	233 (85.3)	228 (57.3)	627 (73.6)	99 (73.3)	153 (85.5)	490 (59.0)	1185 (72.4)
	TR	43 (43.9)	195 (71.4)	139 (34.9)	498 (58.5)	49 (36.3)	112 (62.6)	255 (30.7)	849 (51.9)
Patients with any serious AE	AC	6 (6.1)	6 (2.2)	10 (2.5)	28 (3.3)	3 (2.2)	3 (1.7)	27 (3.3)	79 (4.8)
	TR	2 (2.0)	2 (0.7)	2 (0.5)	5 (0.6)	1 (0.7)	0	3 (0.4)	7 (0.4)
Patients with any severe AE	AC	3 (3.1)	8 (2.9)	36 (9.0)	108 (12.7)	1 (0.7)	5 (2.8)	58 (7.0)	160 (9.8)
	TR	1 (1.0)	5 (1.8)	17 (4.3)	68 (8.0)	0	2 (1.1)	23 (2.8)	88 (5.4)
Patients discontinued due to AEs	AC	5 (5.1)	43 (15.8)	26 (6.5)	123 (14.4)	7 (5.2)	30 (16.8)	44 (5.3)	177 (10.8)
	TR	3 (3.1)	36 (13.2)	14 (3.5)	107 (12.6)	6 (4.4)	22 (12.3)	25 (3.0)	148 (9.0)
AEs occurring in ≥3% of participants[a]									
Dizziness	AC	7 (7.1)	85 (31.1)	38 (9.5)	212 (24.9)	9 (6.7)	44 (24.6)	45 (5.4)	376 (23.0)
	TR	6 (6.1)	85 (31.1)	35 (8.8)	199 (23.4)	9 (6.7)	43 (24.0)	34 (4.1)	338 (20.6)
Somnolence	AC	9 (9.2)	78 (28.6)	21 (5.3)	129 (15.1)	12 (8.9)	46 (25.7)	32 (3.9)	219 (13.4)
	TR	7 (7.1)	78 (28.6)	20 (5.0)	127 (14.9)	11 (8.1)	46 (25.7)	31 (3.7)	210 (12.8)
Peripheral oedema	AC	1 (1.0)	34 (12.5)	10 (2.5)	75 (8.8)	8 (5.9)	27 (15.1)	56 (6.7)	168 (10.3)
	TR	1 (1.0)	32 (11.7)	9 (2.3)	60 (7.0)	6 (4.4)	23 (12.8)	46 (5.5)	131 (8.0)
Weight increased	AC	0	32 (11.7)	1 (0.3)	32 (3.8)	5 (3.7)	24 (13.4)	13 (1.6)	115 (7.0)
	TR	0	29 (10.6)	0	26 (3.1)	3 (2.2)	20 (11.2)	9 (1.1)	97 (5.9)
Thirst	AC	3 (3.1)	17 (6.2)	0	1 (0.1)	0	1 (0.6)	1 (0.1)	3 (0.2)
	TR	3 (3.1)	16 (5.9)	0	1 (0.1)	0	0	0	2 (0.1)
Nausea	AC	5 (5.1)	15 (5.5)	15 (3.8)	20 (2.3)	6 (4.4)	1 (0.6)	37 (4.5)	52 (3.2)
	TR	4 (4.1)	13 (4.8)	13 (3.3)	11 (1.3)	1 (0.7)	0	23 (2.8)	37 (2.3)
Constipation	AC	6 (6.1)	37 (13.6)	9 (2.3)	42 (4.9)	1 (0.7)	7 (3.9)	14 (1.7)	65 (4.0)
	TR	3 (3.1)	33 (12.1)	6 (1.5)	29 (3.4)	1 (0.7)	6 (3.4)	9 (1.1)	47 (2.9)
Face oedema	AC	0	11 (4.0)	2 (0.5)	3 (0.4)	0	6 (3.4)	5 (0.6)	10 (0.6)
	TR	0	11 (4.0)	2 (0.5)	3 (0.4)	0	6 (3.4)	5 (0.6)	9 (0.5)
Dry mouth	AC	0	0	11 (2.8)	68 (8.0)	0	0	9 (1.1)	72 (4.4)
	TR	0	0	7 (1.8)	62 (7.3)	0	0	8 (1.0)	65 (4.0)

