

New Antiepileptics Effective, Less Toxic for Elderly

BY MARK BLOOM
Contributing Writer

BOSTON — A Veterans Affairs cooperative study of epilepsy in the elderly has found that two newer agents are as effective as carbamazepine at controlling seizures but are far less likely to cause unpleasant side effects.

The newer antiepileptic drugs (AEDs), gabapentin (Neurontin) and lamotrigine (Lamictal), were matched against carba-

mazepine in a 1-year, 18-center randomized double-blind study of 593 patients, said A. James Rowan, M.D., professor of neurology at Mount Sinai School of Medicine, New York.

Lamotrigine was significantly superior to gabapentin from the standpoint of patient retention over the length of the study. Neither of the newer agents was significantly better than carbamazepine in preventing seizures, said Dr. Rowan, who was codirector of the VA study.

Optimal doses of AEDs may be lower in the elderly patients, he reported at a meeting on epilepsy in the elderly sponsored by Boston University. The mean plasma levels of all three drugs were low "but that seems to be enough for this population," he said.

The patients were 60 years or older (mean age 72.8 years) with a history of one or more seizures and no previous AED therapy, or inadequate therapy.

The patients were titrated to the target

doses, 600 mg for carbamazepine, 1,500 mg for gabapentin, and 150 mg for lamotrigine. Clinicians had the flexibility to titrate further for tolerability, and after 12 months the mean doses were 582 mg for carbamazepine, 1,614 mg for gabapentin, and 152 mg for lamotrigine.

At the end of 12 months, "carbamazepine had significantly more side effects than lamotrigine or gabapentin," which led to earlier termination of therapy, according to Dr. Rowan. In the nurs-

- In clinical trials for DPNP, the most common adverse events were: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia
- Nausea rates in pooled analysis of 60 mg/day and 120 mg/day were 22% and 30% respectively vs 9% placebo. Nausea generally occurred within the first week of treatment, with a median duration of 6 days
- In DPNP clinical trials, the discontinuation rate due to adverse events was 14% for Cymbalta (20-120 mg/day) vs 7% for placebo

Contraindications

- Cymbalta is contraindicated in patients with a known hypersensitivity to duloxetine or any of the inactive ingredients
- Cymbalta should not be used in combination with monoamine oxidase inhibitors (MAOIs) and is contraindicated for at least 14 days after discontinuation of an MAOI. After stopping therapy on Cymbalta, at least 5 days should be allowed before starting on an MAOI
- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma

To find out more about how Cymbalta can give new hope to your patients with DPNP, visit www.insideCymbalta.com or ask your Lilly Representative.

Important Safety Information

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or thioridazine and not in patients with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: Patients being treated with an antidepressant should be observed closely for clinical worsening and suicidality, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Cymbalta should not be administered to patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min) or any hepatic insufficiency.

Cymbalta should generally not be prescribed to patients with substantial alcohol use.

Most common adverse events (≥ 5% and at least twice placebo) in diabetic peripheral neuropathic pain (DPNP) clinical trials were: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.



Reference:

1. Data on file, Lilly Research Laboratories.

See Brief Summary of full Prescribing Information at the end of this advertisement.

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ing home world, he added, adverse side effects and drug interactions, which are often promptly noted and reported in younger epilepsy patients, may be unnoticed or underreported among the elderly.

Of the 197 original carbamazepine patients, 72 finished the study (37%). That compared with 95 of 193 gabapentin patients (49%) and 114 of 197 patients in the lamotrigine arm (58%).

Among the neurologic side effects, carbamazepine led to

sedation for 51%, cognitive symptoms for 32%, dizziness for 32%, mood alteration for 4%, and gait disturbance for 29%. By contrast, in the gabapentin arm 46% of patients reported sedation, 29% with cognitive symptoms, 28% with dizziness, 26% with mood alterations, and 29% with gait disturbances. In the lamotrigine arm, 40% reported sedation, 23% cognitive symptoms, 27% dizziness, 30% mood alteration, and 28% gait disturbance. ■

AED/Drug Interactions Pose Risk in the Aged

Drug interactions are common with antiepileptic drugs taken by elderly patients, and these patients take a lot of medicine, Thomas R. Browne, M.D., said at the meeting.

