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IN THIS ISSUE

JANUARY 2005
VOL. 21, NO. 1 • (pages 1-8)

Study argues ACE inhibitors should not be used in some heart patients

Trial results should change practice immediately, physician says

A new study argues that many heart patients receiving modern conventional therapy do not benefit from angiotensin-converting-enzyme (ACE) inhibitors if the patients have stable coronary heart disease and preserved left ventricular function.

The double-blind, placebo-controlled trial studied 8,290 patients, who were randomly assigned to receive either trandolapril at a dose of 4 mg per day or matching placebo. The patients, who were followed for a median of 4.8 years, had normal or near-normal left ventricular function, as indicated by left ventricular ejection fraction of greater than 40%. The study found no evidence that the addition of an ACE inhibitor provides "further benefit in terms of death from cardiovascular causes, myocardial infarction, or coronary revascularization."

The results of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial were presented at the Nov. 7 American Heart Association Scientific Sessions in New Orleans and also appeared in the Nov. 11 issue of the *New England Journal of Medicine*.

"With PEACE, we have shown that a huge number of people don't benefit from ACE inhibitors, specifically patients who have either normal or mildly depressed pump function — an ejection fraction equal to or greater than 40%," says **Michael Domanski**, MD, a cardiologist who is the head of the National Heart, Lung, and Blood Institute (NHLBI)'s Clinical Trials Scientific Research Group in Bethesda, MD. NHLBI, part of the National Institutes of Health, funded the study.

"If you have greater than or equal to 40% [ejection fraction], assuming you are treated in other modern ways as indicated [with statins, for example], these drugs don't benefit you. All they have to offer you are side effects."

PEACE was the last of three large international clinical trials that tested whether ACE inhibitors benefit heart disease patients who do not have heart failure. In the other two trials, HOPE (Heart Outcomes Prevention Evaluation) and EUROPA (European Trial on Reduction of Cardiac Events

with Perindopril in Stable Coronary Artery Disease), ACE inhibitors reduced morbidity and mortality in patients with stable coronary artery disease (or multiple risk factors) and without heart failure.

Reviewers of the study have tried to offer ideas as to why PEACE had this outcome. Some suggested that the trial involved lower-risk patients, such as those with a relatively low concentration of LDL cholesterol. Possibly more of them were using statins and had undergone previous coronary revascularization. Another suggestion is that not all ACE inhibitors are equally effective.

Domanski dismisses the last possibility. "I think we have taken care of that problem," he says. "Trandolapril has been shown in other studies of the same sort of dosing regimen to be effective in reducing mortality following heart attacks in patients for whom it is indicated. I think that is clearly a concern set aside by the fact that we know trandolapril works in a setting where it would be expected to. It's a completely hollow argument, frankly."

He thinks that practice should change immediately based on the results of PEACE. "The second someone reads [the article], they should say, 'Let's not be treating these people with ACE inhibitors.' They do have side effects."

Regardless of the mechanisms accounting for the failure of trandolapril to reduce the rate of cardiovascular events, the most important finding in the PEACE trial is that, after the exclusion of high-risk patients with diabetes mellitus, patients with known vascular disease who do not have a history of heart failure or left ventricular systolic dysfunction have a low risk of subsequent cardiovascular events when treated with a statin and other contemporary therapies, writes **Bertram Pitt**, MD, professor of internal medicine at the University of Michigan School of Medicine in Ann Arbor. His comments appeared in an editorial accompanying the article.

"In view of the low cardiovascular risk in this group of patients, it is doubtful that the use of an ACE inhibitor or an angiotensin-receptor blocking agent — even if effective in reducing the rate of cardiovascular events — would be cost-effective."

Wider application of strategies known to be effective (such as statin therapy, weight reduction, and glucose and blood-pressure control) as well as strategies currently under investigation could minimize the risk of cardiovascular events and possibly reduce the financial burden associated with vascular disease, he adds.

Although Pitt says he will no longer recommend an ACE inhibitor to patients like those included in the PEACE trial, he is not yet ready to eliminate the use of ACE inhibitors to treat all patients who have vascular disease without left ventricular systolic dysfunction. "Ongoing vascular inflammation, the production of reactive oxygen species, and plaque instability need to be re-evaluated in low-risk patients who are receiving contemporary therapy to determine their ability to predict cardiovascular events and thus to allow the selection of those at increased cardiovascular risk for ACE inhibition or other strategies."

There certainly are people who have reduced pump function below 40% ejection fraction — factors that would make sense to treat, Domanski says. The ones who would benefit have worse pump function than the patients studied in

Drug Formulary Review (ISSN#1548-2790), including **Drug Criteria & Outcomes**™, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Drug Formulary Review**, P.O. Box 740059, Atlanta, GA 30374.

