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Pregabalin (Lyrica®): Part II

by Chadrick Lowther, Pharm.D.

Introduction: Pregabalin (Lyrica®; Pfizer) is classified as a miscellaneous analgesic and anticonvulsant.¹⁻⁴ Pregabalin received Food and Drug Administration (FDA) approval on December 30, 2004, for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN); moreover, pregabalin is approved for use as adjunctive therapy for adult patients with partial onset seizures.^{3,5} Pregabalin is structurally related to gabapentin (Neurontin®; Pfizer).^{4,6}

Gabapentin was approved by the FDA on December 30, 1993, for adjunctive therapy in the treatment of partial seizures in adults and pediatric patients (3-12 years of age) and also approved in 2002 for pain management of PHN in adults.⁶ However, during the past 12 years, off-label use has accounted for the largest percentage of gabapentin prescriptions.⁷ Some of these off-label uses include: panic disorder, migraine prophylaxis, social phobia, mania, bipolar disorder, and alcohol withdrawal.⁸ Gabapentin lost its product exclusivity on May 24, 2005, and subsequently Pfizer introduced pregabalin with an FDA-approved indication for DPN.^{5,7}

Please see Pharmacotherapy Update Volume VIII, No. V Sept/Oct 2005

for Part I, which focuses on pregabalin pharmacology, pharmacokinetics, and select clinical trials.

Part II consists of numerous topics on pregabalin including, warnings and precautions, adverse reactions, drug interactions, and dosing.

Warnings and Precautions: In patients with seizure disorders, pregabalin should be withdrawn slowly (i.e., over a 1 week period) to reduce the potential for seizures.⁴

The initial clinical trials of pregabalin were halted because of concerns of drug-induced tumors in mice. Subsequent studies in rats showed no problems, and there is no evidence that the drug causes tumors in humans therefore prompting clinical trials to restart. As stated in the product labeling, in various patient populations consisting of 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. However, it was impossible to determine whether the incidence noted in these cohorts was or was not affected by pregabalin treatment.⁴

Similarly, clinical experience during the development of gabapentin provides no direct means to assess its



potential for inducing tumors in humans. As stated in the product labeling, clinical studies in adjunctive therapy in epilepsy comprising 2085 patient-years of exposure in patients >12 years of age, new tumors were reported in 10 patients, and pre-existing tumors worsened in 11 patients during or up to 2 years following discontinuation of gabapentin. Without knowledge of the background incidence and recurrence in a similar population not treated with gabapentin, it is impossible to know whether the incidence seen in this cohort was or was not affected by treatment.⁶

Patients should be educated that pregabalin can cause dizziness and somnolence; therefore, the ability to drive or operate machinery may be impaired.⁴ Additionally, the concurrent use of alcohol or central nervous system (CNS) depressants can potentiate the sedation induced by pregabalin.^{3,4} More patients treated with pregabalin reported blurred vision compared to placebo. Thus, patients should contact their prescribing physician if changes in vision occur. In comparison, visual field defects have also been reported with the use of gabapentin.⁶

Pregabalin caused weight gain in patients more frequently than placebo and was not limited to patients with edema. There were no clinically important changes in blood pressure associated with weight gain in trials, however, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.⁴ The concurrent use of pregabalin and thiazolidinedione antidiabetic agents [e.g., pioglitazone (Actos[®]) and rosiglitazone (Avandia[®])] was associated with higher frequencies of peripheral edema compared to patients taking either drug alone.^{3,4} Congestive heart failure may be a risk associated with the use of pregabalin due to the risk for increased peripheral edema.^{3,4}

Finally, treatment with pregabalin has been associated with elevations in creatinine kinase (CK).⁴ In premarketing trials, three patients were reported to have rhabdomyolysis, but a causal relationship has not been determined. Patients should be instructed to contact their physician if they experience unexplained muscle pain, tenderness, or weakness. In contrast, no elevations in CK are reported in the gabapentin product labeling.⁶