For instance, some of the drugs will adhere to antacids and will decrease their concentrations. Aspirin will interfere with the protein-binding sites of phenytoin and depakote, decreasing the total concentration while the free level stays the same.

Theophylline, a treatment for chronic asthma, blocks the GABA receptor and can cause seizures. In persons who have seizures, this will lower the seizure

threshold, but patients who don't have seizures may develop what appear to be new-onset seizures if they have toxic levels of theophylline.

Phenytoin should be avoided in patients on warfarin. Seizures in the elderly are often due to strokes, and people who have strokes may be taking warfarin. Yet warfarin and phenytoin can have a biphasic interaction, said Dr. Browne, professor of neurology at Boston University.

Gabapentin and levetiracetam, both excreted by the kidney, are better choices for new-onset patients because they don't affect warfarin.

CYMBALTA® (duloxetine hydrochloride) Delayed-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE: Cymbalta is indicated for the treatment of major depressive disorder (MDD). Cymbalta is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

CONTRAINDICATIONS: Hypersensitivity—Known hypersensitivity to duloxetine or any of the inactive ingredients. **Monoamine Oxidase Inhibitors (MAOIs)**—Concomitant use with Cymbalta is contraindicated (see WARNINGS). **Uncontrolled Narrow-Angle Glaucoma**—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

WARNINGS: Clinical Worsening and Suicide Risk—Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

The following symptoms - anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania - have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Prescriptions should be written for the smallest quantity of capsules consistent with good patient management and to reduce the risk of overdose. If discontinuing treatment, the medication should be tapered.

MAOIs — In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

PRECAUTIONS: General—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Because it is possible that duloxetine and alcohol may interact to cause liver injury, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use.

Effect on Blood Pressure—In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (see ADVERSE REACTIONS, vital sign changes). **Activation of Mania/Hypomania**—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of Cymbalta-treated patients and 0% (0/777) of placebo treated patients. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. **Controlled Narrow-Angle Glaucoma**—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (see CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). **Discontinuation of Treatment with Cymbalta**—Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (see ADVERSE REACTIONS, Electrocardiogram Changes). In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (see ADVERSE REACTIONS, Electrocardiogram Changes). In clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 11 years, the mean baseline fasting blood glucose was 163 mg/dL, and the mean baseline hemoglobin A1c (HbA_{1c}) was 7.8%. In these studies, small increases in fasting blood glucose were observed in Cymbalta-treated patients compared to placebo at 12 weeks and routine care at 52 weeks. The increase was similar at both time points. Overall diabetic control did not worsen as evidenced by stable HbA_{1c} values and by no differences in incidence of serious and non-serious diabetes-related adverse events relative to placebo or routine care. Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—Potential for Other Drugs to Affect Cymbalta—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. **Inhibitors of CYP1A2**—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. **Inhibitors of CYP2D6**—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). **Potential for Duloxetine to Affect Other Drugs—Drugs Metabolized by CYP1A2**—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. **Drugs Metabolized by CYP2D6**—Cymbalta is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (eg, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. **Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs—Alcohol**—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (see PRECAUTIONS, Hepatotoxicity). **CNS Acting Drugs**—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. **Potential for Interaction with Drugs that Affect Gastric Acidity**—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors—See CONTRAINDICATIONS and WARNINGS. **Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis**—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m² basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors. **Mutagenesis**—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. **Impairment of Fertility**—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m² basis) did not alter mating or fertility.

Pregnancy—Pregnancy Category C—animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m² basis, in rats; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m² basis in rabbits). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m² basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis in rabbits). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent