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IN THIS ISSUE

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VHA consultants strive to improve pharmacy position in member hospitals

Managing high-cost, high-risk drugs always will be a challenge

A national health cooperative is using a team of in-house consultants to help increase the efficiency of pharmacy departments in member hospitals.

The program has resulted in a typical 10-to-1 return on investment (3-to-1 guaranteed) for the hospitals that use the service — by getting member hospitals more involved in clinical pharmacy and improving the position of the pharmacy departments.

VHA, based in Irving, TX, presently has more than 1,400 hospital members. The consulting team has helped at least 100 of the hospitals so far, often working four or five engagements at one time.

The pharmacy consultants look not only at cost, but at quality and at getting the hospital pharmacy involved in patient-focused care, says **Bruce Weiner**, RPh, MS, FASHP, a senior director who oversees VHA's pharmacy consulting services.

Weiner has been working with VHA for four years to form the pharmacy consultant team. He has hired a former director of pharmacy who specializes in operations; he also has clinical pharmacists on board who have worked in hospital pharmacy for more than 10 or 20 years.

The team approaches the pharmacy department and director as partners, Weiner says. The director is consulted before and throughout the evaluation process. "We don't want to run the pharmacy. We want to work with them to make their pharmacy better."

Although the pharmacy team offers a variety of consulting services, about 75% of the requests involve evaluating the hospital's formulary. "Sometimes, the director of pharmacy will have a new clinical pharmacy coordinator, and wants to give that person a road map to focus on," Weiner says. The consultants then look at the whole formulary and set the goals for the clinical coordinator.

The entire process, from initial on-site hospital visits to the presentation of recommendations, usually takes about 10 weeks, more if the hospitals need help implementing the findings. Some of the service can be

duplicated across hospitals, but the team also has to tailor its approach to the different specialties each facility offers.

Standardizing the drugs

One important service regarding the formulary is to help hospitals plan and implement standardization and utilization programs for their most commonly used drugs. The consultants found that hospitals often were purchasing multiple drugs that were similar in chemical composition and had the same clinical purpose.

The team also helps member hospitals benchmark their pharmacy purchasing patterns with other VHA members and examine drug costs in hospital departments that have high drug usage, such as intensive care units, the VHA says.

Weiner estimates that the consultant team can help hospitals save between 10% and 30% on the drugs they buy most often.

Here are the following nine drug product categories that VHA says commonly represent more than 60% of most hospital pharmacy budgets:

- Glycoprotein IIb/IIIa inhibitors
- $5HT_3$ receptor antagonists
- Low molecular weight heparins
- Anticoagulants
- Antibiotics
- Antifungals
- Oncolytics
- Oncology adjuvants
- Critical care medications

The process of evaluating a formulary never ends, Weiner says. "Although we identify opportunities to reduce costs, new drugs are being introduced every year that further increase the pharmacy budget and as such, serve as new challenges."

There are always the "low-hanging fruit" that go from trade name to generic and result in significant cost savings, he continues. However, then there are the drugs such as nesiritide (Natrecor) that has expensive reimbursement issues that may result in reduced payments to hospitals.

"Pharmacists need to be creative in ways to assure appropriate utilization of that very expensive drug," he says. "It's important to state that although we've identified specific areas to reduce costs, in the future the challenge will be to find ways to reduce costs of those new high-cost, high-technology drugs." ■

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Pharmacists urged to ask patients about CAM use

More turning to alternative therapies due to cost

Health trend researchers are urging pharmacists more than ever to ask patients about possible use of complementary and alternative medicine (CAM). Not only are cost concerns driving more lower-income, uninsured patients to try alternative therapies, but many of these patients aren't telling their health care providers about these treatments.

The people who are concerned about the cost of their health care may be particularly vulnerable as they seek cheaper — and potentially ineffective or unsafe — care outside the realm of conventional

medicine, says **Ha T. Tu**, MPH, a health researcher for the Center for Studying Health System Change (HSC) in Washington, DC. HSC is a nonpartisan policy research organization funded principally by the Robert Wood Johnson Foundation.

HSC recently released data showing that nearly 6 million adults in America have turned to CAM because they say their conventional medical treatment is too expensive. The study is based on the 2002 National Health Interview Survey, a nationally representative government survey conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics. Tu is a co-author of the study.

These millions of adults who use CAM because of cost concerns were four times as likely to be uninsured as the 38 million Americans who use CAM to treat specific health conditions without citing cost as a reason. In addition, they were almost twice as likely to have low incomes, defined as below 200% of the federal poverty level.