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Subscription rates: One year (12 issues), $499. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue date. **Back issues**, when available, are $80 each. (GST registration number R128870672.)

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PEACE. Other indications for ACE inhibitors include high blood pressure and diabetes.

Some other studies, however, would make it sound that ACE inhibitors should be in the drinking water, he says, when in fact PEACE shows otherwise. The bottom line is that PEACE clearly identified the group of patients who would not benefit from ACE inhibitors, Domanski says. "It is easy to figure out who shouldn't have them based on this study." ■

Program improves heart patients' outcomes

Hospital pharmacists key to success

A discharge program that placed cardiovascular patients on appropriate medications and scheduled follow-up care not only reduced the patients' risk of readmission to the hospital, but also significantly decreased their risk of death.

In 1998, researchers at LDS Hospital and Intermountain Health Care (IHC) in Salt Lake City instituted a new discharge form and protocol to ensure cardiovascular patients were being discharged with the necessary medications.

The six-year study of the program focused on the appropriate prescribing of aspirin, statins, beta-blockers, angiotensin-converting enzyme inhibitors, and warfarin at hospital discharge.

"Around 1996-1997, there was clear evidence in the literature that certain medications had significant benefit in long-term outcomes for coronary artery disease, atrial fibrillation, and heart failure," explains **Donald Lappe**, MD, chief of cardiology at LDS Hospital and one of the researchers. "Yet, both locally and around the nation, patients with those diseases were being treated with those appropriate medications only about 50% of the time."

The biggest impact is for secondary prevention, he says. "No one was really clearly defined as being accountable to achieve that treatment goal."

The researchers decided that the accountability occurs when a person is discharged from the hospital with heart problems. "The magic of that is we know the person has coronary artery disease, atrial fibrillation, or heart failure. It is a measurable time, and one when you typically have the patient's attention," Lappe says.

The process included a mandatory checklist for physicians regarding the appropriate medications at discharge. The researchers compared 26,000 patients who were hospitalized with heart problems before 1998 with 31,465 heart patients who were discharged from 10 IHC hospitals after 1998.

Within a year, the health system went from about 60% overall achievement of the discharge medications for the appropriate diagnosis to above 90%, Lappe says. Those results have now been sustained for five to six years in a row.

"[Using our own database], we've tested the hypothesis that this would make a difference, and it certainly has. Thousands of lives were saved, readmissions were saved, and health care costs were saved — just through best practice treatments. There is not much out there that has showed such huge a reduction of adversities through relatively simple means."

Meet resistance head-on

After reviewing the literature, the researchers saw this was the "right place, right time, and right goals to set," Lappe says. It helped that a cardiovascular clinical program oversees cardiovascular services throughout IHC.

The researchers began with the 10 largest hospitals in the health system and quickly moved to the rest. The researchers engaged cardiologists, surgeons, and primary care doctors first to make sure they were well educated as to the importance of these clinical goals.

Doing this presented two challenges. One was determining who is responsible for the patients after the medications were prescribed at discharge. There was the typical disagreement over who would follow the patient: Who is going to be responsible to check the liver function test? Who is going to titrate it? The interventional cardiologist didn't claim responsibility, but placed it on the primary care physician. The primary care physician, on the other hand, would say that since the cardiologist didn't prescribe the medication, it must not be important.

To overcome the confusion, the researchers defined the roles of responsibility. "We communicated across all caregivers as to how the process will carry out and who has what accountability so the ball wasn't dropped through this lapse of understanding," Lappe says.

An even more important cultural change among physicians entailed saying they were

accountable to evidence-based health care practice, he continues. "There are clear evidence-based standards in these particular goals that say it is the right thing to do. That resistance was minor when we said these are national standards, not IHC dictating how you should carry out practice."

The researchers also provided some implementation tools for each hospital, such as cards that reminded people about the protocol, Lappe says. "Then we had a simple piece of paper, a data collection tool, and we fed the data back."

Pharmacists were an important part of the process, he says. "In some of the hospitals, the pharmacist would review the chart before the patient went home and remind the physician to prescribe the medicines if they hadn't already been prescribed. The pharmacists were the primary ones responsible for the success. In the hospitals where we used nurses or discharge managers to fulfill this role, the pharmacists worked hand-in-hand to help them achieve it. They were indispensable in all of our facilities."

Lappe says he has learned from this experience that you need to communicate, to educate, and to align and engage all the different components of the health care process.

For instance, it was critical that the researchers get nursing on-line with the program. "Nurses can remind doctors without conflict if something didn't occur."

Overall, Lappe thinks that you manage what you measure. These data were measured at the hospital level and resulted in the different institutions comparing results. "Doctors are competitive people," he says. "If one hospital was doing a better job, people could see that, and I think that enhanced the other hospitals so that internally they would try to manage themselves to achieve this goal."

