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LYRICA® FOR THE TREATMENT OF NEUROPATHIC PAIN DISORDERS

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Nervous system dysfunction leading to neuropathic pain can occur from many causes: infection, trauma, metabolic abnormalities, chemotherapy, surgery, irradiation, neurotoxins, inherited neurodegeneration, nerve compression, inflammation, tumor infiltration, and spinal cord injuries. Diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are two manifestations of nervous system dysfunction that result in neuropathic pain. Early treatment of underlying causes is the key to successful therapy.[1]

Neuropathic pain is usually described as tingling, burning, lancinating, or shooting; however, many patients with neuropathic pain also complain of sharp, aching, or throbbing pain.[1] Current options for treating neuropathic pain include gabapentin, tricyclic antidepressants (TCAs), opioid analgesics (i.e. codeine, oxycodone, morphine sulfate), tramadol, and topical therapies (i.e., capsaicin, lidocaine).[1,2] More recently, duloxetine (Cymbalta®) was the first FDA-approved treatment for pain caused by diabetic peripheral neuropathy.[12]

About three million people, or 20-24% of the US diabetic population, are affected by DPN. Symptoms in the lower limbs and feet can persist for many years and reduce health-related quality of life. Important risk factors for the development of this condition are duration of diabetes mellitus and glycemic control.

'Shingles' or herpes zoster infection is associated with a vesicular dermatomal rash that is typically accompanied by pain. About one million people in the US are affected by this condition, which is commonly associated with allodynia. About 50% of individuals over the age of 70 years have pain that persists for 12 months even after healing. [3]

Gabapentin was the first oral medication approved for the treatment of PHN and is widely used off label for DPN. It is believed to act as an analgesic primarily via calcium channel blockade. In addition, gabapentin enhances gamma-aminobutyric acid (GABA) turnover in the CNS, attenuating glutamate-mediated excitotoxic neurotransmission.[1] Due to fewer side effects (compared to TCAs) and few drug interactions, gabapentin is extensively used to treat neuropathic pain. However, gabapentin shows nonlinear bioavailability and requires titration to the higher doses, which makes it cumbersome to use in clinical practice. A few disadvantages of other available agents used for treatment of neuropathic pain include: a slow onset of analgesic action (e.g., TCAs, capsaicin), adverse effects (e.g.,

INSIDE THIS ISSUE:

Table 1. Clinical Trial Experience of Pregabalin in Diabetic Peripheral Neuropathy (DPN).

Study	Demographics	Design	Dose*	Number of subjects	Response (%)
Rosenstock et al.[4]	Symmetrical painful symptoms in distal extremities for 1-5 years. Mean duration of diabetes was 9.3 years	8-week randomized, DB, PC, FD study	Pregabalin 300 mg Placebo	76 70	40% 14.5%
Sharma et al.[5,6]	Painful DPN of 1-5 years duration	6-week randomized, DB, PC, parallel group study	Pregabalin 150 mg/d Pregabalin 600 mg/d Placebo	79 82 85	NR 39% 15%
Iacobellis et al.[7]	DPN of 1-5 years	5-week randomized, DB, PC study	Pregabalin 75mg/d Pregabalin 300 mg/d Pregabalin 600 mg/d Placebo	77 81 82 97	NR 45.7 48.1 17.5

* all doses administered in three divided doses. DB-double-blind; PC-placebo-controlled; FD-fixed dose; d=day; NR-not reported; NS- not significant

TCAs and opiates), potential opioid-related dependency, and need for combination therapy. [2]

Pregabalin (Lyrica®) was developed by Pfizer as a follow-up compound to gabapentin. It has been approved by the FDA for neuropathic pain associated with DPN and PHN and is expected to be released in 2005. In addition, pregabalin has demonstrated efficacy in epilepsy and generalized anxiety disorder (GAD). [2,3] Pregabalin will be classified as a controlled substance, class IV or V, due to low abuse characterized by euphoria in a minority of patients (Personal Communication with Pfizer Inc. 01/26/05). This article will examine the safety, efficacy, and tolerability of pregabalin for the management of pain that results from shingles or diabetes-related nerve damage.

Pharmacology and Pharmacokinetics

Pregabalin is the pharmacologically active S-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid.[2] It has a similar pharmacological profile to that of gabapentin. The mechanism of action of pregabalin may involve reduction of excitatory neurotransmitter release by binding to the α_2-δ protein subunit of voltage-gated calcium channels.

