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Drug therapy lab safety monitoring can be improved

New research has shown that a computerized tool in the hands of health care professionals who work together can effectively increase the number of patients who receive laboratory safety monitoring of drug therapy. What isn't yet known, according to lead researcher **Marsha Raebel**, PharmD, investigator and pharmacotherapy research and clinical trials manager for Kaiser Permanente Colorado, is whether the additional safety monitoring translates into improved patient outcomes.

"We found that you can make a difference in how much safety monitoring is done and that pharmacists can have an impact," she tells *Drug Formulary Review*. "We still need to determine if it affects outcomes."

Raebel says while there have been many calls for increased safety monitoring, there has been relatively little in scientific literature documenting that interventions improve the rate of monitoring.

The research report, published in the May issue of *Pharmacotherapy*, says suboptimal laboratory monitoring of drugs that pose a risk of organ system toxicity or electrolyte imbalance or of drugs that require dosage adjustment in patients with organ dysfunction is considered a medication error. Laboratory monitoring medication errors occur when indicated tests are not conducted, when an avoidable delay in responding to abnormal test results occurs, or when follow-up of laboratory results is inadequate.

The randomized trial examined whether a computerized model that alerts pharmacists to missing laboratory results increases the percentage of patients who receive guideline-recommended safety monitoring during ongoing drug therapy. The trial was conducted at Kaiser Permanente Colorado's outpatient medical offices with some 340,000 individuals randomly assigned to either the intervention group or control group (usual care) at the beginning of the study. Each month, new members were randomly assigned; by the end of the study, more than 400,000 individuals had been included.

To create the intervention tool, staff from the departments of pharmacy, research, primary care, laboratory, and clinical technology collaborated to

develop and implement computer programming to link drug and laboratory data. From the linked data, the researchers provided reports of drug dispensing coupled with drug-specific laboratory parameters that were missing (either a lab test had not been ordered or a patient did not comply with undergoing a test). Daily reports were electronically sent to the clinical pharmacy call center, where a centralized team of clinical pharmacists telephoned patients to address drug-related issues.

Two drugs dropped

Although 14 drugs were initially selected for the study, two (ticlopidine and felbamate) subsequently were dropped due to a low number of prescriptions. Raebel tells *DFR* the researchers looked at many sources for published monitoring guidelines and compiled from them a list of drugs for which monitoring was recommended. They cut that list to those they had the capability to monitor and then asked clinicians to determine which of those drugs would be most important to monitor. "It was important that the final list was agreed to by everyone," she said, "specifically relating to safety monitoring and not to efficacy."

Selection criteria applied in the process included FDA black box warnings, published clinical guidelines, perceived potential for adverse consequences related to a lack of monitoring, and current intervention services for the drugs (such as warfarin already being monitored by the clinical pharmacy anticoagulation services).

The final list of study drugs included amiodarone, atorvastatin, carbamazepine, divalproex, gemfibrozil, lithium, lovastatin, metformin, phenytoin, pioglitazone, simvastatin, and theophylline.

A guideline was developed to help call center pharmacists manage abnormal lab results. Primary care administrators, key physician clinicians, pharmacists and pharmacy administrators, and health plan researchers reviewed and approved the guideline. When lab results were abnormal, the call center pharmacists used standardized scripts and wrote notes in the electronic medical record that were forwarded to the patients' providers. If urgent actions were needed, the pharmacists telephoned the providers directly.

During the study, some 9,139 patients received ongoing therapy with at least one of the study drugs. Of this group, 470 patients were prescribed two study drugs and 21 were prescribed three, resulting in 9,651 individual patient-drug combinations. The researchers said they found no significant difference between the 4,515 patients in the intervention group and the 4,624 patients in the control group.

Significantly improved monitoring

Drug therapies were monitored in the recommended time frame in 64% of patient-drug combinations in the intervention group, compared with 58% in the control group. Improvements in intervention group monitoring were statistically significant for amiodarone, theophylline, carbamazepine, lithium, phenytoin, and metformin.

Call center pharmacists ordered 1,981 lab tests for study drugs and patients completed 1,472 of the tests, although not all were completed in the recommended time frame. The most common pharmacist intervention was ordering a serum creatinine level for 558 patients taking metformin. Other interventions included ordering

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liver enzyme tests, complete blood counts, or serum drug concentrations in 364 patients taking carbamazepine; liver enzyme tests or serum drug concentrations in 326 patients taking phenytoin; serum creatinine concentrations, complete blood counts, and/or serum drug concentrations in 267 patients taking lithium; and serum drug concentrations in 250 patients taking theophylline.