Adverse Reactions: Greater than 10,000 patients from various patient populations have received pregabalin. The majority of patients were treated with pregabalin for 6 months or more, and over 1,400 patients have been treated for at least 2 years.² The most common adverse events in all controlled clinical trials (in all patient populations) compared to placebo were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and abnormal thinking.⁴ The adverse events most commonly leading to discontinuation in all controlled clinical trials of pregabalin were dizziness and somnolence. Patients, although less frequently, discontinued pregabalin due to ataxia, confusion, asthenia, abnormal thinking, blurred vision, incoordination, and peripheral edema.¹

Gabapentin exhibits a similar adverse reaction profile as pregabalin.³ Common adverse events associated with the use of gabapentin include dry mouth, diarrhea, infection, ataxia, and abnormal thinking.⁶ The most common events leading to discontinuation were dizziness, somnolence, and nausea.¹

Drug Interactions: Oral contraceptives containing norethindrone and ethinyl estradiol (e.g., Loestrin[®], Ortho-Novum[®], and FemHRT[®]) have no effects on the pharmacokinetic profile of pregabalin.^{2,4} Also, lorazepam (Ativan[®]), oxycodone (e.g., OxyContin[®] and RoxicodoneTM), phenytoin (Dilantin[®]), carbamazepine (Tegretol[®]), valproic acid (e.g., Depakene[®] and Depakote[®]), lamotrigine (Lamictal[®]), tiagabine (Gabitril[®]), phenobarbital (Luminal[®]), topiramate (Topamax[®]), glyburide (DiaBeta[®]), furosemide (Lasix[®]), insulin preparations, and metformin (Glucophage[®]) had no effects on the pharmacokinetic profile of pregabalin.⁴

Since pregabalin is excreted predominantly unchanged in the urine and does not bind to plasma proteins, interactions with other medications are presumed to be negligible; however, thiazolidinediones have the potential to increase the fluid-retaining effects when taken concomitantly with pregabalin. The concomitant use of pregabalin with another CNS depressant agents has the potential for additive effects.²

Drug-drug interactions have been reported when taken concurrently with gabapentin.⁴ Agents demonstrating a possible, moderate severity interaction with gabapentin are phenytoin (Dilantin[®] or Phenytek[®]), fosphenytoin (Cerebyx[®]), felbamate (Felbatol[®]), and propranolol (Inderal[®]). Phenytoin and fosphenytoin levels may be elevated when these agents are given concurrently with gabapentin. Therefore, levels should be monitored and adjusted accordingly. A competition for renal elimination sites can occur with felbamate decreasing clearance, thereby increasing felbamate concentrations; monitor levels and adjust accordingly. Movement disorders attributed to elevated gabapentin levels are possible with concomitant use of propranolol due to an unknown mechanism.³²

Pregnancy/Lactation: There are no adequate and well-controlled studies evaluating pregabalin use in pregnant women. Pregabalin is classified as pregnancy-risk category C, which is the same risk category as gabapentin.⁴ Pregnancy-risk category C is defined as either animal studies having adverse effects to the fetus with no controlled studies in women, or studies in women and animals are not available. Therefore, pregabalin should only be used in pregnancy if the potential benefits outweigh the risks to the fetus. It is not known if pregabalin is excreted in human milk.⁶

In male rats, fertility studies have demonstrated a decreased sperm count and motility, increased sperm abnormalities, reduced fertility, increased fetal abnormalities, and indicated a male-mediated teratogenicity.⁴ The effects on sperm and fertility were reversible in these studies, which were conducted over a 3- to 4-month period.⁴ After 3 months in healthy male volunteers, there was no difference in pregabalin- and placebo-treated patients with regards to sperm motility.

