CHAPTER **47**

PREGABLIN THERAPY

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Pregablin (Lyrica®) is a new Food and Drug Administration-approved medication that has indications for diabetic peripheral neuropathy, postherpetic neuralgia, and adjunctive treatment for partial onset seizures. The true mechanism of action for pregablin is unknown. In animal models, it is thought that pregablin binds to the alpha2-delta subunit of voltage gated calcium channels in central nervous system tissues. It is suggested that pregablin reduces the excessive release of several neurotransmitters. Pregablin is not active at serotonin, dopamine and opiate receptors, does not alter cyclooxygenase enzyme activity, and does not block sodium channels. Pregablin is different from calcium channel blockers that bind to the A1 subunit of calcium channels.

The peak plasma concentrations occur within 1.5 hours and the values are linear. The oral bioavailability of pregabalin is 90% and is independent of dose. A steady state is achieved in 24-48 hours after repeated dosing. Pregablin can also be taken with or without food. Pregablin does not bind to plasma proteins and has a negligible metabolism in humans. Approximately 90% of the administered dose is excreted unchanged in the urine. The elimination of pregablin is closely proportional to creatinine clearance. In individuals with renal impairment, the dose needs to be reduced in line with creatinine clearance. There is also some indication that the pregablin oral clearance tends to decrease with increasing age.

There were no clinically significant pharmacokinetic interactions based on pharmacokinetic studies or population analyses with pregablin and the following medications: glyburide, insulin, metformin, furosemide, oxycodone, gabapentin, lorazepam, ethanol, oral contraceptives, and a number of antiepileptic drugs. The concomitant use of pregablin and thiazolidinedione antidiabetic drugs caused an increase in weight gain and edema. Pregablin may increase the effects of oxycodone, lorazepam, and ethanol on psychomotor impairment. The concomitant use with other antipsychotics, antidepressants, and narcotics may cause an addictive effect. Pregablin is a schedule V controlled substance. No blood monitoring is necessary with pregablin.

There were six double-blinded studies used to compile data for the treatment of neuropathic peripheral neuropathy and postherpetic neuralgia. The trials compared pregabalin doses of 75, 150, 300, and 600 mg to placebo to determine the efficacy and safety of the treatment. The 3 studies relating to peripheral neuropathy enrolled 729 patients. All of the studies determined that pregablin was effective and safe in treating diabetic neuropathy. Two of the studies also concluded an improvement in sleep patterns and one an overall improvement in quality of life. The studies determined that there were few side effects to the medication and few study dropouts.

The most common side effects in the pregablin trials were dizziness (29%) and somnolence (22%). The placebo treated patients showed side effect rates of 9% and 8%. Four percent of each of these led to withdrawal from the study. Blurred vision occurred in 6% of pregablin patients and 2% of placebo patients. A weight gain of 7% or more over baseline weight occurred in 8% of pregablin patients and 2% of placebo patients. The biggest weight gain occurred in diabetic patients with an average of 3.5 pounds. Peripheral edema occurred in 6% of pregablin patients versus 2% of placebo patients. Pregablin, therefore, should be used with caution in patients with congestive heart failure. The safety and efficacy of pregablin has not been established in pediatric patients. A pregnancy Category C designation has been given to the medication. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity.

Pregablin is available in capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg (Figure 1). The maximum recommended dose for

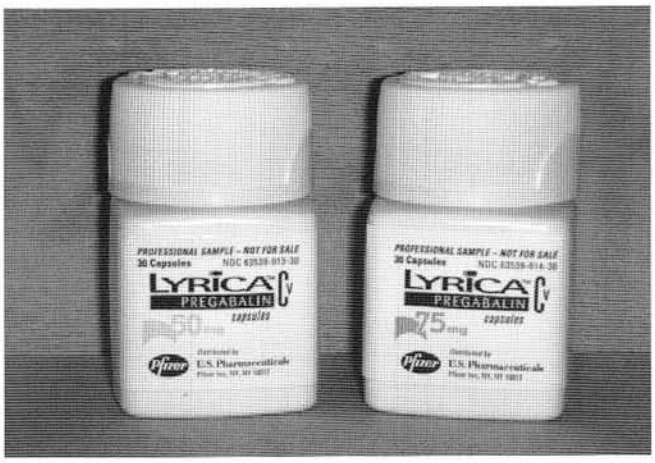

Figure 1. Pregabalin

patients being treated for painful neuropathy is 300 mg/day. With the number of dosing options, the medication can be titrated to the most efficacious level. In those patients with renal impairment, the dose should be adjusted based on creatinine clearance (mL/min) ≥ 60: 300 mg, 30-60: 150 mg, 15-30: 75 mg, and < 15: 25-50 mg. A supplementary dose should also be given after dialysis in some patients.

In 2004, the American Diabetes Association estimated that 18.2 million Americans have diabetes. As the rate of disease continues to rise, so will the prevalence of diabetes-related conditions. Diabetic peripheral neuropathy can be a challenging condition to manage. In the clinical trials, pregablin was found to be the most effective in treating diabetic peripheral neuropathy at 300 mg per day. Overall the medication was shown to be effective, safe, and well tolerated in the clinical trials. One study showed an overall improvement in quality of life with the reduction in neuropathic pain. As with all new medications, the physician should proceed cautiously and inform the patient of the risks of the medication, until the long term treatment statistics are known. Since gaining FDA approval in 2005, pregabalin has shown promising results in the treatment of painful diabetic peripheral neuropathy.

BIBLIOGRAPHY

Berger A, Dukes E, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain.* 2004;5:143-9.

Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60:1274-83.

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;105:133-41.

Hurley R, Chatterjea D, Rose Feng M, Taylor CP, Hammond DL. Gabapentin and pregabalin can interact synergistically with naproxen to produce antihyperalgesia. *Anesthesiology.* 2002;97:1263-73.

Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology.* 2004;63:2104-10.

Package insert of Lyrica by Pfizer Pharmaceuticals.

Randinitis EJ, Posvar EL, Alvey CW, Sedman AJ, Cook JA, Bockbrader HN. Pharmacokinetics of pregabalin in subjects with various degrees of renal function. *J Clin Pharmacol.* 2003;43:277-83.

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

Sabatowski R, Galvez R, Cherry DA, et al, and the 1008-045 Study Group. 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;109:26-35.