Of the 1,472 tests the pharmacists tracked that were eventually completed, 307 (21%) yielded abnormal results, including 181 serum drug concentrations outside the therapeutic range and 126 instances of abnormal serum creatinine, alanine aminotransferase, aspartate aminotransferase, thyroid-stimulating hormone levels, and complete blood counts.

Raebel says the computerized alert system used by clinical pharmacists collaborating with physicians effectively increased the percentage of patients who received recommended laboratory monitoring during long-term therapy with drugs that can cause organ system toxicity or electrolyte imbalances or with drugs that require dosage adjustment when patients have organ dysfunction.

According to the study, among the drugs associated with the greatest differences in monitoring between the intervention and control groups were lithium and carbamazepine. "These were the only study drugs for which three laboratory monitoring tests were recommended," the report said. "Increasing numbers of recommended tests may increase the opportunities for monitoring errors. Even with knowledge of drug toxicity, busy prescribers can easily forget to order all of the recommended laboratory tests when prescribing drugs with several toxicity risks and many recommended monitoring tests. Monitoring may have improved in the intervention group at least partly because the computerized alert served as a reminder by highlighting missing test results for the call center pharmacists."

No difference for some drugs

In contrast, Raebel said, monitoring did not differ between intervention and usual-care patients receiving pioglitazone and those receiving the combination of a statin plus gemfibrozil, drugs for which only one lab test is recommended. Monitoring rates in both groups were relatively high and Raebel speculated the reasons for the lack of difference may differ from the reasons for the drugs with three recommended laboratory monitoring tests. "Physicians might be more knowledgeable about recommended monitoring for these two drugs than for others, or the finding could have been a ceiling effect given that the monitoring rates were relatively high in each group," she said.

For patients prescribed divalproex, monitoring did not differ between intervention and usual care. Raebel said that although the study design did not enable the researchers to evaluate reasons for the intervention's ineffectiveness in these patients, possible reasons include differences in patient characteristics between groups, such as seizure vs. mental health diagnosis or high vs. low drug doses, and differences in provider characteristics, such as their clinical judgment about importance of lab monitoring for divalproex.

"Our findings exemplify the utility of merging pharmacy and laboratory data and of providing that information to clinical pharmacists who focus on improving the quality and safety of care for ambulatory patients," Raebel wrote. "A barrier to the involvement of pharmacists in this type of initiative is that they cannot easily access patients' clinical data in many ambulatory settings. Our system overcomes this barrier because it can be implemented in essentially any health care setting where pharmacy dispensing information and laboratory claims data are available and can be linked."

Raebel points out that published recommendations often don't give specific monitoring frequencies, only saying monitoring tests should be performed "periodically" or "as appropriate." The researchers asked clinicians for guidance on intervals a prudent physician would follow. She said they were looking for the lowest test frequency a wise clinician would follow. The resulting study guidelines call for testing every six months or one year, depending on the drug.

She tells us there are two main messages people should take from the research: 1) many facilities have the ability to link laboratory and pharmacy data and doing so can help identify gaps in laboratory monitoring; and 2) by encouraging collaboration, it is possible to increase what experts have said is appropriate safety monitoring.

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Hospitals need better ADR reporting systems

The first study to evaluate adverse drug reactions (ADRs) in a large population of hospitalized

Medicare patients has found that only 53% of hospitals representing 67% of the patients studied appeared to have functional systems for reporting ADRs. Lead researcher **C.A. Bond**, PharmD, of the Texas Tech University Health Sciences Center department of pharmacy practice, says that finding suggests that Medicare and perhaps the Joint Commission on Accreditation of Healthcare Organizations may need to consider strengthening requirements for reimbursement and accreditation to mandate such reporting systems. The study was published in the May issue of *Pharmacotherapy*.

"Expanding the E-code system to include specific drugs recently approved by FDA would not be difficult," Bond wrote. "Strengthening reporting systems and expanding the E-code system this way could create a robust post-marketing surveillance system for newly approved drugs. This also would help satisfy the demands of professional organizations and the public to improve the safety of the drug therapy system in the United States. In addition, expanding (or enforcing) Medicare ADR reporting with an expanded E-code system could correct problems that have been identified with FDA's MedWatch programs and adverse event reporting system. Data not only could be collected faster, but also could be compared with other drug classes or individual drugs much faster. This database also would be larger than FDA's current ADR database."

Bond tells *Drug Formulary Review* no one really knows how much of a problem there is in reporting ADRs because of the lack of an accurate reporting system. "We rely largely on voluntary reporting rather than a systematic effort," he says. "Addressing this problem would require a major initiative. The Joint Commission would have to require reporting and the federal government would have to create a repository for the information."

Bond said that while improved hospital systems have resulted in fewer medication errors over the last 10 years, little attention has been directed to the safety of individual drugs and devices. But with the recall of Celebrex and Vioxx due to the increased risk of associated cardiovascular events, health care professionals and the general public have begun to focus on drug adverse effects.