"It is somewhat troubling because the evidence seems to show that they are resorting to CAM because they can't afford conventional care," Tu says. The situation may not improve soon. "Our organization tracks a lot of trends in the health system over time, such as looking at the implications of rising costs. It seems to us that as health care costs keep rising well above the rate of income growth, this group of 6 million people is likely to grow."

Tu also is concerned about another finding in the data: In more than half of the cases where CAM is being used because of cost concerns, the patients did not tell their health care providers about using the therapies. Or if they did, the providers were not always well versed about the therapies' potential side effects.

"It's difficult to keep up with all the herbal remedies as well as prescription drugs. [The herbal remedies] can number in the thousands," Tu says.

She is quick to point out that not all of the 6 million CAM users are a cause for concern for heath care providers. "We try not to say that in our analysis. The conditions some of these people are . . . [treating] with CAM are conditions like colds, and they are using echinacea to treat it. While the jury might be out about whether that is an effective treatment, there is no evidence it does any harm."

Instead, the researchers highlight the use of two herbal remedies that are thought to cause serious side effects. St. John's wort was used by one in eight of all CAM users citing cost concerns. Known as a potential treatment for depression, the herbal remedy may have potentially dangerous side effects when used with other drugs.

Kava was used by one in 12 of this subgroup of the study. Kava is used to treat anxiety, stress, and insomnia, and has been linked to liver damage.

It might not occur to patients that an herbal remedy might react with a prescription drug, Tu says. "Consumers often think that because a product is 'natural,' it is likely to be safe." Patients with multiple health conditions also might not be able to recall all the medications — CAM remedies included — that they have taken.

For these reasons, Tu urges pharmacists to be proactive and ask patients about possible CAM use. "Asking is something the health system can do without adding to cost," she says. It also may be the only opportunity to provide basic education to the patients about CAM therapies.

The study did not indicate where these CAM users found information about the therapies. Tu suggests that pharmacists direct patients to the web site of the National Center for Complementary and Alternative Medicine, a center of the National Institutes of Health. The site, http://nccam.nih.gov, has a comprehensive health information site, which includes alerts on drug interactions, harmful side effects, and public health advisories. ■

Aromatase inhibitor shows promise in reducing breast cancer recurrence

Physicians are divided on its use

New research shows that aromatase inhibitor anastrozole (Arimidex) may be more effective than tamoxifen in preventing recurrence of breast cancer.

These results from the breast cancer trial "Arimidex, Tamoxifen, Alone, or in Combination (ATAC)" were published Dec. 8 on *The Lancet* web site. They were also presented at the San Antonio Breast Cancer Symposium in December.

The researchers wanted to compare anastrozole to tamoxifen for five years in more than 9,000 postmenopausal women with localized breast cancer. Tamoxifen is the standard adjuvant endocrine treatment, but recurrences and side effects limit its usefulness, the researchers say. The patients were followed for a median of 68 months. The

researchers found that anastrozole significantly prolonged disease-free survival and time to recurrence, and significantly reduced distant metastases and contralateral breast cancers. Fewer patients taking the anastrozole withdrew from the study compared to those taking tamoxifen. In addition, anastrozole was associated with fewer side effects; however, arthralgia and fractures increased.

The researchers conclude that the "present data suggest that it is not appropriate to wait five years to start an aromatase inhibitor." "Furthermore," they say, "the higher rates of recurrence (especially in years one to three), and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, lend support to the approach of offering the most effective and well-tolerated therapy at the earliest opportunity. Five years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive localized breast cancer."

Some physicians, however, think the use of anastrozole as the initial therapy may be premature. In November, a Technology Assessment Panel from the American Society of Clinical Oncology (ASCO) in Alexandria, VA, updated ASCO's recommendations on adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer. The guidelines did not endorse the use of aromatase inhibitors as initial adjuvant therapy, and the chairman of the panel told media outlets that the new study results would not change the recommendations.

Here are the panel's general guidelines for use of aromatase inhibitors:

• **Postmenopausal women with hormone receptor-positive breast cancer may substitute an aromatase inhibitor for tamoxifen as initial adjuvant therapy.** Alternatively, women still can begin treatment with tamoxifen and plan to switch to an aromatase inhibitor after two to five years. "It not clear at this time which strategy is superior," the panel says.

• **Postmenopausal women who currently are taking tamoxifen may consider switching to an aromatase inhibitor after two to five years of tamoxifen therapy.**

• **Women who switch to an aromatase inhibitor may continue this therapy for two to three more years, but no longer than five years.** Women are advised that the result of treatment with an aromatase inhibitor for longer than five years has not been studied and should only be done in the context of a clinical trial.