Table 2. FDA-Approved Dosages of Pregabalin and Gabapentin^{4,6,8}

<i>Indication</i>	<i>Pregabalin Dosage</i>	<i>Gabapentin Dosage</i>
Neuropathic pain associated with diabetic peripheral neuropathy (DPN)	<p>Initial dose: 50 mg TID</p> <p>Dose may be titrated within 1 week based on efficacy and tolerability to a maximum recommended dose of 100 mg TID (300 mg daily).</p> <p>These doses are valid for individuals with a creatinine clearance of ≥ 60 mL/min.</p> <p>There is no evidence to suggest additional benefit with doses of 600 mg daily.</p>	<p><i>Off-label dosing:</i></p> <p>During the first 4 weeks, the starting dose of gabapentin is 900 mg daily and may be increased to 3600 mg daily as tolerated.</p> <p>This dosing schedule is effective for pain and sleep difficulties in patients suffering from DPN.</p> <p>Gabapentin requires dose adjustment in patients with renal dysfunction.</p>
Postherpetic neuralgia	<p>Initial dose: 50 mg TID or 75 mg BID (150 mg/day)</p> <p>Dose may be titrated within 1 week based on efficacy and tolerability to 300 mg daily.</p> <p>The maximum recommended dose is 300 mg BID or 200 mg TID (600 mg daily); however, the risk of side effects increases with this dosing schedule.</p> <p>These doses are valid for individuals with a creatinine clearance of ≥ 60 mL/min.</p>	<p>Initial dose: 300 mg once daily, titrated slowly up to maximum dose of 1800 mg/day</p> <p>Some studies demonstrated 3600 mg daily divided dosing with minimal additional benefit.</p> <p>Gabapentin requires dose adjustment in patients with renal dysfunction.</p>
Epilepsy	<p>Initial dose: 50 mg TID or 75 mg BID (150 mg/day)</p> <p>Based on the patient's response and tolerability, the dose may be increased to a maximum dose of 600 mg daily.</p>	<p>> 12 years of age: 300 mg TID, titrated as tolerated to doses as high as 3600 mg/day.</p> <p>3 to 12 years of age: 10 to 15 mg/kg/day titrated to 25 to 35 mg/kg/day in patients 5 years of age and older and 40 mg/kg/day in patients 3 to 4 years of age.</p> <p>Gabapentin requires dose adjustment in patients with renal dysfunction.</p>

Pregabalin dosing adjustments should be made in individuals with renal dysfunction. Elderly patients should be considered for age-related reductions in renal clearance. Dosing of pregabalin in pediatric patients has not been studied. Refer to Table 3 for appropriate dosage adjustments of pregabalin in patients with renal dysfunction. When discontinuing pregabalin, taper gradually over a minimum of 1 week.

BID: Twice daily; TID: Three times daily

Investigational Uses: Pfizer is currently evaluating pregabalin for use in fibromyalgia syndrome (FMS), epilepsy monotherapy, and panic disorder. Additionally, Pfizer may submit for the FDA-approval of pregabalin for the treatment of generalized anxiety disorder (GAD).³³

Cost: Pregabalin is available as a capsule in the following strengths: 25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg. All strengths of pregabalin are nominally priced at \$1.60/capsule. A cost comparison of pregabalin and gabapentin is located in Table 4.

Table 3. Dosage Adjustments of Pregabalin in Renal Impairment⁴

<i>Creatinine Clearance (CrCl)</i>	<i>Total Pregabalin Daily Dose^a (mg/day)</i>			<i>Dosing Regimen</i>
≥ 60 mL/min	150	300	600	Divided 2 or 3 times daily
30 to < 60 mL/min	75	150	300	Divided 2 or 3 times daily
15 to < 30 mL/min	25 to 50	75	150	Divided once or twice daily
< 15 mL/min	25	25 to 50	75	Once daily
Supplementary dosage following hemodialysis (mg) ^b				
Patients on the 25 mg once daily regimen: take one supplemental dose of 25 mg or 50 mg				
Patients on the 25 to 50 mg once daily regimen: take one supplemental dose of 50 mg or 75 mg				
Patients on the 75 mg once daily regimen: take one supplemental dose of 100 mg or 150 mg				

^aTotal daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

^bSupplementary dose is a single additional dose.

Table 4. Cost Comparison³⁴

Drug	Formulary Status	Dosage form	Strength	Cost (AWP) Price/Unit
Gabapentin*	NF	Solution	250 mg /5 ml	\$ 0.23 / ml
	F	Capsule	100 mg	\$ 0.39
		Capsule	300 mg	\$0.67
		Capsule	400 mg	\$ 0.83
		Tablet	600 mg	\$ 1.00
		Tablet	800 mg	\$ 1.00
Pregabalin (Lyrica®)	F	Capsule	25 mg	\$ 1.60
			50 mg	
			75 mg	
			100 mg	
			150 mg	
			200 mg	
			225 mg	
			300 mg	

AWP= Average Wholesale Price; F= Formulary; NF= Non-formulary

* All gabapentin AWP's are for generic products.