After oral administration in 86 healthy volunteers, pregabalin was rapidly absorbed and displayed linear pharmacokinetics. Time to peak plasma concentration is 1.3 hours. The oral bioavailability of pregabalin is 90%. Absorption of pregabalin is delayed with food; however, the extent of absorption is not affected. Pregabalin undergoes negligible hepatic metabolism and does not bind to plasma proteins. It is 98% renally eliminated, so dosage adjustment is necessary in renally impaired patients. The elimination half-life is 6 hours (4.6-6.8 hours following a single 300 mg dose). Clearance of pregabalin is directly proportional to creatinine clearance (CrCl).

Clinical Trials

Rosenstock et al [4] evaluated the efficacy and safety of pregabalin in a two-phase trial: a one-week baseline phase and an eight-week, fixed dose, double-blind treatment phase. The study was a randomized, double-blind, placebo-controlled trial (Table 1). Patients were randomized to pregabalin 300 mg/day (administered in three divided doses) or placebo. Mean pain score was the primary efficacy parameter. Secondary efficacy parameters included the Short-Form McGill Pain Questionnaire (SF-MPQ), sleep score, Patient and Clinical Global Impressions of Change (PGIC,CGIC), SF-36 Health Survey (SF-36), and Profile of Mood States (POMs). This study showed a statistically significant decrease in mean pain score for pregabalin compared to placebo (-2.5 vs. -0.8, p=0.0001). By week one, the pregabalin arm showed a 2.2 mean pain score decrease compared to 0.4 in the placebo group (p=0.0001), significant improvement in weekly mean sleep interference scores ($p<0.001$), and improvements on the SF-MPQ ($p<0.05$), PGIC (p=0.001), CGIC (p=0.004), SF-36 ($p<0.03$), and POMs subscales ($p<0.03$). The most common ad-

Table 2. Clinical Trial Experience of Pregabalin in Postherpetic Neuralgia (PHN).

Study	Demographics	Design	Dose (mg/d)*	Number of subjects	Response (%)
Dworkin et al [8]	Pain persisting >3 months following herpes zoster skin rash. Mean age 71.5 years. Mean duration of PHN, 33.8 months	8-week randomized, DB, PC, parallel group, multicenter study	Pregabalin 600 [α] Placebo	89 84	50 20
Van Seventer et al.[9]	PHN $\geq$ 3 months duration. Mean age 70.7 years	13-week randomized, DB, PC, multicenter study	Pregabalin 150 [β] Pregabalin 300 [β] Pregabalin 300/600 [β] Placebo [β]	87 98 90 93	26.4 26.5 37.5 7.5
Sabatowski et al.[10]	PHN of >6 months. Mean age of 71.3 years	8-week randomized, DB, PC, multicenter study	Pregabalin 150 Pregabalin 300 Placebo	81 76 81	26 28 10

*Doses administered in three divided doses unless otherwise noted. [α] Patients with a CrCl 30-60 ml/min received pregabalin 100 mg three times a day. [β]Administered in two divided doses. DB=double-blind; PC=placebo-controlled.

verse effects reported were dizziness (27%), somnolence (15%), infection (11%), and peripheral edema (8%). This study showed that pregabalin is effective and well tolerated in decreasing the pain, mood disturbances, and sleep disruption associated with DPN.

Sharma et al [5,6] compared the safety and efficacy of pregabalin 150 mg/day, pregabalin 600 mg/day, and placebo, administered in three divided doses, in a six-week study. This was a randomized, double-blind, placebo-controlled, parallel-group trial (Table 1). Mean pain score was the primary efficacy parameter. Pregabalin 600 mg/day was significantly better than placebo (p=0.0002). When comparing the secondary efficacy measures, pregabalin was significantly better than placebo in daily sleep interference score (p=0.0004), SF-MPQ, CGIC, PGIC, and SF-36. The most common adverse events included: dizziness and somnolence. The authors concluded that pregabalin 600 mg/day was safe and effective in reducing DPN-associated pain.