Continued next page

Table IV. Contd

		PHN				DPN			
		Japanese trial (A0081120)[16]		Pooled data from Western trials		Japanese trial (A0081163)[7]		Pooled data from Western trials	
		Placebo (N = 98)	Pregabalin [pooled treatment groups] (N = 273)	Placebo (N = 398)	Pregabalin [pooled treatment groups] (N = 852)	Placebo (N = 135)	Pregabalin [pooled treatment groups] (N = 179)	Placebo (N = 830)	Pregabalin [pooled treatment groups] (N = 1637)
Fatigue	AC	1 (1.0)	1 (0.4)	15 (3.8)	29 (3.4)	1 (0.7)	0	18 (2.2)	71 (4.3)
	TR	0	0	12 (3.0)	25 (2.9)	1 (0.7)	0	15 (1.8)	64 (3.9)
Headache	AC	1 (1.0)	8 (2.9)	19 (4.8)	57 (6.7)	2 (1.5)	1 (0.6)	60 (7.2)	105 (6.4)
	TR	1 (1.0)	6 (2.2)	15 (3.8)	32 (3.8)	1 (0.7)	1 (0.6)	39 (4.7)	73 (4.5)
Vision blurred	AC	1 (1.0)	9 (3.3)	11 (2.8)	49 (5.8)	3 (2.2)	2 (1.1)	8 (1.0)	53 (3.2)
	TR	1 (1.0)	9 (3.3)	9 (2.3)	41 (4.8)	2 (1.5)	2 (1.1)	4 (0.5)	43 (2.6)
Gait disturbance	AC	1 (1.0)	4 (1.5)	2 (0.5)	31 (3.6)	0	1 (0.6)	0	22 (1.3)
	TR	0	3 (1.1)	2 (0.5)	29 (3.4)	0	1 (0.6)	0	21 (1.3)

a MedDRA® coding for AE preferred terms applied. MedDRA® terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

AC = all-causality; **AE(s)** = adverse event(s); **DPN** = diabetic peripheral neuropathy; **MedDRA** = Medical Dictionary for Regulatory Activities; **PHN** = postherpetic neuralgia; **TR** = treatment related.

Weight gain analyses summarized those participants who were identified as experiencing weight gain as an AE in the original trials based on the clinical judgement of the study investigators (reported as number and percent of participants). Summaries of the measurement of bodyweight change from baseline (mean weight [kg] of all participants in each treatment group) were reported for comparisons within, and not between, study populations due to potential baseline differences between PHN and DPN patients and those in Japan and the West.

Blood glucose and HbA_{1c} levels were also reviewed in the Japanese trials as these are of specific concern in diabetic populations and may be impacted by bodyweight.

1.5 Study Population

A total of 371 (placebo N = 98; pregabalin N = 273) and 314 (placebo N = 135; pregabalin N = 179) participants were included in the safety analyses of the Japanese PHN and DPN trials, respectively.[7,16] Data from these trials were compared with the pooled data from five Western trials conducted in PHN patients (placebo N = 398; pregabalin N = 852) and the pooled data from nine Western trials conducted in DPN patients (placebo N = 830; pregabalin N = 1637). The dosing regimen for each of the pregabalin arms in each trial are shown in tables I and II. The median dose of pregabalin in each pooled cohort (PHN and DPN patients in Japan and the West) was 300 mg/day. Demographics of the Japanese patients and their Western counterparts are summarized in table III.

2. Safety Outcomes

The most commonly reported AEs (all-causality and treatment-related) for each treatment group in the Japanese and Western trials are shown in table IV. The majority of AEs were of mild to moderate severity.