The program has been a remarkable event, he says. "It's unconscionable that everyone in the country does not achieve this level because it is so important. We need to start looking and delivering this level of excellence to the people we serve." ■

JCAHO: USP/NF Chapter 797 compliance confusing

Hospitals should have action plan in place now

In the April 2004 issue of its *Perspectives* publication, the Joint Commission on Accreditation of Healthcare Organizations announced it would begin in July to survey compliance with the new chapter in the 2004 United States Pharmacopeia-National Formulary (USP-NF), titled "USP Tests and Assays Chapter 797, Pharmaceutical Compounding, Sterile Preparations."

The chapter details requirements for the compounding, preparation, and labeling of sterile drug preparations and applies to health care institutions, pharmacies, physician practices, and other facilities that prepare or compound sterile preparations, the Joint Commission says. In its announcement, the Joint Commission said its surveyors would address these requirements during surveys of organizations that compound sterile products (for example, intravenous solutions, eye drops) in the following ways:

- Surveyors would help organizations become aware of these new requirements (if they were unaware).
- Noncompliance with the major requirements in this *USP-NF* chapter that relate to Joint Commission standards would be scored at the appropriate element of performance effective immediately using the appropriate track record for compliance with the new requirements.

The announcement apparently confused many health care facilities. They wondered about the applicability of the requirements in Chapter 797, how the Joint Commission would be surveying them, and the expected time frame for compliance. The confusion was discussed in the October issue of *Joint Commission Perspectives*. On June 3, an advisory panel of 13 pharmacists and other health care professionals met to provide advice on realistic time frames for compliance with the requirements, as well as to "establish compliance priorities based on patient risk and safety," the Joint Commission says. The panel made recommendations on how organizations can achieve compliance with the chapter's requirements.

Joint Commission expects a plan

Here is what the Joint Commission says it will include in the survey:

- Provisions of Chapter 797 that are equivalent to the current elements of performance of the 2004 Joint Commission standards.
- By now, organizations should have conducted a risk assessment, or gap analysis, of

their compliance to all provisions of Chapter 797 and have developed a plan for each section of the chapter with specific time frames. The plan should include "any potential renovations or new facility construction and new equipment with budget provisions and completion/acquisition dates," the Joint Commission says. The organization also should select time frames based on its analysis of workload and sterile compounding risk levels and available resources.

The Joint Commission realizes this task may be overwhelming. To help, the advisory panel suggests that organizations focus their efforts on these priorities:

- Personnel training and evaluation
- Beyond-use dating and labeling
- Verification of automated compounding devices
- Finished preparation release checks and tests
- Aseptic technique

Hospitals looking for guidance in complying with the requirements can consider several tools offered by the American Society of Health-System Pharmacists (ASHP) in Bethesda, MD. One is the "ASHP Self-Assessment Tool for Compounding Sterile Preparations." This tool includes a 75-question survey that addresses all aspects of the USP chapter, ASHP says. Answers to the survey questions will help users determine their institution's compounding risk level and current level of compliance with the standards. After completing the survey, users will receive a percentage score and a list of resources to assist with meeting the requirements.

Another tool, ASHP's "797 Compliance Advisor," allows users to assess risk levels, perform gap analyses, and create action plans for compliance with the new sterile preparation requirements. The advisor features a survey that evaluates a facility's risk level and assesses its compliance with each of the 12 quality domains addressed in Chapter 797. After completion of the survey, the user will receive a series of reports detailing areas that conform to the USP standards, as well as an action plan to bring areas that need attention into compliance. The tool also allows users to update their progress and compare their performance against other participating facilities. This service costs $799. ■

NEWS BRIEFS

Report: Almost half of Americans use at least one prescription drug

Almost half of all Americans take at least one prescription medicine and one in six take three or more medications, according to the U.S. Department of Health and Human Services' annual checkup on Americans' health.

The report, *Health, United States 2004*, presents the latest health data collected by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics and dozens of other federal health agencies, academic and professional health associations, and international health organizations.

The latest report shows prescription drug use is rising among people of all ages, and use increases with age. Five out of six people age 65 and older are taking at least one medication, and almost half the elderly take three or more.

Adult use of antidepressants almost tripled between 1988-1994 and 1999-2000. Ten percent of women age 18 and older and 4% of men now take antidepressants. Prescriptions for nonsteroidal anti-inflammatory drugs, antidepressants, blood glucose/sugar regulators, and cholesterol-lowering statin drugs, in particular, increased notably between 1996 and 2002.

The National Health and Nutrition Examination Survey found a 13% increase between 1988-1994 and 1999-2000 in the proportion of Americans taking at least one drug and a 40% jump in the proportion taking three or more medicines. Forty-four percent reported taking at least one drug in the past month and 17% were taking three or more in the 2000 survey.