Iacobellis et al [7] conducted a 5-week randomized, double-blind, placebo-controlled study (Table 1). The study compared the safety and efficacy of pregabalin 75 mg/day, 300 mg/day, 600 mg/day, or placebo, administered in three divided doses. The primary efficacy parameter was mean pain score. Secondary efficacy parameters included SF-MPQ, sleep interference score, CGIC, PGIC, and the proportion of patients who responded to treatment. Significant improvements in mean pain score were seen in patients receiving pregabalin 300 and 600 mg/day (p=0.0001) compared to placebo. The number of responders to pregabalin was significantly better than placebo: 45.7% of patients responded to pregabalin 300 mg/day, 48.1% to pregabalin 600 mg/day, and 17.5% responded to placebo; (p=0.001). Patients who received 75 mg/day of pregabalin reported similar pain scores as patients receiving placebo. The most common adverse events included dizziness and somnolence. Pregabalin 300 and 600 mg/day was safe and effective in reducing DPN associated pain and reducing sleep interference.

Dworkin et al [8] carried out an eight-week, multicenter trial to evaluate the efficacy and safety of pregabalin in patients with PHN. This was a randomized, double-blind, placebo-controlled, parallel-group study. (Table 2) Patients were dosed based on renal function such that patients with a CrCl >60 ml/min received pregabalin 200 mg three times a day and patients with a CrCl between 30 and 60 ml/min received 100 mg three times a day. The primary efficacy measure was the difference between pregabalin and placebo in the mean pain

Table 3. Most common adverse effects (%) in treatment of DPN.[4]

Adverse Event	Pregabalin n=89 (%)	Placebo n=84 (%)
Dizziness	25 (28.1)	10 (11.9)
Time median to onset (days)	2 to 3	-
The median duration (days)	33	3
Somnolence	22 (24.7)	6 (7.1)
Time median to onset (days)	2 to 3	
The median duration (days)	53	17
Peripheral edema	17 (19.1)	2 (2.4)
The median time to onset (days)	24	-
The median duration (days)	31	-
Amblyopia	10 (11.2)	1 (1.2)
Dry mouth	10 (11.2)	2 (2.4)

ratings (average of last 7 days was tabulated) at 8 weeks. Secondary endpoints included additional pain ratings, sleep interference, quality of life, mood, and patient and clinician ratings of global improvement. Patients treated with pregabalin had greater decreases in pain compared to placebo (endpoint mean scores 3.60 vs. 5.29, p = 0.0001). The proportion of patients with ≥30% and ≥ 50% decreases in mean pain scores were 63% and 50% in the pregabalin arm, respectively vs. 25% and 20% in the placebo arm, respectively (p=0.001). Compared to placebo, sleep also improved in patients treated with pregabalin (p = 0.0001). Pregabalin treatment was associated with greater global improvement than treatment with placebo (p=0.001). The authors concluded that treatment of PHN with pregabalin is safe and effective for relieving pain and sleep interference and has acceptable tolerability compared to placebo.

Van Seventer et al [9] compared twice-daily pregabalin to placebo in a 13-week study. This was a randomized, double-blind, placebo-controlled, multicenter study (Table 2). The trial compared the safety and efficacy of pregabalin 150 mg/day, 300 mg/day, 300/600 mg/day (patients with a CrCl between 30 and 60 ml/min received pregabalin 300 mg/day and those with CLcr >60 ml/min received 600 mg/day), or placebo. The mean pain score was improved for all pregabalin groups compared with placebo (for pregabalin 150 mg/day, p=0.005, for pregabalin 300 mg/day, p=0.0002, and for pregabalin 300/600 mg/day, p=0.0002). The most common adverse events were dizziness, somnolence, and peripheral edema.

Sabatowski et al [10] conducted an 8-week, randomized, double-blind, placebo-controlled, multicenter study (Table 2). Patients received pregabalin 150 mg/day administered in three divided doses, pregabalin 300 mg/day administered in three divided doses, or placebo. The primary efficacy measure was the mean pain score. The secondary efficacy measures were the mean sleep interference score, PGIC, CGIC, SF-36, Zung Self-Rating Depression Scale, and VAS of the SF-MPQ. The mean pain scores at end of follow-up (intention-to-treat, ITT population) were 5.14 (p=0.0002), 4.76 (p=0.0001), and 6.33 for pregabalin 150 mg/day, pregabalin 300 mg/day, and placebo, respectively. Pain relief was evident during the first week of treatment and was maintained for the duration of the study. Mean sleep interference scores (ITT population) were 3.13 (p=0.0003) for pregabalin 150 mg/day, 2.81 (p=0.0001) for pregabalin 300 mg/day, and 4.24 for placebo. The most frequently reported adverse events (≥ 10%) were dizziness, somnolence, peripheral edema, headache, and dry mouth.