Dizziness, somnolence, peripheral oedema and weight gain were the most commonly reported AEs in the Japanese trials, and these findings were consistent with the pooled Western data

(table IV). A total of 126 participants from the preceding Japanese PHN trial and 123 participants from the preceding Japanese DPN trial continued into open-label, long-term extension studies.[6,35] Of these, 95 patients (75.4%) completed the PHN extension period and 97 patients (78.9%) completed the DPN extension period.[6,35] It should be noted that in the Japanese PHN trial, treatment with pregabalin was discontinued without a dose-tapering period in participants who did not enter the long-term study at the completion of the 13-week double-blind phase. The incidence of treatment-related AEs 1 week after discontinuation (during the follow-up period) was 4.0% (2/50 participants), 0% (0/45 participants), 2.3% (1/43 participants) and 6.1% (2/33 participants) in the placebo group and pregabalin 150, 300 and 600 mg/day groups, respectively. In the pregabalin groups, stomach discomfort and dizziness were reported as AEs and were mild in severity. These results suggest that withdrawal and rebound effects were manageable; therefore, further discussion is not provided in this article.

When the AE data were distributed by age (18–64 years, 65–74 years, >74 years), the distribution of AEs was fairly consistent across age groups, with the following exceptions: dizziness occurred more frequently in older versus younger DPN patients with pregabalin, especially in those aged >74 years; in patients with PHN, there was a trend for peripheral oedema to be reported more frequently in older (≥65 years) versus younger patients (<65 years).

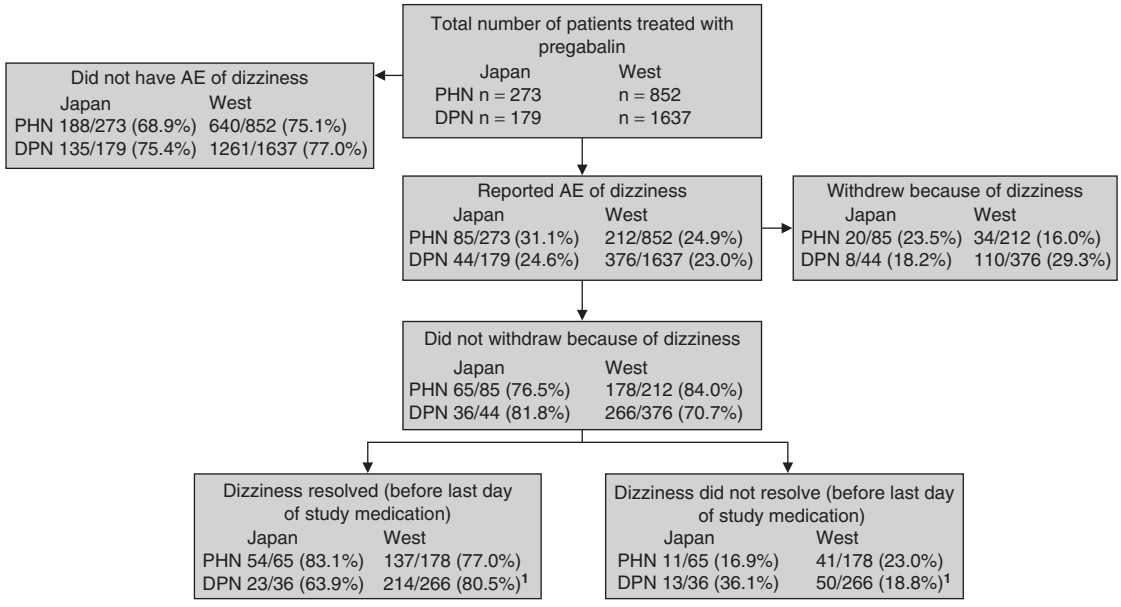
Evaluations of the most commonly reported AEs (dizziness, somnolence, peripheral oedema and weight gain) are summarized below.

Table V. Frequency and median time of onset of most common adverse events (all-causality)

Adverse event	Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 600 mg/day	
	N (%)	Days	N (%)	Days	N (%)	Days	N (%)	Days
Japanese trials								
PHN [N]	98		87		89		97	
Dizziness	7 (7.1)	17.0	10 (11.5)	2.0	27 (30.3)	5.0	48 (49.5)	4.0
Somnolence	9 (9.2)	4.0	19 (21.8)	2.0	22 (24.7)	3.5	37 (38.1)	4.0
Peripheral oedema	1 (1.0)	93.0	4 (4.6)	11.0	12 (13.5)	29.0	18 (18.6)	20.0
Weight increased	0	NA	1 (1.1)	8.0	17 (19.1)	57.0	14 (14.4)	41.0
DPN [N]	135		NA		134		45	
Dizziness	9 (6.7)	5.0	NA	NA	26 (19.4)	6.0	18 (40.0)	6.0
Somnolence	12 (8.9)	8.0	NA	NA	28 (20.9)	4.5	18 (40.0)	5.5
Peripheral oedema	8 (5.9)	36.0	NA	NA	19 (14.2)	22.0	8 (17.8)	28.5
Weight increased	5 (3.7)	57.0	NA	NA	17 (12.7)	28.0	7 (15.6)	19.0
Western trials[a]								
PHN [N]	398		302		312		154	
Dizziness	38 (9.5)	8.0	52 (17.2)	2.0	94 (30.1)	3.0	57 (37.0)	4.0
Somnolence	21 (5.3)	5.0	32 (10.6)	3.0	53 (17.0)	4.0	37 (24.0)	4.0
Peripheral oedema	10 (2.5)	27.5	16 (5.3)	23.0	43 (13.8)	16.0	16 (10.4)	22.5
Weight increased	1 (0.3)	56.0	5 (1.7)	17.0	16 (5.1)	12.0	10 (6.5)	14.5
DPN [N]	830		212		474		603	
Dizziness	45 (5.4)	9.0	20 (9.4)	3.5	110 (23.2)	3.0	185 (30.7)	4.0
Somnolence	32 (3.9)	3.0	11 (5.2)	5.0	67 (14.1)	3.0	89 (14.8)	4.0
Peripheral oedema	56 (6.7)	35.0	8 (3.8)	30.0	38 (8.0)	27.0	91 (15.1)	19.0
Weight increased	13 (1.6)	40.0	9 (4.2)	20.0	24 (5.1)	18.0	55 (9.1)	26.0

a Pooled data for Western PHN pregabalin 75 mg/day and DPN pregabalin 75 mg/day and 150–600 mg/day groups not shown.

DPN = diabetic peripheral neuropathy; **NA** = not applicable; **PHN** = postherpetic neuralgia.



1 Dizziness outcome at end of study unknown for 2 of 266 patients in Western trials.

Fig. 1. Pregabalin-treated patients who experienced dizziness (all-causality) in Japanese and Western trials. **AE** = adverse event; **DPN** = diabetic peripheral neuropathy; **PHN** = postherpetic neuralgia.

2.1 Dizziness

A slightly higher proportion of patients in Japan experienced dizziness as an AE (all-causality) with pregabalin treatment (31.1% and 24.6% for PHN and DPN, respectively) than in the pooled Western data (24.9% and 23.0% for PHN and DPN, respectively) [table IV].

In the PHN patients who experienced dizziness (all-causality) with pregabalin 150, 300 or 600 mg/day, the median times of onset were 2–5 days (Japan) and 2–4 days (pooled Western data). In DPN patients, the median times of onset were 6 days (Japan) and 3–4 days (pooled Western data) [table V].

Of the total pregabalin-treated patients (all doses), 23.5% (PHN) and 18.2% (DPN) [Japan] and 16.0% (PHN) and 29.3% (DPN) [pooled Western trials] withdrew from trials because of dizziness (all-causality). In patients who experienced dizziness and remained in the trials, symptoms of dizziness were resolved before the end of pregabalin treatment in the majority of cases (PHN = 83.1%, DPN = 63.9% [Japan]; and PHN = 77.0%, DPN = 80.5% [pooled Western data]) [figure 1].

2.2 Somnolence

As with dizziness, more patients in Japan experienced somnolence with pregabalin than in the West. In Japan, somnolence as an AE (all-causality) was reported in 28.6% and 25.7% of PHN and DPN patients, respectively, compared with 15.1% and 13.4%, for PHN and DPN, respectively, in the Western trials (table IV).

In the PHN patients who experienced somnolence (all-causality) with pregabalin 150, 300 or 600 mg/day, the median times of onset were 2–4 days (Japan) and 3–4 days (pooled Western data). In DPN patients, the median times of onset were 4.5–5.5 days (Japan) and 3–5 days (pooled Western data) [table V].