The annual report to Congress showed that health expenditures climbed 9.3% in 2002 to $1.6 trillion. Although prescription drugs comprise only one-tenth of the total medical bill, they remain the fastest growing expenditure. The price of drugs rose 5%, but wider use of medicines pushed total expenditures up 15.3% in 2002. Drug expenditures have risen at least 15% every year since 1998.

Other findings include:

- Three times as many white adults as black or Hispanic adults took antidepressants.
- Boys were prescribed drugs to treat attention deficit hyperactivity disorder twice as often as

girls, but antidepressants were prescribed to boys and girls at the same rates.

• Private health insurance covered almost half of prescription drug costs in 2002, up from a quarter in 1990. People paid 30% out of their own pockets.

The full *Health, United States* report is available on the CDC web site at www.cdc.gov/nchs/. ▼

FDA announces new radio-frequency ID initiative for drugs

The U.S. Food and Drug Administration (FDA) has published a Compliance Policy Guide (CPG) for implementing radiofrequency identification (RFID) feasibility studies and pilot programs that are designed to enhance the safety and security of the drug supply. The FDA says this action continues its commitment to promote the use of RFID by the U.S. drug supply chain by 2007.

In a related action, the FDA announced that it is creating an internal RFID Workgroup whose charge is to monitor adoption of RFID in the pharmaceutical supply chain, proactively identify regulatory issues raised by the use of this new technology, and develop straightforward processes for handling those issues. The FDA contends that the workgroup will improve communication with members of the supply chain on RFID-related issues and should facilitate both the performance of pilot studies and the collection of data needed to formulate policy.

The FDA also applauded the initiatives announced by the pharmaceutical companies Pfizer, GlaxoSmithKline, and Purdue Pharma, all of which plan to place RFID tags on at least one of their products.

RFID technology makes it easier to ensure that drugs are authentic, and it also creates an electronic pedigree, or record of the chain of custody, from the point of manufacture to the point of dispensing, the FDA says. Electronic pedigrees should allow wholesalers and retailers to rapidly identify, quarantine, and report suspected counterfeit drugs and conduct efficient, targeted recalls. The FDA considers electronic pedigrees to be a type of "electronic safety net" that uses technology that allows illicit drug transactions to be rapidly identified and, potentially, transmitted to the FDA.

These actions are steps in implementing a major recommendation of the FDA's report, issued Feb. 18, 2004, titled "Combating Counterfeit Drugs." The report recommended that RFID technology be in widespread use throughout the pharmaceutical industry by 2007.

The FDA will consider all public comments in any revision of the CPG.

Those interested in commenting on the CPG may submit their comments to: www.fda.gov/dockets/ecomments/. ▼

FDA strengthens labels on two types of antibiotics

The U.S. Food and Drug Administration (FDA) has announced labeling changes regarding penicillin G benzathine and penicillin G procaine injectable suspension (Bicillin CR) and penicillin G benzathine injectable suspension (Bicillin LA). These changes include: 1) a new boxed warning against intravenous use, which has been associated with serious adverse effects in post-marketing reports, including cardiorespiratory arrest and death; and 2) a precautionary note for penicillin G benzathine and penicillin G procaine injectable suspension explaining it is not for treatment of syphilis.

King Pharmaceuticals, the manufacturer of these products, has also issued a "Dear Doctor" letter, highlighting these changes. The letter reminds practitioners that penicillin G benzathine injectable suspension is the only currently approved penicillin G benzathine product indicated for the treatment of syphilis and that penicillin G benzathine and penicillin G procaine injectable suspension should not be administered in place of penicillin G benzathine injectable suspension for this purpose. Administration of penicillin G benzathine and penicillin G procaine injectable suspension instead of penicillin G benzathine injectable suspension in the treatment of syphilis may result in inadequate treatment.

To help health professionals better distinguish between the two types of antibiotic, King Pharmaceuticals has modified the cartons and syringe labels. The background colors for the CR cartons have been changed from white to pale green (Bicillin CR) and pale purple (Bicillin CR 900/300). Bicillin LA cartons will retain the white background. The statement "Not for the Treatment of Syphilis" has also been added in red text to both the Bicillin CR and Billin CR 900/300 syringe labels.

For more information, see www.fda.gov/bbs/topics/ANSWERS/2004/ANS01329.html. ▼

Rx drug law may help low-income Medicare beneficiaries

Low-income people with Medicare who sign up for new Part D drug plans and receive the additional subsidies — an estimated 8.7 million people — are projected to pay 83% less for prescription drugs in 2006 than they would have spent if the Medicare drug law had not been enacted, according to a new report released today by the Kaiser Family Foundation in Washington, DC. Those who enroll in the new drug benefit but do not receive the low-income subsidies — an estimated 20.3 million people — are projected to pay on average 28% less out-of-pocket for their prescription drugs as a result of the new law, the analysis finds.