ADRs are a leading cause of death

This study reviewed literature from 1964 to 1996 and found that overall incidence of ADRs in hospitalized patients was 6.7% (range, 1.2-24.1%) and of fatal ADRs 0.32% (range, 0.1-0.85%). "These aggregate figures translate to 2,216,000 hospitalized patients per year who experience a serious ADR and 106,000 a year who die from an ADR," he said. "Fatal ADRs rank fourth to sixth in leading causes of death. As sobering as these figures appear, ADRs also are one of the more frequent causes of hospitalization (3.7-6.5% of patients). Cost estimates for these ADRs are $1.56-$4 billion a year, and as many as half of them may be preventable."

The most common drug classes associated with ADRs in this study were cardiotonic glycosides, adrenal corticosteroids, antineoplastic agents, anticoagulants, and analgesics. And the most common associated diagnoses were hypertension, congestive heart failure, atrial fibrillation, volume depletion disorders, and atherosclerotic heart disease.

Relative to frequency of reported ADRs, risk of death was higher when an ADR was associated with cardiotonic glycosides, antineoplastic and immunosuppressive drugs, and anticogulants. The ADRs were most frequently associated with essential hypertension (27.6%), congestive heart failure (19.54%), volume depletion disorders (14.7%), and atherosclerotic heart disease (12.21%).

Relative to frequency of diagnosis, ADRs were more commonly reported in patients with cardiac dysrhythmias, volume depletion disorders, hypopotassemia, hyposmolarity and/or hyponatremia, and atrial fibrillation. Relative to the mean death rate in patients who experienced an ADR, those more likely to die if they experienced an ADR were those diagnosed with atrial fibrillation, volume depletion disorders, or congestive heart failure.

Bond tells *DFR* he was surprised at the number of cases involving volume depletion disorders, saying he did not expect those diagnoses to contribute as many cases as they did. Three of the four top diagnoses associated with risk of ADRs were volume depletion or electrolyte disorders. Bond said these disorders may be overlooked as potential risk factors for ADRs. On the other side, Bond said he was surprised that antidiabetic agents were not higher on the list of those associated with ADR risk.

While the rate of ADRs found in this study (1.73%) was lower than the average of 6.7% found in previous studies, Bond said extrapolation of the data still resulted in 212,128 Medicare patients experiencing an ADR, and projected that nearly 600,000 of all 34.3 million U.S. hospital patients experience an ADR.

Data likely underreport frequency

"These data reflect real-world reporting systems, which most likely report only serious ADRs

that can clearly be identified and linked to specific drugs," he said. "Previous studies of ADRs and adverse drug events (ADEs) specifically looked for ADRs or ADEs as part of the study protocols and thus were more likely to reveal ADRs and ADEs. The 1.73% rate of ADRs found in our study was similar to the 1.5% observed in a recent study involving 4.3 million patients with ADEs who visited doctors' offices, hospital outpatient clinics, and emergency facilities."

The study found that experiencing an ADR while hospitalized substantially increased the risk of death. Bond said the finding reflected some 20% increase in mortality associated with an ADR in hospitalized patients. Extrapolating that finding to all patients suggested that 2,976 Medicare patients a year and 8,336 total patients a year die in U.S. hospitals as a result of ADRs, or about 1.5 patients per hospital per year.

"Logically," Bond said, "it would appear that elderly Medicare patients are less likely than younger patients to survive an ADR. Considering that up to 50% of ADRs may be preventable, this finding is significant."

In addition to the increased risk of death associated with an ADR, the increase in costs is significant. Average hospital length of stay increased by 8.25% (0.55 day) or an additional 77,769 days for all study patients with an ADR. Extrapolating that finding to the entire population of Medicare patients resulted in 118,200 additional hospital days associated with ADRs.

Increased costs are significant

Bond said in his study, the total cost for patients with an ADR increased an average of $2,401 per patient (19.86% increase), or an additional $339,496,598 for all study patients. Extrapolating that finding to the entire Medicare population resulted in $516,034,829 in costs associated with ADRs.

Drug costs for patients with an ADR increased an average of $175 per patient (9.15% increase) or an additional $24,744,650 for all study patients. For the entire Medicare population, additional drug costs associated with ADRs would be $37,611,868. Laboratory costs increased an average of $44 per patient (2.82% increase) and extrapolate to $9,456,698 in additional laboratory costs for all Medicare patients associated with ADRs.

Fatal adverse drug events that resulted in legal judgments or settlements cost an additional $1.1 million per death. And adverse drug events that caused permanent disability and resulted in legal judgments or settlements cost an additional $4.3 million per patient. Also, 13% of patients who experienced an adverse drug event that led to litigation received average settlements and judgments of $3.1 million per patient.