Of the total pregabalin-treated patients (all doses), 10.3% (PHN) and 10.9% (DPN) [Japan] and 19.4% (PHN) and 34.2% (DPN) [pooled Western data] withdrew from trials because of somnolence

(all-causality). In patients who experienced somnolence and remained in the trials, symptoms of somnolence were also resolved before the end of pregabalin treatment in many patients (PHN = 74.3%, DPN = 73.2% [Japan]; and PHN = 69.2%, DPN = 74.3% [pooled Western data]) [figure 2].

2.3 Peripheral Oedema

In Japan, 12.5% (PHN) and 15.1% (DPN) of pregabalin patients experienced peripheral oedema as an AE (all-causality) compared with 8.8% (PHN) and 10.3% (DPN) in the West (table IV).

In the PHN patients who experienced peripheral oedema with pregabalin 150, 300 or 600 mg/day, the median times of onset were 11–29 days (Japan) and 16–23 days (pooled Western data) [table V]. In DPN patients, median times of onset were 22–28.5 days (Japan) and 19–30 days (pooled Western data) [table V].

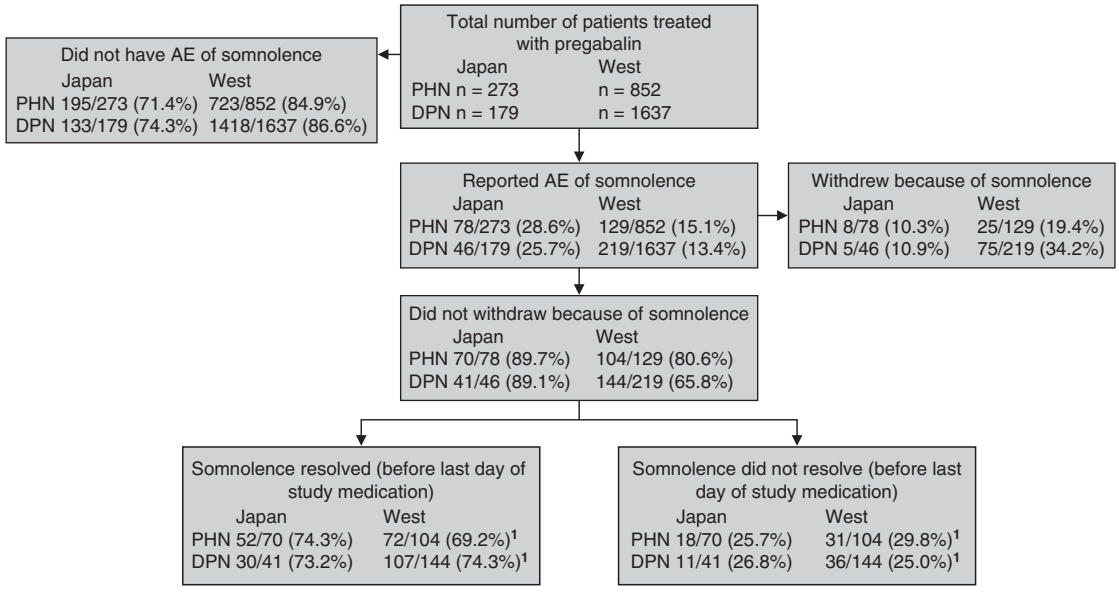
There were no incidents of severe peripheral oedema in the Japanese trials. A small minority of peripheral oedema AEs were reported as severe in the Western trials (PHN 0.2% [2/852]; DPN 0.3% [5/1637]).

2.4 Weight Gain

Weight gain as an AE (all-causality) was experienced in 11.7% (PHN) and 13.4% (DPN) of patients in Japan compared with 3.8% (PHN) and 7.0% (DPN) in the Western trials (table IV).

In the PHN patients who experienced weight gain with pregabalin 150, 300 or 600 mg/day, the median times of onset were 8–57 days in Japan compared with 12–17 days in the Western trials. In DPN patients, median times of onset were 19–28 days (Japan) and 18–26 days (pooled Western data) [table V].

Mean changes from baseline in bodyweight were greater, on average, for pregabalin-treated patients than placebo-treated patients in Japan (PHN: 0.0 kg, 0.7 kg, 1.6 kg and 1.8 kg in the placebo, 150, 300 and 600 mg/day groups, respectively; DPN: 0.1 kg, 1.6 kg and 1.7 kg in the placebo, 300



1 Somnolence outcome at end of study unknown for 1 of 104 and 1 of 144 patients in Western PHN and DPN trials, respectively.