Toxicity and Safety

The most commonly reported adverse events reported in clinical trials with pregabalin are dizziness, somnolence, peripheral edema, headache, blurred vision, constipation, dry mouth, and diarrhea. [2,3] The adverse effect profile for pregabalin in patients with DPN and PHN is listed in Tables 3

Table 4. Most common adverse effects (%) in the treatment of PHN.[8]

	Pregabalin	Placebo
Adverse Event	**n=76 (%)**	**n=70 (%)**
Dizziness	27 (35.5)	8 (11.4)
Somnolence	15 (19.7)	2 (2.9)
Infection	11 (14.5)	4 (5.7)
Peripheral edema	8 (10.5)	1 (1.4)
Euphoria	4 (5.3)	0 (0)
	Days	**Days**
Time to onset		
Dizziness	≤ 1 day	≤1 day
Somnolence	≤ 1 day	≤1 day
Peripheral edema	31 days	4 days (1 patient)
Duration		
Dizziness 10.5	10.5 days	3.5 days
Somnolence 30.0	30 days	4 days
Peripheral edema	18 days	53 days (1 patient)

and 4, respectively.

Dosing and Administration

Formal dosing recommendations await FDA approval of the final labeling. Based on clinical trial data and approved doses in Europe, the dosage range for the treatment of neuropathic pain (DPN and PHN) is expected to be 150-600 mg/day administered in two or three divided doses (with or without food). An initial dose of 150 mg/day may be increased to 300 mg/day after 3-7 days and to 600 mg/day after an additional 7 days. [2,3] Pregabalin will be available as 25, 50, 75, 100, 150, 200, 225 and 300 mg capsules.

Contraindications/Precautions

Pregabalin is contraindicated in patients with a known hypersensitivity to this agent. Moreover, it seems prudent to avoid pregabalin in patients with gabapentin hypersensitivity given the structural similarities between these two agents. Central nervous system (CNS) depression may occur in patients treated with pregabalin, thus, counseling should include warnings about performing tasks that mandate mental acuity. Pregabalin should not be acutely discontinued; instead, a gradual tapering of 1 week is recommended. Physical and psychological dependence may occur in pregabalin-treated patients; it should be avoided in patients with a history of substance abuse. Pregabalin will accumulate in patients with renal insufficiency, so cautious dosage adjustment is necessary. Finally, experience with pregabalin is limited in pregnant and lactating women, adolescents, and infants.

Cost

The cost for Lyrica® (pregabalin) has not been established. Table 5 lists average retail costs from 3 pharmacies in Gainesville, FL.

Summary

Even though diabetic neuropathic pain affects over 3.7 million individuals in the US, until 2004, no treatment had been FDA approved for this indication. Gabapentin is frequently used off-label for neuropathic pain. Based on the clinical trial data, FDA has approved pregabalin for three indications: neuropathic pain associated with DPN, PHN, and as adjunctive therapy in the treatment of partial seizures in adults. Pregabalin has also been evaluated for treatment of GAD.

Pregabalin has a rapid onset of analgesic effect. In contrast to gabapentin , pregabalin exhibits linear pharmacokinetics and does not require po-

Table 5. The average retail cost of frequently used agents for the treatment of neuropathic pain.

Drug	Dose	One-month of therapy (dollars)
Duloxetine (Cymbalta®)	60 mg/d	111.98
Lidocaine patch (Lidoderm®)	one 5% patch daily	277.8
Gabapentin (Neurontin®)	1800 mg/day	257.68 (brand) 195.18 (generic)
Amitriptyline (Elavil®)	100mg/day	10.41 (generic)

tentially lengthy or complicated dose titration. Pregabalin may be titrated to the effective target dose of 300 to 600 mg/day over one week. Multiple clinical studies have shown that pregabalin, at dosages of 150 to 600 mg/day, demonstrates significant efficacy for improving pain and pain-related sleep interference as early as one week after starting treatment. Pregabalin appears to be well tolerated; the most common adverse effects are dizziness and somnolence. Pregabalin offers clinicians another agent with which to treat neuropathic pain syndromes and may prove to be particularly useful in patients who have not responded to or did not tolerate other treatments.

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