• **There are no data to recommend taking tamoxifen *after* an aromatase inhibitor.**

In addition, the panel says, women who develop invasive hormone receptor-positive breast cancer while taking tamoxifen for breast cancer risk reduction, and women who cannot take tamoxifen because of high risk of severe side effects, or who have tried tamoxifen and had to stop because of severe side effects, might be advised to consider using an aromatase inhibitor. ■

FDA recommends limiting COX-2 inhibitors use

An advisory committee should meet this month

The questions continue about the safety of COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs).

First Merck withdrew rofecoxib (Vioxx) from the market in late September 2004 because of increased risk of heart attack and stroke. Then, on Dec. 9, the FDA announced that a boxed warning was being added to the label of valdecoxib (Bextra), a COX-2 inhibitor indicated for the treatment of osteoarthritis, rheumatoid arthritis, and dysmenorrhea. The addition strengthens previous warnings about the risk of life-threatening skin reactions and says that the use of valdecoxib in patients undergoing coronary artery bypass graft surgery is contraindicated.

On Dec. 17, the National Institutes of Health (NIH) announced that it was suspending the use of COX-2 inhibitor celecoxib (Celebrex) for all participants in a large colorectal cancer prevention clinical trial conducted by the National Cancer Institute (NCI). The study, called the Adenoma Prevention with Celecoxib trial, was stopped because analysis by an independent Data Safety and Monitoring Board showed a 2.5-fold increased risk of major fatal and nonfatal cardiovascular events for participants taking the drug compared to those on a placebo. Pfizer has agreed to voluntarily suspend direct-to-consumer advertising of celecoxib while the FDA evaluates the data on adverse events associated with the drug.

Then, on Dec. 20, the NIH halted a clinical trial involving nonsteroidal anti-inflammatory drugs in patients at risk of developing Alzheimer's disease. Preliminary information from the study showed some evidence of increased risk of

cardiovascular events, when compared to placebo, to patients taking naproxen (Aleve).

These announcements frustrated consumers and led some politicians and health care professionals to place partial blame for the potential problems on the FDA's drug approval process.

The FDA, however, issued statements defending its drug evaluations, and on Dec. 23, issued a Public Health Advisory summarizing the agency's recent recommendations regarding the use of NSAIDs, including COX-2 inhibitors. The agency says this advisory is an interim measure, pending further review of data.

Here are the FDA's recommendations:

• **Physicians prescribing celecoxib or valdecoxib should consider this emerging information when weighing the benefits against risks for individual patients.** Patients who are at a high risk of gastrointestinal bleeding, have a history of intolerance to nonselective NSAIDs, or are not doing well on nonselective NSAIDs may be appropriate candidates for COX-2 selective agents.

• **Individual patient risk for cardiovascular events and other risks commonly associated with NSAIDs should be taken into account for each prescribing situation.**

• **Consumers are advised that all over-the-counter (OTC) pain medications, including NSAIDs, should be used in strict accordance with the label directions.** If use of an (OTC) NSAID is needed for longer than 10 days, a physician should be consulted.

The FDA says it is collecting and will be analyzing all available information from the most recent studies of rofecoxib, celecoxib, valdecoxib, and naproxen, and other data for COX-2 selective and nonselective NSAID products to determine whether additional regulatory action is needed. An advisory committee meeting is planned for this month. The Public Health Advisory is available online at www.fda.gov/cder/drug/advisory/nsaids.htm. ■

FDA: Gefitinib (Iressa) does not prolong survival

The FDA issued a statement last December urging patients who take gefitinib (Iressa) to consult their physicians, since gefitinib failed to show in a clinical trial an overall survival advantage in treating patients with lung cancer.

The trial, which compared gefitinib with placebo in patients with non-small cell lung cancer who had failed other courses of cancer therapy, showed no survival benefit from taking gefitinib.

FDA approved gefitinib on May 2, 2003, under the agency's accelerated approval (Subpart H) program, for the treatment of patients with non-small cell lung cancer who had failed two or more courses of chemotherapy. Gefitinib was approved because the data from clinical trials showed that it caused significant shrinkage in tumors in about 10% of patients, and this was thought likely to increase patients' overall survival time.

Under the agency's accelerated approval program, the sponsor must study the drug further after approval to verify the expected clinical benefit. After the approval of gefitinib in 2003, AstraZeneca conducted a study in approximately 1,700 patients to determine whether the drug would in fact prolong survival in comparison to patients taking placebo. The results of this study indicate that the drug did not prolong survival.

The FDA has the authority to remove a drug from the market if a postmarketing clinical study fails to verify clinical benefit. After the FDA has evaluated the recent study results, it will determine whether gefitinib should be withdrawn from the market or if other regulatory actions are appropriate.