Fig. 2. Pregabalin-treated patients who experienced somnolence (all-causality) in Japanese and Western trials. **AE** = adverse event; **DPN** = diabetic peripheral neuropathy; **PHN** = postherpetic neuralgia.

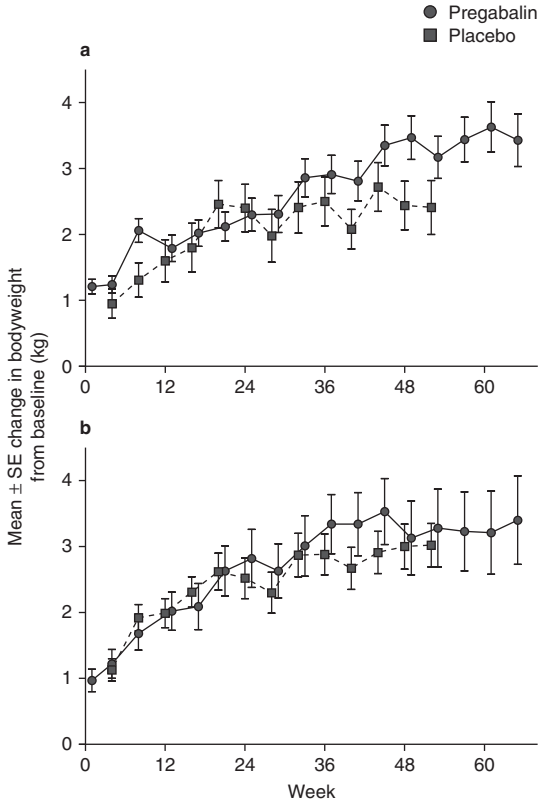


Fig. 3. Change in bodyweight from baseline in Japanese randomized controlled trials and open-label extension studies for (**a**) postherpetic neuralgia and (**b**) diabetic peripheral neuropathy. Placebo group = RCT → open-label, long-term study (52 weeks in total; data of placebo treatment not included). Pregabalin groups (all doses) = RCT → open-label, long-term study (65 weeks in total). **RCT** = randomized controlled trial; **SE** = standard error.

and 600 mg/day groups, respectively) and in the West (PHN [five trials pooled]: 0.2 kg, 1.0 kg, 1.7 kg and 1.8 kg in the placebo, 150, 300 and 600 mg/day groups, respectively; DPN [nine trials pooled]: 0.2 kg, 0.3 kg, 1.1 kg, 1.7 kg, 2.0 kg and 2.1 kg in the placebo, 75, 150, 300 and 600 mg/day, and flexible dose 150–600 mg/day groups, respectively).

The change in patients' bodyweight from baseline was monitored over the course of the Japanese open-label extension studies. The increase in bodyweight levelled off over the course of continued pregabalin treatment in patients treated with either pregabalin or placebo during the randomized controlled trials (figure 3).

2.5 Blood Glucose and HbA_{1c} Levels

Mean blood glucose levels (SD) remained stable in PHN and DPN patients throughout the Japanese randomized controlled trials. Scores from baseline to week 13 were 97.0 mg/dL (19.2) to 94.9 mg/dL (19.8; PHN) and 145.6 mg/dL (48.9) to 150.2 mg/dL (59.8; DPN). Stable HbA_{1c} levels were also evident in the Japanese trials. Mean HbA_{1c} levels (SD) were 5.4% (0.7) and 5.3% (0.7; PHN) and 7.0% (1.1) and 7.1% (1.3; DPN) at baseline and week 13, respectively.

3. Summary

Dizziness, somnolence, peripheral oedema and weight gain were the most commonly reported AEs in PHN and DPN patients from Japan and the West treated with pregabalin. Dizziness and somnolence appeared early in the course of treatment with pregabalin, but resolved before the end of the trials in the majority of patients. The incidence of dizziness and somnolence was slightly greater in the Japanese trials than in the pooled Western trials. As bodyweight was lower, on average, in the patients in Japan than those in the West (table III), the increased incidence of these AEs within the Japanese patients may reflect a potentially greater exposure to pregabalin for a fixed dose (e.g. 300 mg/day) per kilogram bodyweight. However, the proportions of participants who discontinued due to these AEs (all-causality) were comparable between Japanese and Western populations.