"Given the nature of hospital reporting systems," Bond said, "these data probably reflect fairly serious ADRs that are easily identified and traced to a specific drug. As such, the data probably underreport the true incidence of ADRs in U.S. hospitals."

Bond tells *Drug Formulary Review* he hopes the research gives hospital pharmacists and clinicians a road map to look at high-risk patients and adjust risk profiles regarding ADR management.

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Pharmacists must involve patients to reduce ADEs

A study by the Institute of Medicine (IOM) says pharmacists and other health care professionals must allow and encourage patients to take a more active role in their own medical care if the number of adverse drug events (ADE) is to be reduced.

One of the most effective ways to reduce medication errors, the report says, is to move toward a model of health care where there is more of a partnership between patients and health care providers. Patients should understand more about their medications and take more responsibility for monitoring those medications, while providers should take steps to educate, consult with, and listen to patients, the IOM said.

Such a paradigm shift is needed because medication errors are "surprisingly common and costly to the nation," according to the report. It said that in hospitals, errors are common during every step of the medication process — procuring the drug, prescribing it, dispensing it, administering it, and monitoring its impact — but they occur most frequently during the prescribing and administering stages. "When all types of errors are taken into account," the IOM said, "a hospital patient can expect on average to be subjected to more than one medication error each day. However, substantial variations in error rates are found across facilities."

The report said there are few estimates of how often preventable ADEs occur, but it estimated at

least 1.5 million such preventable ADEs in the United States each year, and the true number is likely much higher. There also are few estimates of the cost of preventable ADEs. One study found that each hospital preventable ADE added about $8,750 to the cost of the hospital stay. Assuming a conservative 400,000 events a year, the total annual cost would be $3.5 billion in this one group. Another study looked at preventable ADEs in Medicare enrollees aged 65 and older, and found an annual cost of $887 million for treating medication errors in this group. "Unfortunately, these studies cover only some of the medication errors that occur each year in this country, and they look at only some of their costs — they do not take into account lost earnings, for example, or any compensation for pain and suffering," IOM said.

Three steps to prevent ADEs

The report suggested three steps for preventing medication errors. The first step is to allow patients to take a greater role in their own care. To make such a change work, according to the IOM, pharmacists, doctors, nurses, and other providers must communicate more with patients at every step of the way and make that communication a two-way street, listening to patients as well as talking to them. Professionals should inform patients about the risks, contraindications, and possible side effects of the medications they are taking and what to do if they experience a side effect. And they should be more forthcoming when medication errors do occur and explain the consequences.

For their part, patients and those helping or representing them should take a more active role in the process. They should be keeping careful records of all medications they are taking and take responsibility for monitoring the medications, including double-checking prescriptions from pharmacies and reporting any unexpected changes in how they feel after starting a new medication.

From a broader perspective, the health care system should be doing a better job of educating patients and providing ways for patients to educate themselves. The IOM said patients should be given opportunities to consult about medications at various stages in their care such as during consultations with providers who prescribe their medications, at discharge from the hospital, at the pharmacy, etc. And there should be a concerted effort to improve the quality and accessibility of medication information provided to consumers.

The second step in reducing medication errors is to make greater use of information technologies in prescribing and dispensing medications. The IOM said prescribers should be using point-of-care reference information accessed over the Internet or through a personal digital assistant to get detailed information about the drugs they prescribe and get help in deciding which drugs to prescribe.

Even more promising, the report said, is the use of electronic prescriptions that can avoid many of the mistakes that accompany handwritten prescriptions. Also, e-prescriptions can be linked to a patient's medical history so that prescribers can check for things such as drug allergies, drug-drug interactions, and overly high doses. And once an e-prescription is in the system, it will follow the patient from the hospital to the doctor's office or from the nursing home to the pharmacy, avoiding many common hands-on errors.

The IOM's third recommendation is to ensure that drug information is communicated clearly and effectively to providers and patients. Noting that some errors occur simply because two different drugs have names that look or sound very similar, it recommended that the drug industry and federal agencies work together to improve drug nomenclature, including not just drug names but abbreviations and acronyms. And the information sheets that accompany drugs should be redesigned, taking into account research that identifies the best methods for communicating information about medications.

ASHP supports IOM recommendations

The American Society of Health-System Pharmacists (ASHP) said it supports the report's recommendations because they "help draw attention to this important patient safety issue." ASHP executive vice president and CEO **Henri Manasse Jr.**, PhD, ScD, said safe medication use starts with team-based care, more effective use of information technology, better patient and practitioner education, engagement of practitioners and patients at all levels, and continuity of care among all health care settings. He said IOM's recommendations aligned closely with ASHP's pharmacy policy and advocacy efforts and said ASHP had already established policy, initiatives, and advocacy efforts for all the IOM recommendations.