Alternative FDA-approved therapies that patients may use include docetaxel (Taxotere) and erlotinib (Tarceva), both of which have been shown in studies to improve survival in patients with non-small cell lung cancer whose cancer has progressed while on previous therapies. ▼

The FDA adds warnings to bevacizumab (Avastin) label

The FDA and Genentech have notified health care professionals about revisions to the label of bevacizumab (Avastin). Bevacizumab, used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma

of the colon or rectum. Arterial thromboembolic events, including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving bevacizumab in combination with chemotherapy as compared to those receiving chemotherapy alone. These events were fatal in some instances.

In randomized, active-control studies, the overall incidence of arterial thromboembolic events was increased with the use of bevacizumab in combination with chemotherapy (4.4% vs. 1.9%). The incidences of both cerebrovascular arterial events (1.9% vs. 0.5%) and cardiovascular arterial events (2.1% vs. 1.0%) were increased in patients receiving bevacizumab in combination with chemotherapy. In addition, there was a correlation between age (65 years and older) and the increase in risk of thromboembolic events. The risk of these events should be viewed in the context of bevacizumab's ability to improve overall survival in patients with metastatic colorectal cancer.

For more information, see www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Avastin. ▼

Computer entry cases medication errors

The United States Pharmacopeia (USP) in Rockville, MD, has reported that nearly 20% of hospital and health system medication errors reported to USP's MEDMARX℠ program in 2003 involved computerization or automation. However, facilities that have implemented computerized prescriber order entry (CPOE) reported fewer harmful errors. According to the 2003 data, automated dispensing devices (ADDs) were implicated in almost 9,000 medication error events with 1.3% of those errors leading to patient harm.

These findings are part of USP's annual report summarizing the data collected by MEDMARX, the national medication error reporting system operated by USP. The report, *MEDMARX 5th Anniversary Data Report: A Chartbook of 2003 Findings and Trends 1999-2003,* analyzes 235,159 medication error records voluntarily reported by 570 hospitals and health care facilities nationwide. The report includes five-year trend analysis of records for 1999-2003, as well as a focus on technology-related errors.

Errors that result from using a computer can occur in any phase of the medication use process: prescribing, transcribing/documenting, dispensing, administering, and monitoring. According to USP's data, most computer entry (CE) errors occurred in either the transcribing/documenting phase or dispensing phase of the medication use process. In 2003, CE errors were the fourth leading cause of medication errors according to MEDMARX data. CE errors have steadily increased and represent 11.5% of all MEDMARX records from 1999 through 2003. The data indicate that nearly three-quarters of all CE errors occur after an order is written but before the medication is administrated to the patient. Other significant findings associated with CE errors:

- **Performance deficit was the most frequently reported cause of error in CE.** A performance deficit is a cause of error in which the health care practitioner has the required skills and knowledge to execute a task but errs nonetheless.
- **Distractions were the leading contributing factor, accounting for 56.5% (3,293) of errors associated with CE.**
- **Wrong-dose errors occurred more frequently in CE records compared to overall 2003 data, indicating that there was a higher occurrence of selecting the incorrect dose when a computer entry system was involved in processing the drug order after it was written.** ▼

Americans still confident about prescription drugs

Most Americans say they're confident about the safety of prescription drugs sold in the United States, according to an Associated Press (AP) poll.

The poll was taken after questions were raised about celecoxib (Celebrex) and more than two months after rofecoxib (Vioxx) was withdrawn from the market. But it was taken before a study raised a possible heart attack-stroke link with naproxen, which is sold over the counter as Aleve.

Just more than eight in 10 people surveyed said they have confidence in the general safety of prescription drugs in this country, the poll conducted for the AP by Ipsos-Public Affairs found. Almost that many said they have confidence in the FDA.

But many of those people admit they have some worries. Only about a third said they were

"very confident" about the safety of prescription drugs in the United States and half said they were "somewhat confident."

About a fourth in the poll said they were "very confident" in the FDA's ability to ensure the safety of prescription drugs, with about half saying they were "somewhat confident." Only one in six people who took prescription drugs of any kind in the last year, 14%, said they have asked their doctor or pharmacist to re-examine the drugs they were taking since rofecoxib was taken off the market in late September and other drugs have been questioned.

The AP-Ipsos poll of 1,002 adults was taken Dec. 17-19 and has a margin of sampling error of ± 3%, slightly higher for the 773 prescription drug users polled. ■

New FDA Approvals

The FDA recently approved these drugs:

• ***Pegaptanib sodium injection (Macugen) by Eyetech Pharmaceuticals and Pfizer.*** The FDA has approved pegaptanib sodium injection (Macugen), a new therapy to slow vision loss in people with neovascular (wet) age-related macular degeneration (AMD). Pegaptanib is a selective vascular endothelial growth factor antagonist. Macugen 0.3 mg should be administered once every six weeks by intravitreous injection into the eye to be treated.

The safety and efficacy of pegaptanib sodium injection was studied in two trials in patients with wet AMD for two years. Patients treated with pegaptanib sodium injection exhibited a significant decrease in vision loss in both trials. Serious adverse events related to the injection procedure included infections, retinal detachment, and traumatic cataract. Other frequently reported adverse events in patients treated with pegaptanib sodium injection were eye irritation, eye pain, hemorrhage under the outer membrane of the eye, and blurred vision. The New Drug Application for pegaptanib sodium injection was received and approved in six months.

• ***Palifermin (Kepivance) by Amgen.*** The FDA has approved palifermin (Kepivance), a new intravenous biologic product, to help reduce the chance that certain cancer patients (those with blood cancers undergoing chemotherapy and radiation in preparation for bone marrow transplants) will develop mucositis. Palifermin also shortens the duration of the condition.

Palifermin is a man-made version of the human protein keratinocyte growth factor (KGF). In a study of 212 patients with leukemia or lymphoma who were receiving high doses of chemotherapy and radiation treatments associated with bone marrow transplantation, 98% of the patients who did not receive palifermin developed severe mucositis compared to 63% of those who received the drug. Also, for those who received the drug, severe mucositis lasted an average of three days, compared to nine days for those receiving a placebo.

The most common side effects of palifermin were skin rash, unusual sensations in the mouth, and increases in blood proteins suggesting pancreatic irritation. No serious side effects have been reported related to use of palifermin. Palifermin has not yet been shown to be safe and effective in patients being treated for forms of cancer other than leukemia or lymphoma. The recommended dosage of palifermin is 60 mcg/kg/day, administered as an IV bolus injection for three consecutive days before and three consecutive days after myelotoxic therapy for a total of six doses.

• ***Pregabalin capsules (Lyrica) by Pfizer.*** The FDA has approved pregabalin capsules (Lyrica) for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN). Pregabalin is the first FDA-approved treatment for both of these neuropathic pain states, which are distinctly different from arthritis or musculoskeletal pain.

The efficacy of pregabalin was established in six double-blind, placebo-controlled trials, three involving patients with DPN and three involving patients with PHN. Pregabalin provided rapid and clinically meaningful pain reduction in a significant portion of patients, with pain relief

COMING IN FUTURE MONTHS

- ■ FDA drug approval trends
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- ■ News from the ASHP Midyear Clinical Meeting and Exhibits
- ■ Medicare changes how it pays some outpatient drugs

beginning as early as the first week of treatment in some patients. Pain relief was sustained in studies of up to 12 weeks duration.

The safety of pregabalin was established in more than 9,000 patients. In all clinical trials, adverse events were mild to moderate. The most common side effects associated with pregabalin compared with placebo included dizziness, somnolence, dry mouth, peripheral edema, blurred vision, weight gain, and difficulty with concentration/attention. The discontinuation rate due to side effects was low.

Pregabalin is expected to be classified as a controlled substance in a category with lower potential for misuse or abuse relative to controlled substances in other categories. Pregabalin currently is under review by the FDA for the adjunctive treatment of partial seizures in adults. In July, Pfizer received European Commission approval to market the drug in European Union member states for the treatment of peripheral neuropathic pain and as adjunctive therapy for partial seizures.

• ***Clofarabine (Clolar) by Genzyme Corp.*** The FDA has approved clofarabine (Clolar) for the treatment of children with refractory or relapsed acute lymphoblastic leukemia (ALL). Clofarabine is the first new leukemia treatment approved specifically for children in more than a decade. Genzyme was expected to make clofarabine commercially available in January. Clofarabine is indicated for the treatment of pediatric patients ages 1-21 years with relapsed or refractory ALL after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

Clofarabine has received orphan drug designation for adult and pediatric ALL. Clofarabine now will have seven years of market exclusivity in pediatric ALL patients. The FDA also recently granted six months of extended market exclusivity to clofarabine under the Best Pharmaceuticals for Children Act. Clofarabine was approved under the FDA's accelerated approval process. Genzyme is committed to continue post-marketing evaluation of clofarabine in pediatric ALL and has submitted a pediatric development plan that includes further study of clofarabine in combination with existing therapies.

The most common adverse effects after clofarabine treatment, regardless of causality, were gastrointestinal tract symptoms, including vomiting, nausea, and diarrhea; hematologic effects, including anemia, leucopenia, thrombocytopenia, neutropenia, and febrile neutropenia; and infection.

Careful hematologic monitoring during therapy is important.