Although peripheral oedema was frequently observed with pregabalin treatment for both PHN and DPN patients, most incidents were mild in severity.

Weight gain was observed with pregabalin treatment for both PHN and DPN patients. However, weight gain stabilized with continued open-label pregabalin treatment in the Japanese extension studies.

Blood glucose and HbA_{1c} levels remained stable throughout the Japanese trials. These results are consistent with a pooled analysis of seven double-blind, randomized, placebo-controlled clinical trials in DPN patients in the West in which

there was no evidence of clinically meaningful changes to laboratory values or HbA_{1c} from baseline to week 13, regardless of pregabalin dose.[31]

Overall, the safety profile in the Japanese clinical trials reported here was similar to that seen in the Western clinical trials of patients with peripheral neuropathic pain. However, it should be noted that there have been some postmarketing reports of headache, nausea and diarrhoea with pregabalin that were not reviewed here.[3]

4. Conclusions

The safety profile of the Japanese populations with PHN and DPN reflected that of similar populations in the pooled Western trials, regardless of the observed differences in mean bodyweight between the two populations. Based on data from randomized controlled trials, patients with PHN and DPN treated with pregabalin should be observed closely for the incidence of dizziness and somnolence, particularly in patients in Japan who typically have a lower mean bodyweight and therefore may experience a greater degree of drug exposure per fixed dose (e.g. 300 mg/day) of pregabalin treatment. Based on the additional characteristics of the data drawn from these trials in Japan and the West, it would appear that symptoms of these common AEs do resolve over time and can be managed without discontinuation of the drug in most cases, regardless of the primary cause of peripheral neuropathic pain.

Acknowledgements

The studies included within this pooled analysis were all sponsored and funded by Pfizer Inc. All authors contributed to the writing, reviewing, preparation and interpretation of the data, and approval of the manuscript. They were also involved in the decision to submit the paper for publication. Setsuro Ogawa has received consultancy fees or lecture fees from Janssen, Hisamitsu, Pfizer, Nippon Shinyaku and Showa Yakuhin Kakou. Jo Satoh has received research funding, lecture fees and consultancy fees from Astellas, Banyu, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Novo Nordisk, Ono, Pfizer, Sanofi-Aventis and Takeda. Akio Arakawa, Tamotsu Yoshiyama and Makoto Suzuki are employees of Pfizer. Medical writing support was provided by Brenda Meyer, PhD, of UBC Scientific Solutions and funded by Pfizer Inc.

The Medical Dictionary for Regulatory Activities (MedDRA®) trademark is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) on behalf of the International Conference on Harmonisation.

References

1. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45 Suppl. 6: 13-8
2. European Medicines Agency. European Public Assessment Report (EPAR) for Lyrica [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000546/WC500046603.pdf [Accessed 2011 Apr 27]
3. Pfizer Inc. Highlights of prescribing information [online]. Available from URL: http://www.pfizer.com/files/products/uspi_lyrica.pdf [Accessed 2011 Jan]
4. Bockbrader HN, Radulovic LL, Posvar EL, et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. J Clin Pharmacol 2010 Aug; 50 (8): 941-50
5. Brodie MJ, Wilson EA, Wesche DL, et al. Pregabalin drug interaction studies: lack of effect on the pharmacokinetics of carbamazepine, phenytoin, lamotrigine, and valproate in patients with partial epilepsy. Epilepsia 2005 Sep; 46 (9): 1407-13
6. Ogawa S, Suzuki M, Arakawa A, et al. Long-term efficacy and safety of pregabalin in patients with postherpetic neuralgia: results of a 52-week, open-label, flexible-dose study. Masui 2010 Aug; 59 (8): 961-70
7. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. Diabet Med 2011 Jan; 28 (1): 109-16
8. News Blaze. Pfizer's Lyrica® (Pregabalin) capsules CV receives approval for treatment of peripheral neuropathic pain in Japan [online]. Available from URL: http://newsblaze.com/story/20101028143802000001.pnw/topstory.html [Accessed 2011 May 17]
9. Opstelten W, Mauritz JW, de Wit NJ, et al. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract 2002 Oct; 19 (5): 471-5
10. Gialloreti LE, Merito M, Pezzotti P, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis 2010 Aug 3; 10: 230
11. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clin Proc 2009 Mar; 84 (3): 274-80
12. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002 Nov-Dec; 18 (6): 350-4
13. Kazuo H, Kazunori H, Keiichi N. Bridging the gap between pain research and treatment – update review: postherpetic neuralgia: diagnosis and treatment. Pain Clinic 2004; 25 (2): 158-65
14. Ziegler D. Treatment of diabetic neuropathy and neuropathic pain: how far have we come? Diabetes Care 2008 Feb; 31 Suppl. 2: S255-61
15. Kawano M, Omori Y, Katayama S, et al. A questionnaire for neurological symptoms in patients with diabetes: cross-sectional multicenter study in Saitama Prefecture, Japan. Diabetes Res Clin Pract 2001 Oct; 54 (1): 41-7