(Editor's note: More information is available on-line at www.iom.edu/CMS/3809/22526/35939.aspx.) ■

NEWS BRIEFS

Hospital uses bar code system to reduce errors

In 2005, Lawrence (KS) Memorial Hospital had a medication error rate that was less than one mistake out of every 10,000 dosages, good but not good enough, according to hospital director of pharmacy and IV therapy **Pat Parker**.

To cut the rate even further, Lawrence Memorial has installed a state-of-the-art bar code system to ensure the right patient gets the right dosage of the right medication at the right time. While some 10% of the nation's hospitals have started using bar codes to track patients and their drugs, Parker told the *Lawrence Journal-World* the hospital's system is one of only a few that gives nurses and doctors access to real-time information on when medications are given.

Here's how the system works:

- When patients are admitted, their medical information is entered into a computer system that generates a bar code, which is added to the patient's wristband.
- Every medication that is dispensed at the hospital is bar-coded.
- Before a patient is given a pill, shot, or IV, the bar-codes are scanned with hand-held scanners. The patient's wristband also is scanned. If there's an error, the system notifies the nurse before the medication reaches the patient.
- The system also alerts the hospital pharmacy when a patient's doctors prescribe conflicting medications.
- As soon as a medication is administered, the information is readily accessible to the patient's doctor and to the hospital's medical and pharmacy staffs.

Parker said that while many hospitals use bar codes, their efforts often are hampered by scanners not working on curved surfaces. And not all drug companies bar code their products.

At Lawrence Memorial, the pharmacy staff puts a flat surface bar code on hundreds of medications before they reach patients. Each is triple-checked before it leaves the pharmacy. To get around the curved surface problem, the hospital uses a bar code that fits in a 1/8-inch square.

"The system makes it very hard to make a medications error," hospital vice president of nursing **Dana Hale** told the newspaper. "If I try to give the patient in Bed 1's pill to the patient in Bed 2, the system tells me not to."

Plans call for adding patient vital signs including temperature, pulse, respiration rate, and blood pressure to the system by year's end. ▼

Hospital med dispensing system pays for itself

O'Bleness Memorial Hospital, Athens, OH, says its OmniRx medication dispensing system from Omnicell Inc., improved emergency department (ED) per patient charge capture in the first year of operation to more than pay for the installation and improved the hospital's bottom line.

The system automates the management and dispensing of medications at the point of use, reportedly increasing patient safety, improving workflow efficiency, and enhancing security. Omnicell says key features include biometric ID, advanced single-dose dispensing, bar code confirmation, the widest range of drawer modules enabling all security levels, integration with a web browser for clinical reference information, and patient medication profiling.

"The results were impressive," hospital pharmacy director **Eric Richards** said. 'They were much better than I thought they'd be." He said his evaluation showed a one-year increase in per patient charge capture of a bit more than 65%, and a department revenue increase that more than paid for the system.

The hospital has added additional Omnicell units in the medical-surgical unit, same-day surgery, and heart catheterization lab because of the performance of the ED system. ■

COMING IN FUTURE MONTHS

- Clinical pharmacists add value to inpatient care
- Labor and delivery drug therapy
- Chapter 797 survey results
- Development and clinical outcomes of pharmacist-managed diabetes care clinics
- Recent advances in neonatal pharmacotherapy

New FDA Approvals

The FDA recently approved these drugs:

• Atripla tablets, a fixed-dose combination of three widely used antiretroviral drugs in a single tablet taken once daily, alone or in combination with other antiretroviral products for treating **HIV-1 infection** in adults, was approved by FDA. Atripla combines the active ingredients in Sustiva (efavirenz), Emtriva (emtricitabine), and Viread (tenofovir disoproxil fumarate). It will be produced by a joint venture of Bristol-Myers Squibb and Gilead Sciences.

FDA said it approved the efavirenz/emtricitabine/tenofovir combination in three months under its fast-track program. The labeling includes a boxed warning that it can cause lactic acidosis. In patients with chronic hepatitis B infection, discontinuing this treatment (which is not approved for this use) can result in severe flare-ups of hepatitis B infection. Other potential serious adverse events include serious liver toxicity, renal impairment, and severe depression. The most common adverse events experienced by participants in the clinical trial for the combination drug included headache, dizziness, abdominal pain, nausea, vomiting, and rash.

• The approved use of Enzon Pharmaceuticals' Oncaspar (pegaspargase) has been expanded to include treating children and adults with newly-diagnosed **acute lymphoblastic leukemia** (ALL) as part of a multiple chemotherapy regimen. FDA initially approved pegaspargase in 1994 only for ALL patients who were allergic to the cancer drug Elspar (L-asparaginase). Agency officials said pegaspargase is one of the first FDA-approved products to come with prescription information in a new format intended to provide clear and concise information to health professionals.