Clofarabine should be diluted per product instructions with 5% dextrose injection, or 0.9% sodium chloride injection, prior to intravenous infusion. The recommended pediatric dose and schedule is 52 mg/m^2 administered by intravenous infusion over two hours daily for five consecutive days. Treatment cycles are repeated following recovery or return to baseline organ function, approximately every two to six weeks. The dosage is based on the patient's body surface area, calculated using the actual height and weight before the start of each cycle. ■

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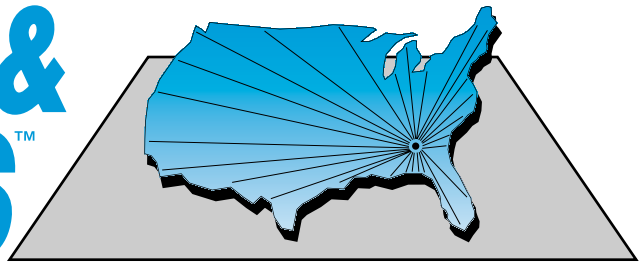

Duloxetine (Cymbalta) Formulary Evaluation

Part 2: Clinical Trial Summary, Treatment of Peripheral Neuropathy, Conclusion/Recommendation

By **Andrea Pierce**, PharmD Candidate
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Clinical trial summary

Duloxetine has been studied in several randomized, placebo-controlled clinical trials. The following three trials determine duloxetine to be efficacious in the treatment of major depressive disorder (MDD) in adults. Duloxetine also has been approved to treat peripheral neuropathy. At the present time, there have not been any studies evaluating duloxetine's efficacy compared to other agents such as selective serotonin reuptake inhibitors (SSRIs) or serotonin/norepinephrine (SNRIs) reuptake inhibitors. All the trials addressed both efficacy and safety issues. The trials compared duloxetine to placebo to determine efficacy. The following fourth study also evaluates its use in peripheral neuropathy.

***Trial 1*:** Detke MJ, Lu Y, Goldstein DJ, et al. **Duloxetine, 60 mg, once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial.** *J Clin Psychiatry* 2002;63:308-315.

This was a prospective, placebo-controlled clinical trial involving 245 patients with diagnosed MDD according to the DSM-IV criteria, who were randomly chosen to receive either placebo or duloxetine 60 mg for a total of nine weeks. The primary efficacy tool used was the Hamilton Rating Scale for Depression (HAM-D) score and was measured at each visit. Other tests used to measure secondary endpoints were the Clinical Global Impressions-Severity Scale (CGI-S), the Patient Global Impressions-Improvement Scale (PGI-I), the Visual Analog Scale (VAS), and the Quality of Life in Depression Scale.

The probability that patients will go into remission is higher in the duloxetine group than in the placebo group (44% vs. 16%). The duloxetine patients also had less painful physical symptoms such as headache and backaches than those patients receiving placebo. There were more duloxetine-treated patients to withdraw from the study than placebo-treated patients (13.8% vs. 2.5%). The main adverse effect reported was nausea (occurring mainly during the first week of treatment) in 46.3% of duloxetine patients, compared to 9% in placebo.

The strengths of the study included randomization, double-blind design, lead-in and lead-out phases, and use of several tests to determine efficacy. The weaknesses include lack of titration schedule, short duration, and the use of a placebo control rather than an active control. In conclusion, duloxetine was shown to be safe and effective in the treatment of MDD and in the reduction of painful symptoms associated with depression.

***Trial 2*:** Goldstein DJ, Mallinckrodt C, Lu Y, et al. **Duloxetine in the treatment of major depressive disorder: A double-blind clinical trial.** *J Clin Psychiatry* 2002;63:225-231.

This trial was a prospective, double-blind placebo-controlled study of the efficacy and safety of duloxetine in the treatment of MDD. This study involved 173 patients randomized to receive duloxetine, placebo, or fluoxetine 20 mg per day (2:2:1 ratio). The fluoxetine arm served as

an internal control group; this study was not designed to be a comparison of fluoxetine and duloxetine. The duloxetine patients were titrated from 40 mg to 120 mg per day during the first three weeks of treatment. The primary endpoint was the HAM-D score with secondary endpoints being the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S, the PGI-I, and the Hamilton Rating Scale for Anxiety (HAM-A).

The results of the study showed a significant decrease in HAM-D scores in the patients treated with duloxetine compared to placebo. The estimated probability of remission after eight weeks of therapy was 56% in the duloxetine group, 32% in the placebo group, and finally 30% in the fluoxetine group. The estimated response rate was 64%, 52%, and 48% for duloxetine, fluoxetine, and placebo, respectively. Duloxetine also was shown to be more efficacious in most of the secondary endpoints than fluoxetine and placebo.

The number of patients who discontinued the study was higher in the duloxetine group than in the placebo group (10% vs. 4.3%). The side effects also were similar to those reported in other studies. The strengths of this study include randomization, double-blind design, and lead-in and lead-out phases.