16. Ogawa S, Suzuki M, Arakawa A, et al. Evaluation of the efficacy and safety of pregabalin in the treatment of postherpetic neuralgia: a randomized, double-blind, multicenter, placebo-controlled study. J Japan Soc Pain Clin 2010; 17 (2): 141-52
17. van Seventer R, Feister HA, Young Jr JP, et al. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. Curr Med Res Opin 2006 Feb; 22 (2): 375-84
18. Tolle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain 2008 Feb; 12 (2): 203-13
19. Zaccara G, Gangemi P, Perucca P, et al. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011 Apr; 52 (4): 826-36
20. Stommel M, Schoenborn CA. Variations in BMI and prevalence of health risks in diverse racial and ethnic populations. Obesity (Silver Spring) 2010 Sep; 18 (9): 1821-6
21. World Health Organization. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004 Jan 10; 363 (9403): 157-63
22. Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005 Jun; 115 (3): 254-63
23. Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004 May; 109 (1-2): 26-35
24. Dworkin RH, Corbin AE, Young Jr JP, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003 Apr 22; 60 (8): 1274-83
25. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. J Pain 2005 Apr; 6 (4): 253-60
26. Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004 Dec 14; 63 (11): 2104-10
27. 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 Aug; 110 (3): 628-38
28. Arezzo JC, Rosenstock J, Lamoreaux L, et al. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. BMC Neurol 2008 Sep 16; 8: 33
29. Semel D, Murphy TK, Zlateva G, et al. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. BMC Fam Pract 2010; 11: 85
30. Sharma U, Griesing T, Emir B, et al. Time to onset of neuropathic pain reduction: a retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. Am J Ther 2010 Nov-Dec; 17 (6): 577-85
31. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008 Jul; 31 (7): 1448-54
32. Pfizer Inc. Protocol A0081071: a randomized double-blind, placebo-controlled, parallel-group, multi-center trial of pregabalin versus placebo in the treatment of neuropathic pain associated with diabetic peripheral neuropathy [online]. Available from URL: http://www.clinicalstudyresults.org/documents/company-study_3972_0.pdf [Accessed 2011 May 17]
33. Pfizer Inc. Protocol A0081030: a 14 week, double-blind, randomized, placebo-controlled, multi-center study to evaluate the safety and efficacy of pregabalin (150 mg-600 mg day) using a flexible, optimized dose schedule in patients with painful diabetic peripheral neuropathy (DPN) [online]. Available from URL: http://www.clinicalstudyresults.org/documents/company-study_2504_0.pdf [Accessed 2011 May 17]
34. Seino Y, Nanjo K, Tajima N, et al. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. J Diabet Invest 2010; 1 (5): 212-28
35. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety evaluation of pregabalin treatment over 52 weeks in patients with diabetic neuropathic pain extended after a phase III double-blind placebo-controlled trial. J Diabet Invest 2011; 2 (6): 457-63

Correspondence: Dr *Setsuro Ogawa*, Professor, Department of Anesthesiology, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail: ogawa.setsurou@nihon-u.ac.jp