The report, based on a model developed by Actuarial Research Corp. (ARC) for the Foundation, estimates out-of-pocket drug spending in 2006 among the 29 million people the Congressional Budget Office (CBO) expects will sign up for Medicare drug plans.

The simulation model generally conforms to CBO's assumptions and projections about Medicare drug benefit spending and participation rates for the new benefit, known as Medicare Part D, and for the low-income subsidy. The projections of out-of-pocket drug spending are based on the likely response of Medicare beneficiaries to the new law. They do not reflect the effects of supplemental coverage that beneficiaries might obtain or take into account premiums paid by beneficiaries, which are estimated by CBO to average $420 for the new Medicare benefit in 2006.

Overall, the analysis projects that three out of four who enroll in plans offering the new benefit (21.6 million people) are expected to have the same or lower out-of-pocket spending in 2006 than they would have without the new Medicare drug law.

The other one in four (7.4 million people) are expected to have higher out-of-pocket spending without taking into account the premium costs for the new coverage, unless they get supplemental coverage from another source.

For most (about 5 million people), the increases are expected to be modest — $250 or less. The 2.4 million people who are projected to face even higher out-of-pocket costs under the new drug benefit in 2006 includes those with relatively high out-of-pocket drug costs who are projected to lose access to more generous prescription drug coverage than the new Medicare benefit provides, especially people who lose their employer plan coverage.

The report and other materials are available on-line at www.kff.org/medicare/med112204pkg.cfm. ■

New FDA Approvals

These drugs recently were approved by the FDA:

• ***Natalizumab (Tysabri) by Biogen Idec and Elan Pharmaceuticals.*** The FDA has licensed a new biologic approach to treat patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of symptom flare-ups or exacerbations of the disease. Natalizumab (Tysabri), the new product, is a monoclonal antibody bioengineered from part of a mouse antibody to closely resemble a human antibody. The product is given intravenously once a month in a physician's office.

Although the cause of MS is unknown, it is widely considered to be an autoimmune disease in which the person's immune system attacks the brain and/or spinal cord. Natalizumab appears to work by binding to these immune system cells, thus preventing them from traveling to the brain where they can cause damage.

Natalizumab's approval is based on positive results seen in patients after one year of treatment.

This product received accelerated approval because it appears to provide substantial benefit for patients with a serious disease. As part of that

COMING IN FUTURE MONTHS

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- A look at polypharmacy in the elderly
- VHA's distribution strategy saves millions in pharmacy costs
- Race-based drug approvals
- News from the ASHP Midyear Clinical Meeting and Exhibits

approval, the manufacturer has committed to continuing its trials of this product for another year.

Natalizumab was evaluated for safety and efficacy in two ongoing randomized, double-blind, placebo-controlled trials in patients with relapsing forms of MS. In the first clinical trial of the product's safety and efficacy, the drug reduced the frequency of relapses by 66% relative to placebo.

In a second trial, patients who had been treated with interferon beta-1a (Avonex), an approved treatment for MS, but who had experienced one or more relapses while on the drug, were randomized to receive natalizumab or placebo. Interferon beta-1a was continued throughout the study for both groups. In this trial, natalizumab reduced the frequency of relapses by 54% relative to placebo.

The most frequently reported serious adverse reactions were infections, including pneumonia, temporary hypersensitivity reactions (such as rash, fever, low blood pressure, and chest pain), depression, and gallstones. These serious adverse reactions were uncommon. Common adverse reactions generally were mild and included nonserious infections (such as urinary tract, lower respiratory tract, GI system, and vaginal infections), headache, depression, joint pains, and menstrual disorders.

• ***Erlotinib (Tarceva), manufactured by OSI Pharmaceuticals, and distributed by Genentech***. The FDA has approved erlotinib (Tarceva) tablets as a single-agent treatment for patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC), the most common form of lung cancer in the United States. Erlotinib is being approved as a treatment for patients whose cancer has continued to progress despite other treatments, including at least one prior chemotherapy regimen.

Erlotinib is a drug that inhibits an enzyme, tyrosine kinase, associated with a human epidermal growth factor receptor (EGFR). The drug has shown improved survival in patients with locally advanced or metastatic NSCLC. Erlotinib received fast track status from FDA during its development.

Safety and efficacy were demonstrated in one randomized trial in 731 patients comparing erlotinib to placebo. The primary endpoint in this trial was survival. The median overall survival was 6.7 months in the erlotinib group compared with 4.7 months in the placebo group.

In about one-third of the patients, tumor cells were examined to see whether they had high or low levels of EGFR. Among the approximately 55% who had high EGFR, the effect on survival was much greater than it was in people whose EGFR levels were low. The relationship will be explored further in the future.