The weaknesses include the use of a placebo control rather than an active control, forced titration to 120 mg/day with the maximum dose not reached until the fourth week of the eight-week study, and 2:2:1 ratio of agents used with the fluoxetine dose not maximized, perhaps in some cases allowing efficacy to be similar to placebo. The investigators concluded that duloxetine is an effective treatment in patients diagnosed with MDD with little risk of serious side effects.

***Trial 3*:** Raskin J, Goldstein DJ, Mallinckrodt CH, et al. **Duloxetine in the long-term treatment of major depressive disorder.** *J Clin Psychiatry* 2003; 64:1,237-1,244.

The study was an open-label, 52-week study to determine the long-term safety of duloxetine in doses up to 120 mg per day for patients with MDD as determined by the DSM-IV criteria. Patients who could not tolerate 80 mg per day of duloxetine were not included in the study. The primary endpoint was determined by the CGI-S, HAM-D, Beck Depression Inventory (BDI-II), and the PGI-I scales with quality of life determined by the patients using the Sheehan Disability Scale.

Of the 1,279 patients beginning the study, only 553 completed it, with 17% discontinuing due to adverse effects. The estimated probabilities of response at 6, 28, and 52 weeks were 62.9%, 84.3%, and 89.1%, respectively. The probabilities of remission were 50.8%, 75.6%, and 81.8% at weeks 6, 28, and 52 weeks, respectively.

The strengths of this study include the length of the study, use of appropriate tests to determine efficacy, and appropriate timing of measurements. The weaknesses in this study include the open-labeled single-arm design, high dropout rate, and the exclusion of patients who were unable to tolerate 80 mg duloxetine per day. In conclusion, duloxetine was well tolerated and efficacious during the 52-week trial in patients who could tolerate the drug at the beginning of their treatment period.

Treatment of peripheral neuropathy

***Trial 4*:** Goldstein DJ, Lu Y, Iyengar S, et al. **Duloxetine in the treatment of the pain associated with diabetic neuropathy.** AAPM presentation from Eli Lilly & Co.; March 3, 2004.

This was a prospective, randomized, placebo-controlled trial to determine the efficacy of duloxetine in the treatment of peripheral neuropathy. Patients received duloxetine 20 mg, 60 mg, 120 mg, or placebo. The primary efficacy endpoint was the decrease in the 24-Hour Average Pain Severity Score. Doses of 60 mg to 120 mg per day were proven to be the most efficacious. The use of concomitant acetaminophen also was lower in the duloxetine-treated patients than the placebo. The results also showed that the patients taking the 60 mg dose had similar efficacy to the 120 mg group with fewer adverse events occurring.

The strengths of the study include randomization, prospective, intent-to-treat, and appropriate measurement tools used. The weaknesses include the use of a placebo control, short duration, and lack of titration schedule. The results of the study determined that duloxetine was efficacious in the treatment of the pain associated with neuropathies with the dose of 60 mg being as effective as the 120 mg dose.

Conclusion/recommendation

Duloxetine appears to be an efficacious treatment for patients suffering from MDD, especially in patients suffering from painful physical symptoms. Its use is limited to the lack of clinical trials comparing it to other SSRIs or SNRIs, but studies currently are under way. Duloxetine also is FDA-approved to treat diabetic peripheral neuropathies. The occurrence of adverse effects appears to be rather low in patients treated with duloxetine. There is a risk of increased blood pressure, but it does not increase the blood pressure as much as venlafaxine. The risk of sexual side effects and weight gain also do not appear to occur as frequently as with other agents used to treat depression. Greater clinical experience with the drug will better define its adverse effect profile. At the present time, the addition of duloxetine to the formulary would be beneficial to several patient populations.

Resources

• Clinical Pharmacology web site. Available at http://cp.gsm.com/. Assessed Oct. 10, 2004.

• Cymbalta web site. Available at www.cymbalta. com. Assessed Oct. 19, 2004.

• Detke MJ, Lu Y, Demitrack MA. Duloxetine, 60 mg, once daily, for major depressive disorder: A randomized double-blind placebo-controlled trial. *J Clin Psychiatry* 2002:63:308-315.

• Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: A double-blind clinical trial. *J Clin Psychiatry* 2002;63:225-231.

• Goldstein DJ, Lu Y, Iyengar S, et al. Duloxetine in the treatment of the pain associated with diabetic neuropathy. AAPM presentation from the Eli Lilly & Co. March 3, 2004.

• Raskin J, Goldstein DJ, Mallinckrodt CH, et al. Duloxetine in the long-term treatment of major depressive disorder. *J Clin Psychiatry* 2003;64:1,237-1,244.