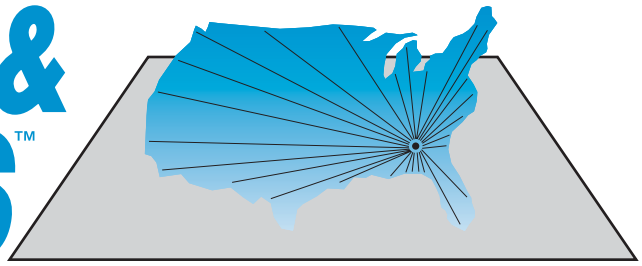
The approval was based on a randomized multicenter trial conducted by the Children's Cancer Group in 118 pediatric patients. Researchers said the trial demonstrated that pegaspargase could be safely and effectively substituted for L-asparaginase as part of a multidrug cancer regimen. Using pegaspargase instead of L-asparaginase reduces the number of drug injections required from 21 injections of L-asparaginase, which has been the standard of care, to three injections of pegaspargase over the 20-week course of treatment.

• Shire Human Genetic Therapies' Elaprase (idursulfase) has been approved as the first product to treat **Hunter syndrome** (mucopolysaccharidosis II, or MPS II), a rare inherited disease that can lead to premature death. FDA officials said idursulfase is a new molecular entity never before marketed in the United States. FDA designated the drug as an orphan product, giving it a seven-year period of exclusive marketing. It was approved after a randomized, double-blind, placebo-controlled study of 96 patients with Hunter syndrome showed that the treated participants had an improved capacity to walk. At the end of a 53-week trial, patients who received idursulfase infusions experienced on average a 38-yard greater increase in the distance walked in six minutes compared to patients on placebo.

The most serious adverse events reported during the trial were hypersensitivity reactions to Elaprase that could be life-threatening. They included respiratory distress, drop in blood pressure, and seizure. Other frequent but less serious adverse events included fever, headache, and joint pain.

FDA said because of the potential for severe hypersensitivity reactions, appropriate medical support should be readily available when idursulfase is administered. And patients and their doctors are encouraged to participate in a voluntary Hunter Outcome Survey that was established to monitor and evaluate the safety and effects of long-term treatment with idursulfase. ■

DRUG CRITERIA & OUTCOMES™



'Montezuma's revenge' to refractory pouchitis? Survey says: Probiotics

By **Frank T. Mitchell**, PharmD Candidate
Auburn (AL) University Harrison School of Pharmacy

Probiotics are defined as "viable microorganisms that (when ingested) have a beneficial effect in the prevention and treatment of specific pathologic conditions."[1] Probiotics have been used for centuries to aid in healing or "normalizing" the human body's gastrointestinal (GI) tract. It wasn't until the turn of the century that the "father of immunology," Elie Metchnikoff noticed that Bulgarian peasants consuming milk products that contained fermenting bacteria seemed to live longer, healthier lives.[2]

There have been many mechanisms proposed by which these bacteria exert their effect and each species or strain has its own niche in which it operates at its maximum benefit. They act by enzymatically degrading toxic materials in the GI tract, attaching or colonizing areas to prevent pathogenic species from obtaining a foothold, and producing environments in which they are better fitted to thrive instead of other species. Most of the bacteria found in the human gut convert lactose into lactic acid, which by itself isn't necessarily caustic to exogenous species. However, coupled with the shear numbers of normal microflora that are able to replicate in their specialized environment, pathogenic strains such as *E.coli* and *Clostridium* aren't able to achieve the numbers needed to cause clinically significant disease.

Beneficial species of bacteria, such as those found within probiotics, are ubiquitous in the food we eat. Yogurt, sauerkraut, alcoholic beverages of many types, kimchi, and some organic baby formulas all contain some form of healthy bacteria.

There also is a plethora or non-FDA-regulated supplements, pharmaceutical-grade supplements, and medical foods available that contain probiotic genera to varying degrees **(see Table, p. 2)**. Not all supplements have the same ratios, combinations, or even the same strains within them. Those deemed to contain *"Lactobacillus"* actually may include one or many of several thousand species under this particular family. Many of these products also have identical types of side effects that require monitoring. For example, increased stomach gas that usually dissipates with continued usage, chest pain, endocarditis, worsening CNS function in patients with hepatic encephalopathy, vomiting, diarrhea, burping, flatulence, phlegm production, and rash have all been reported with probiotics containing *Lactobacillus*.[3-6]

There also have been case reports of two infants receiving Culturelle® as a dietary supplement in the setting of short bowel syndrome that developed *Lactobacillus* septicemia. Upon removal of the probiotic and treatment with antibiotics the infections cleared.[7] Most products indicate safety in children 12 years of age and older with varying dosing regimens depending on the disease state or condition being treated.