Formulary Status: Pregabalin has been added to the Cleveland Clinic Formulary of Accepted Drugs.

The Drug Enforcement Agency (DEA) scheduled pregabalin as a controlled substance (Schedule V) in July 2005.

Since pregabalin exhibits CNS activity, it was evaluated for potential abuse in recreational drug users. In a study of recreational users (n=15) of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of “good drug effect,” “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose).

In controlled clinical studies in over 5500 patients, 4% of pregabalin-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, or diarrhea, which are suggestive of physical dependence.

Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

Conclusion: Pregabalin is structurally related to gabapentin; however, it has increased binding affinity for the alpha₂-delta voltage-gated calcium channels. This increased receptor activity allows for decreased doses of pregabalin compared to gabapentin. Pregabalin has been shown to be effective in clinical trials and is FDA-approved for management of DPN, PHN, and adjuvant therapy of partial seizures. Pregabalin is currently being evaluated for off-label uses such as GAD, fibromyalgia, and panic disorder. The side effect profile of pregabalin is similar to gabapentin with dizziness and somnolence being the most commonly reported. Depending on the dose, pregabalin is more expensive than gabapentin which is available generically. Finally, current research is evaluating the potential benefit of pregabalin in patients with refractory neuropathic pain.

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Formulary Update

The Pharmacy and Therapeutics Committee met on Thursday, December 15, 2005, and the following decisions were made:

Formulary Additions:

1.) Pregabalin (Lyrica®): Pregabalin is FDA-approved for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and as an adjunct therapy for patients with partial-onset seizures. Although it is a structural analogue of gamma-aminobutyric acid (GABA), its exact mechanism is unknown. Common adverse effects associated with pregabalin use include headache, dizziness, fatigue, somnolence, weight gain, and gastrointestinal symptoms. Its use is also associated with peripheral edema; therefore, caution should be used when administering pregabalin concomitantly with other drugs that cause edema (e.g., thiazolidinediones). Pregabalin does not affect the plasma concentrations of other anticonvulsants. Effective doses for treating peripheral neuropathy and epilepsy range from 150 to 600 mg/day. Please refer to product labeling for initial dosing and dose titration recommendations, and for dose adjustments in patients with renal insufficiency. Because pregabalin use resulted in euphoria when studied in recreational drug users, it is ranked as a Schedule V controlled substance. To avoid withdrawal-like symptoms, pregabalin should not be abruptly discontinued rather it should be tapered gradually over a minimum of 1 week. Pregabalin is available as 25-, 50-, 75-, 100-, 150-, 200-, 225-, and 300-mg capsules.

2.) Acamprosate (Campral®): Acamprosate is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence that are abstinent at treatment initiation. It is believed that acamprosate balances GABA and glutamate activity in the CNS. In clinical trials, acamprosate enhanced abstinence and reduced drinking-rates in alcohol-dependent patients; however, it does not appear to be more effective than naltrexone. It can be used as an alternative to naltrexone in patients with liver disease, or in those receiving concomitant opioid therapy or methadone. Acamprosate use is associated with diarrhea, nausea, anxiety, depression, dizziness, and insomnia. Although naltrexone increases acamprosate peak concentration, dosage adjustments are not necessary when these agents are co-administered. The recommended dose is two 333 mg tablets three times daily. This dose should be reduced to one 333 mg tablets three times daily in patients with CrCl 30-50 mL/min. Acamprosate is contraindicated in patients with CrCl <30 mL/min. Therapy should be initiated as soon as possible after alcohol withdrawal. Therapy should be continued even if the patient relapses; optimal treatment lengths have not been established. Acamprosate is available as 333 mg tablets.

3.) Daclizumab (Zenapax®): Daclizumab is restricted for the outpatient treatment of multiple sclerosis in patients who have failed to respond adequately to conventional first-line therapies and for whom other alternative salvage therapy options are not appropriate or contraindicated.

Formulary Restrictions:

Bevacizumab (Avastin™): The restriction for bevacizumab (Avastin™) use has been changed to the following:

- 1.) Department of Hematology and Medical Oncology
- 2.) Staff Ophthalmologists (retina specialists) for intravitreal injection only for age-related macular degeneration.

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