• USPDI Updates On-line, Vol. 122. Thomson Micromedex web site. Available at www.micromedex.com. Assessed Oct. 18, 2004.

• Wyeth-Ayerst web site. Available at: www.wyethayerst.com. Assessed Oct. 25, 2004. ■

IN THE PIPELINE

• Kosan Biosciences has announced that the FDA has granted the company's anticancer compound 17-allylamino-17-demethoxy-geldanamycin (17-AAG), an analog of the polyketide geldanamycin, orphan drug status for the treatment of **multiple myeloma**.

• Schering-Plough is initiating two large international clinical trials to evaluate the use of peginterferon alfa-2b (PegIntron) and ribavirin (Rebetol) combination therapy in patients chronically infected with **hepatitis C virus genotype 1** who have specific unmet medical needs.

• Vion Pharmaceuticals has been granted orphan drug designation from the FDA for VNP40101M (Cloretazine) for the treatment of **acute myelogenous leukemia**.

• Kosan Biosciences has announced that the FDA has granted its anticancer compound 17-allylamino-17-demethoxy-geldanamycin, or 17-AAG, orphan drug status for the treatment of **chronic myelogenous leukemia**.

• Bayer Pharmaceuticals Corp. and Onyx Pharmaceuticals have announced that sorafenib (BAY 43-9006) has been granted orphan drug status by the FDA for the treatment of **renal cell carcinoma**.

• Peninsula Pharmaceuticals has announced that the FDA has granted fast-track designation for doripenem (S-4661) for the treatment of **nosocomial pneumonia**, including ventilator-associated pneumonia.

• Neurocrine Biosciences has initiated a Phase I clinical trial with its proprietary compound, urocortin 2, to evaluate the safety, pharmacokinetics,

and pharmacodynamics of urocortin 2 in healthy volunteers and also expects to initiate a Phase II clinical study in patients with **mild-to-moderate congestive heart failure** in early 2005.

• Hybridon has begun patient enrollment of a Phase II trial of HYB2055 (IMOxine) in renal cell carcinoma.

• Alexion Pharmaceuticals has initiated the treatment phase in the Phase III TRIUMPH trial, evaluating the investigational drug eculizumab in patients with **paroxysmal nocturnal hemoglobinuria**.

• Vertex Pharmaceuticals has initiated a Phase Ib clinical trial for VX-950, an investigational oral protease inhibitor for the treatment of **hepatitis C virus infection**.

• Pharmasset has initiated a Phase II clinical study to assess the safety, tolerability, and antiviral effect of substituting Racivir (RCV) for lamivudine, 3TC (Epivir) in treatment-experienced **HIV-infected individuals**.

• CuraGen Corp. has announced that the FDA has granted orphan drug designation to CR002, a fully human monoclonal antibody, as a potential treatment to slow the progression of **IgA nephropathy and delayed kidney failure** in patients affected by the disease.

• Vasogen has reached full enrollment in its 500-patient Phase III SIMPADICO trial of immune modulation therapy (Celacade) for the treatment of **peripheral arterial disease**.

• Lorus Therapeutics has initiated a clinical trial of its antisense drug, GTI-2040, in combination with docetaxel and prednisone in **hormone refractory prostate cancer**.

• YM BioSciences and its majority-owned subsidiary CIMYM have announced that the Office of Orphan Products Development of the FDA has granted orphan drug designation to their EGF receptor monoclonal antibody, TheraCIM hR3, for the **treatment of glioma**.

• Human Genome Sciences has begun dosing patients in a Phase II clinical trial of albumin-interferon alpha (Albuferon) in combination with ribavirin to evaluate the safety, tolerability, and efficacy of albumin-interferon alpha in patients with **chronic hepatitis C** who failed to respond to previous interferon alpha-based treatment regimens.

• BioMarin Pharmaceutical expects to initiate a six-week, multicenter, international, double-blind, placebo-controlled Phase III clinical trial of sapropterin hydrochloride (Phenoptin) in **phenylketonuria** in the first quarter of 2005. ■

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.

5. Duloxetine also has been approved to treat:
   A. diabetes.
   B. hypercholesterolemia.
   C. peripheral neuropathy.
   D. All of the above

6. At the present time, there have not been any studies evaluating duloxetine's efficacy compared to other agents used to treat major depressive disorder such as selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors.
   A. True
   B. False

7. Duloxetine appears to be an efficacious treatment for patients suffering from major depressive disorder, especially in patients suffering from painful physical symptoms.
   A. True
   B. False

8. Duloxetine use is associated with which of the following adverse effects?
   A. Increased blood pressure
   B. Sexual side effects
   C. Weight gain
   D. All of the above