Common side effects reported with erlotinib in clinical trials were diarrhea, rash, nausea, and vomiting. Erlotinib may cause fetal harm when administered to pregnant women.

The FDA reviewed the application for erlotinib using the "rolling review" procedures that are available to new drug applications designated as "fast track." In rolling review, the FDA starts reviewing specific components of a drug approval application even before all the application components have been submitted to the agency. For erlotinib, the first piece of the application was submitted in January 2004, and the last portion in July 2004. ■

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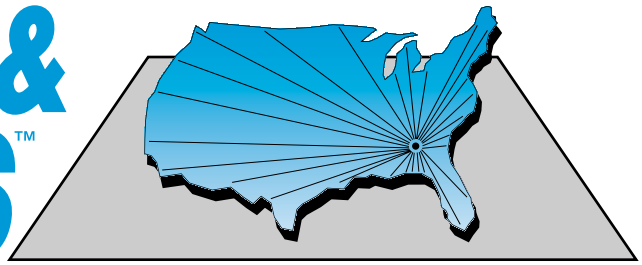

Duloxetine (Cymbalta) Formulary Evaluation

Part 1 of 2: Mechanism of Action, Pharmacokinetics, Indication, Dosing, Special Populations, Safety, and Cost

By **Andrea Pierce**, PharmD Candidate
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Background

The U.S. Food and Drug Administration (FDA) approved duloxetine (Cymbalta), marketed by Eli Lilly & Co., on Aug. 3, 2004, for the treatment of major depressive disorder (MDD) in adults. Duloxetine is a serotonin-norepinephrine reuptake inhibitor. It not only treats the depressive symptoms, but also reduces the painful physical symptoms of depression (e.g., back pain, headaches, neck pain, etc). Duloxetine was the first drug to receive FDA approval to specifically treat the pain associated with diabetic peripheral neuropathy. It is also being investigated for the treatment of stress urinary incontinence. It already is being marketed in Europe to treat incontinence under the name Yentreve, and the FDA currently is evaluating its efficacy for that indication.

Venlafaxine (Effexor) was chosen for comparison purposes in this review as a representative antidepressant agent having similar pharmacology as duloxetine.

Mechanism of action

Duloxetine is a reuptake inhibitor of both serotonin and norepinephrine. It belongs to the same drug class as venlafaxine, even though structurally it resembles fluoxetine (Prozac). Like venlafaxine, duloxetine is a stronger inhibitor of serotonin reuptake than norepinephrine reuptake. It has no effect on the dopaminergic, histaminergic, muscarinic, alpha 1 adrenergic receptors, 5-$HT_{1A,}$ 5-$HT_{1B,}$ 5-$HT_{1D,}$ 5-$HT_{2A,}$ 5-$HT_{2C,}$ opioid receptors, or monoamine oxidase (MAO). In stress incontinence, duloxetine inhibits the serotonin and the norepinephrine reuptake, causing the detrusor muscle and the urethral sphincter to increase activity, leading to improved bladder control.

Pharmacokinetics

Absorption

• Duloxetine is an oral agent that appears to have a 70% bioavailability based on urinary excretion. For regular-release venlafaxine, 92% is absorbed, but only 12.6% is available to the systemic circulation due to first-pass metabolism. The extended-release venlafaxine is approximately 45% available to the systemic circulation.

• Duloxetine has a two-hour delay after oral administration before absorption begins due to its enteric coating, with the peak concentration occurring six hours after dosing. Peak concentration is achieved in one to two hours with the immediate-release venlafaxine tablets and in about 5.5 hours with the extended-release capsules.

• If given in the evening, absorption of duloxetine occurs within three hours after oral administration, and clearance is increased 30% compared to morning administration.

• When duloxetine is given with food, the time to peak concentration is delayed to six to 10 hours, but it does not affect the peak concentration. With venlafaxine, time of day and food have no effect on absorption. Venlafaxine should be given with food to decrease gastrointestinal adverse effects.

Distribution:

• Duloxetine has greater than 90% protein

binding, while venlafaxine has 30% protein binding. Therefore, there is a higher risk of drug interaction with highly bound agents with duloxetine vs. venlafaxine.

• Both are widely distributed throughout the body.

• Steady state is achieved after three days dosing with both duloxetine and venlafaxine.

• Duloxetine has a volume of distribution (V_d) of 1640 L, while venlafaxine's steady-state V_d is 7.5 ± 3.7 L/hour/kg.

Metabolism

• Duloxetine undergoes hepatic metabolism through the CYP1A2 and CYP2D6. Venlafaxine also is metabolized mainly by the CYP2D6 and undergoes first-pass metabolism to its main active metabolite O-desmethylvenlafaxine.

• Duloxetine has a half-life of approximately 12 hours (ranging from 8 to 17 hours). Venlafaxine has a half-life of five hours with the metabolite having a half-life of 11 hours.