To date, there is little scientific evidence that directly promotes any one species over another with regard to treating disease.

There are many small trials with limited data comparing a probiotic product to placebo, but no head-to-head trials comparing one product to another were found. Emerging data and ongoing trials are showing promising results in the conditions of diarrhea (both infectious and antibiotic-associated), HIV/AIDS-associated diarrhea, irritable bowel syndrome, ulcerative colitis,

Table

Common Species	Unique Properties	Products with this Bacteria
L. acidophilus	Produce H_2O_2 and lactic acid	Lactinex®, VSL#3®, Flora-Q™, Culturelle® (GG subspecies *only*)
L. bulgaricus	Produces lactic acid	Lactinex®, VSL#3®
L. paracasei	Complements *L. acidophilus* growth	Flora-Q™, VSL#3®
S. thermophilus	Grows in extremes of temperatures	Flora-Q™, VSL#3®
Saccharomyces boulardii (actually a yeast)	Matures to full colonies extremely fast	Florastor™
Bifidobacterium	Inhibit *E. coli* and *Candida albicans*	Flora-Q™, VSL#3®

Crohn's disease, enteral feeding diarrhea, small bowel bacterial overgrowth, pouchitis, *H. pylori* gastroenteritis, and lactose intolerance. Though the power of many of these trials is diminished by relatively small study populations, low consistency of the species being tested, and length of study, many arrive at the same positive outcomes under correlative study conditions.

Most of the current studies alone are weak; however, probiotic therapy warrants reconsideration due to new emerging studies and replicative positive results. Probiotics are a unique group of products because of their use in both treating disease and enhancing overall health in a variety of patient settings. Ultimately, probiotics may have a significant place in therapy for an array of gastrointestinal conditions.

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HRT, calcium with vitamin D in postmenopausal women? An update on the Women's Health Initiative

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In 1991, the Women's Health Initiative (WHI) was established to address cardiovascular disease, cancer, and osteoporosis in postmenopausal women. It was a 15-year, multimillion-dollar project that included 161,808 women aged 50-79 years.

Over its 15-year course, recommendations for diet and medication therapies have been made from the data collected in the ongoing trials. Now, in 2006, more updates and conclusions have been made regarding medication therapy in various diseases concerning postmenopausal women.

A large component of this massive project was several randomized controlled clinical trials concerning hormone replacement therapy (HRT), dietary modifications, and calcium plus vitamin D supplementation. Investigators specifically assessed the risks and benefits of these interventions and their ability to delay mortality and improve morbidity.

Stroke

The estrogen plus progestin therapy, which was one of the HRT trials, was stopped in 2002 after approximately five years of treatment because the results were showing an increased risk of stroke and breast cancer with therapy.

At that time, it was unknown whether the estrogen-alone trial would have similar effects. However, in 2004, results were emerging that demonstrated an increased risk of stroke with estrogen-only therapy as well. This trial, therefore, was discontinued after an average of seven years

of follow-up and approximately one year earlier than the planned stop date. This trial included 10,739 women ages 50-79 years that had undergone a hysterectomy. They were randomized to receive 0.625 mg of daily conjugated equine estrogen (CEE) (n = 5,310) or placebo (n = 5,429). From this trial, stroke, venous thrombosis, breast cancer, and coronary heart disease risks were assessed.

During the trial, there were 168 strokes in the CEE group vs. 127 in the placebo group. The majority of strokes, 84.5% in the CEE group and 74.8% in the placebo group, were ischemic; however, there was no significant difference in ischemic stroke based on age, race, ethnicity, years postmenopause or bilateral oophorectomy, prior history of CVD or hormone use, body mass index, hypertension, diabetes mellitus, smoking, Framingham risk score, vasomotor symptoms, or concurrent statin or aspirin use.

Although these results strengthened previous findings implicating estrogen, not progestin, as the more likely cause of stroke, the overall effects of estrogen alone or estrogen plus progestin are similar in that both increase the incidence of ischemic stroke in postmenopausal women.

Venous Thrombosis

Because estrogen-only HRT showed an increase in ischemic stroke, it is not surprising that the results in the venous thrombosis (VT) trial also showed that estrogen only-therapy increased the risk of VT. During this seven-year trial, VT occurred in 111 (2%) women who were assigned to receive CEE, and in 86 (1.6%) women who were taking placebo. Of the VTs that occurred, 85 (75%) in the CEE group were deep vein thrombosis (DVT) compared to 59 (67%) in the placebo group, and 27 (24%) and 28 (33%) events in the CEE and placebo group, respectively, were thought to be procedure-related. Therefore, estrogen-alone HRT showed an increase risk of VT, again suggesting that estrogen is the most likely cause, not the progestin.