Excretion

• Duloxetine — 70% excreted as metabolites in the urine and 20% in the feces.

• Venlafaxine — 36%-60% excreted through the urine.

• Duloxetine has a clearance of 114 L/hour, while venlafaxine has a mean ± SD steady-state plasma clearance of venlafaxine is 1.3 ± 0.6 L/hour/kg.

Onset of action

• Response to therapy was seen in three weeks in patients treated with duloxetine, while venlafaxine patients showed a response in 2-3 weeks.

Indications

Duloxetine is indicated for the treatment of depression in adults. It also is indicated to treat pain associated with diabetic neuropathy. Studies are currently under way to determine its efficacy in the treatment of stress urinary incontinence.

Venlafaxine is approved to treat anxiety, depression, and social phobia. Unlabeled uses include diabetic neuropathy, neuropathic pain, menopausal symptoms, fibromyalgia, headaches, and premenstrual dysphoric disorder.

Dosing

***Duloxetine*:**

• Duloxetine is available as oral capsules in the strengths of 20 mg, 30 mg, and 60 mg.

• Depression: Initially 40-60 mg per day as a single dose or in two divided doses. The maximum dose has been determined to be 120 mg, but no increase in efficacy is seen with the higher dose.

• Diabetic neuropathy: 60 mg given once a day; 120 mg per day has been used, but no increase in efficacy was noted.

***Venlafaxine*:**

• Venlafaxine is available in immediate-release (IR) tablets (25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg) and extended-release (XR) capsules (37.5 mg, 75 mg, 150 mg).

• Depression: Venlafaxine IR — 75 mg/day in 2-3 divided doses and may be increased by 75 mg/day every 4 days to a maximum of 225 mg/day. XR — Initially 75 mg per day; can begin at a dose of 37.5 mg/day and increase to 75 mg/day in 4-7 days. Increase dose by 75 mg every 4 days to goal dose, not to exceed 225 mg day.

• Both agents can

Table 1: Adverse Drug Reactions**

Adverse Effect	Duloxetine %	Placebo %	Effexor XR %	Placebo %
Nausea	20	7	31	12
Dry mouth	15	6	12	6
Constipation	11	4	8	5
Vomiting	5	3	4	2
Decreased appetite	8	2	8	4
Weight loss	2	1	3	0
Dizziness	9	5	20	9
Somnolence	7	3	17	8
Tremor	3	1	5	2
Sweating	6	2	14	3
Blurred vision	4	1	4	< 1
Insomnia	11	6	17	11
Decreased libido	3	1	3	< 1
Abnormal orgasm	3	1	3	< 1
Erectile dysfunction	4	1	4	< 1
Delayed ejaculation	3	1	16	< 1
Hypertension	N/A	N/A	4	1
Nervousness	< 1%	< 1%	10	5
Abnormal dreams	< 1%	< 1%	7	2

** No studies have directly compared to duloxetine and venlafaxine. These numbers are from the package inserts of the two agents.

be dosed daily.

Special populations

Duloxetine should be avoided in patients with hepatic failure. In patients with mild-to-moderate renal failure, no dosing adjustment is needed. It is recommended to avoid use of duloxetine in patients with severe renal impairment or end-stage renal disease.

The dose of venlafaxine should be decreased 50% in patients with moderate hepatic impairment. In patients with renal impairment, the dose is individualized based on creatinine clearance.

Administration of duloxetine and venlafaxine

- Swallow capsules whole.
- Do not cut, chew, or crush capsules (duloxetine capsules or extended-release venlafaxine products).

Nausea, dry mouth, sweating, weight loss, and gastrointestinal problems occurred more frequently with both drugs compared to placebo **(see Table 1)**. Nausea was more prevalent during the first week of therapy with duloxetine. It can be decreased in patients by starting with the 30 mg per day capsules the first week and titrating to 60 mg per day by the end of the week. Venlafaxine XR had higher rates of dizziness, somnolence/insomnia, hypertension, sweating, abnormal dreams, and nervousness when compared to placebo than duloxetine. The risk of seizures is also higher in patients taking venlafaxine than in the duloxetine-treated patients. Both groups had sexual adverse effects, with venlafaxine XR having a substantially elevated rate of delayed ejaculation compared to placebo. However, caution must be used in comparing these values, as they are not derived from directly comparative trials.

Drug interactions

Duloxetine is metabolized by the CYP2D6 and CYP1A2 enzymes. There is a moderate risk of drug interactions with duloxetine because it is both a CYP2D6 substrate and an inhibitor there **(see Table 2)**.

- Inhibitors of 1A2 — Duloxetine concentration is increased (e.g., fluvoxamine, cimetidine, quinolones).
- Inhibitors of 2D6 — Duloxetine concentration is increased (e.g., paroxetine, fluoxetine, quinidine).
- Use caution in drugs metabolized through the CYP2D6 enzyme that have a narrow therapeutic index.
- Do not use duloxetine and venlafaxine or other serotonin agents in combination with each other due to risk of serotonin syndrome.
- Do not use with monoamine oxidase inhibitors (MAOIs) or with drugs that have MAOI activity (procarbazine or linezolid). Wait at least two weeks after MAOI agent discontinued before starting either duloxetine or venlafaxine.
- Do not use with tricyclic antidepressants (TCAs).
- Due to its metabolism through the CYP2D6 enzymes, venlafaxine has similar drug interactions as duloxetine.

Pregnancy rating

- Both duloxetine and venlafaxine have a pregnancy rating of category C.
- Avoid use in lactation

Table 2: Precautions/Warnings

Duloxetine	Venlafaxine
Risk of hepatotoxicity. Use caution in patients who ingest large amounts of alcohol. Avoid in patients with hepatic failure.	Use caution in patients with liver disease. Decrease dose by 50%.
Avoid in patients with severe renal impairment or end-stage renal disease.	Use caution in patients with renal impairment. Individualize dose based on CrCl.
Slight increase in blood pressure. (2 mmHg systolic and 0.5 mmHg in diastolic)	Risk of sustained hypertension. Monitor blood pressure often. Consider decreasing dose or discontinuing in patients who experience new onset hypertension.
Avoid use in combination with other serotonergic agents due to risk of serotonin syndrome.	Avoid use in combination with other serotonergic agents due to risk of serotonin syndrome.
Use with CNS depressants can slow motor function.	Use with CNS depressants can slow motor function.
Do not discontinue abruptly due to risk of withdrawal symptoms (abnormal dreams, headache, irritability, insomnia).	Do not discontinue abruptly due to risk of withdrawal symptoms (abnormal dreams, headache, irritability, insomnia).
Caution in patients with history of manic episodes.	Caution in patients with history of manic episodes.
Supervise patients with history of suicidal ideations.	Supervise patients with history of suicidal ideations.
Caution in patients with anorexia nervosa.	Caution in patients with anorexia nervosa.
	Caution in patients with history of seizures.
	Use caution in patients with history of cardiovascular events such as myocardial infarction and unstable heart disease.

if possible with both agents.

Contraindications

Similar in both duloxetine and venlafaxine.

- Hypersensitivity to duloxetine/venlafaxine.
- Use with MAOIs.
- Duloxetine is contraindicated in patients with narrow angle glaucoma due to increased risk of mydriasis.

Storage

Capsules should be stored at 25°C (77°F) and away from sunlight. Excursions are permitted to 15°-30°C (59°-86°F).

Potential for medication error

There is a potential for duloxetine and venlafaxine to be confused, especially during verbal communication. Another possible error could occur if duloxetine and fluoxetine were confused with each other, especially with written orders because they look alike and also are available in similar strengths. Educating the staff on the potential of these errors occurring is key in maintaining patient safety.

Cost

The cost of the duloxetine and the extended-release venlafaxine is similar **(see Table 3)**. The immediate-release tablets are not as expensive, but more tablets per day will have to be taken to get the equivalent dose of the extended-release capsules, causing the cost to increase, and compliance may not be as good.

Patient information for duloxetine and venlafaxine

- If a dose is missed, take as soon as you remember and continue the next day with the regular dosing schedule. Do not double doses.
- Avoid alcohol.
- Drowsiness may occur, so use caution in activities that require alertness (driving, operating heavy machinery, etc.).
- Notify physician if you become pregnant or are breast-feeding. ■

Table 3: Cost

Cymbalta	30mg $2.85 per capsule	60mg $2.85 per capsule
Effexor XR	75mg $2.73 per capsule	150mg $2.97 per capsule
Venlafaxine (immediate release)	37.5mg $1.51 per tablet	75mg $1.51 per tablet

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A statement of credit requires a passing score of 70% or higher. When a passing test and evaluation form are received, a statement of credit and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

1. Duloxetine has been investigated for treatment of:
   A. depressive symptoms.
   B. pain associated with diabetic peripheral neuropathy.
   C. stress urinary incontinence.
   D. All of the above

2. Like venlafaxine, duloxetine is a stronger inhibitor of serotonin reuptake than norepinephrine reuptake.
   A. True
   B. False

3. Duloxetine should be avoided in patients with:
   A. hepatic failure.
   B. severe renal impairment.
   C. end-stage renal disease.
   D. All of the above

4. Patients taking duloxetine should be encouraged to:
   A. not double doses.
   B. avoid alcohol.
   C. use caution in activities that require alertness (driving, operating heavy machinery, etc.).
   D. notify physician in the case of pregnancy or breast-feeding.
   E. All of the above