Coronary Heart Disease

In February 2006, the effects of CEE on coronary heart disease were published in *Achieves of Internal Medicine*. It showed that estrogen-only HRT neither increased nor decreased the risk of coronary heart disease in postmenopausal women. There were 201 (3.8%) coronary events, which were defined as non-fatal myocardial infarction or coronary death, compared to 217 (4%) reported among women taking placebo. The difference between these groups was not statistically significant. Also, one year into this seven-year study, women taking CEE had a greater increase from baseline in high-density lipoprotein (HDL) and triglyceride (TG), but decreased low-density lipoprotein (LDL) and total cholesterol compared to placebo.

The data from this seven-year study showed that CEE offers no more coronary protection than placebo.

Breast Cancer and Mammography

One outcome that differed from the estrogen plus progestin trial was released in April of 2006. This arm focused on the effects of estrogen-only HRT in breast cancer and mammography screening. The study showed that 104 (2%) women in the CEE group and 133 (2.5%) women in the placebo group were diagnosed with breast cancer and that 36% vs. 28%, respectively, had abnormal mammograms.

This difference was primarily in the assessment of abnormal findings during routine mammograms where a higher percentage in the CEE group required short interval follow-up. There was no statistical difference in suspicious abnormalities or ones that were suggestive of malignancy between the two groups. Therefore, after seven years of treatment, estrogen alone did not seem to increase a women's risk of breast cancer; however, it did increase the frequency of mammography screening due to the increase in short interval follow-up recommended after abnormal results.

Calcium and Vitamin D

Not only did the WHI assess the outcomes of HRT, but also the risks and benefits of calcium plus vitamin D supplementation in postmenopausal women. In a randomized, double-blind, placebo-controlled trial, patients received 500 mg of elemental calcium as calcium carbonate with 200 IU of vitamin D3 twice daily (n = 18,176) or placebo (n = 18,106). The results of this study were released in February 2006, after seven years.

One aspect of the trial compared whether calcium plus vitamin D could be used as primary prevention of colorectal cancer, as previous studies had indicated. The WHI found no statistically significant difference between the calcium plus vitamin D group and placebo. There were 168 (0.92%) cases of colorectal cancer reported in the prevention group vs. 154 (0.85%) reported in the placebo group and there was no difference in tumor characteristics, screenings, or symptoms. Daily supplementation with calcium plus vitamin D for seven years had no effect on the incidence of colorectal cancer among postmenopausal women.

Another outcome the WHI assessed was whether calcium with vitamin D prevented hip and other fractures in healthy postmenopausal women. Although the hip bone mineral density was slightly higher (1%) in patients taking calcium plus vitamin D, there was no statistical difference in fracture among either group. The results also showed that the calcium with vitamin D group had a higher incidence of kidney stones compared to placebo, 449 (2.5%) patients and 381 (2.1%) patients, respectively. This was the only significant difference found between the groups when assessing safety and tolerability.

Conclusion

It is estimated that 17% of all women will experience a hip fracture during their lifetime, which may lead to disability and a decreased quality of life. Heart disease, breast cancer, and colon cancer are the first-, second-, and third-leading causes of death, respectively, in postmenopausal women. More than 240,000 women die each year of heart attacks; this accounts for 22% of all deaths among U.S. women. The number of deaths from breast cancer and colon cancer are equally as astounding with more than 46,000 and 28,000, respectively. Currently, it still is recommended that physicians take careful consideration and assess the potential risks vs. benefits before prescribing estrogen-only HRT.

Although the results from this project did not show the outcomes that health care practitioners had hoped for, they did make the medical world more aware of postmenopausal symptoms and diseases and the need for better treatment.

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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.

9. It has been postulated that probiotics work in which of the following ways?

A. They act by enzymatically degrading toxic materials in the GI tract.
B. They act by attaching or colonizing areas to prevent pathogenic species from obtaining a foothold.
C. They act by producing environments in which they are better fitted to thrive instead of other species.
D. All of the above

10. Results from studies of estrogen-only HRT showed:

A. an increased risk of ischemic stroke.
B. an increased risk of venous thrombosis.
C. an increased frequency of mammography screening due to the increase in short interval follow-up recommended after abnormal results.
D. neither increased nor decreased the risk of coronary heart disease in postmenopausal women.
E. All of the above

11. Daily supplementation with calcium plus vitamin D for seven years had no statistically significant effect on the incidence of colorectal cancer among postmenopausal women.

A. True
B. False

12. Although the hip bone mineral density was slightly higher in patients taking calcium plus vitamin D, there was no statistical difference in fracture among either group.

A. True
B. False