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FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met November 15, 2005. 4 products were added in the *Formulary* and none were deleted. A restriction on the use of 1 drug was lifted.

◆ ADDED

Citalopram
(generic)

Dexrazoxane
(Zinecard® by Pfizer)*

Fomepizole
(Antizol® by Orphan Medical)

Fondaparinux
(Arixtra® by GlaxoSmithKline)**

**Restricted to chemotherapy prescribers*
***Restricted to Hematology approval*

◆ DELETED

None

◆ CRITERIA FOR USE CHANGED

Lepirudin (Refludan® by Berlex)***

****No longer requires Hematology approval*

Citalopram is a selective serotonin reuptake inhibitor (SSRI). It was evaluated for re-addition in the *Formulary* because it is now available as an inexpensive generic alternative to brand name SSRIs, including escitalopram (Lexapro®). In June 2003, citalopram was deleted from the *Formulary* and escitalopram was added. At that time, both products were deemed equivalent. Citalopram was 13% more expensive than escitalopram. Now that citalopram is available as a generic, escitalopram is 23 times more expensive!

There are 6 SSRIs on the market, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. All, except escitalopram and sertraline, are available as generics.

There are now strong financial incentives to try generic SSRIs to

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NEWS

Medicare Part D: The Devil We Don't Know

By now, almost everyone has heard about Medicare Part D, which is part of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Patients and their providers are bracing themselves for the largest expansion in coverage since the program's inception in 1965, which begins this month. A great deal of anxiety, especially among patients, has been created with this legislation.

Simply put, Medicare, the federal program that pays for healthcare for seniors over 65 and those permanently disabled, will now cover outpatient prescriptions. Prior to this, Medicare only covered outpatient injectable medications in certain settings, such as kidney dialysis and infusion centers, and prescription medications for very ill patients such as oral antineoplastics for cancer patients and immunosuppressants for transplant recipients.

When Medicare was created in the 1960s, almost all healthcare was provided in a hospital setting. Relatively few prescription drugs existed, and drugs were generally inexpensive. As more useful prescription medications were marketed, much of medical treatment migrated to outpatient settings. Medicare programmatically lagged behind. While the need for prescription coverage for Medicare recipients has been recognized for at least a decade, the costs of funding such a project always served as a deterrent to any useful updates. The Congressional Budget Office estimates that spending for Medicare will increase by $405 billion over the 2004-2013 period with this new legislation.

While providing prescription coverage is certainly an improvement, the way the Centers for Medicare and Medicaid Services (CMS) are implementing Part D is creative but confusing. Private insurance companies and pharmacy benefit managers (PBMs) offer plans using guidelines for rules and formularies mandated by CMS. Negotiating with pharmaceutical manufacturers is left to these private entities.

While the intent of this strategy was to promote competition, the myriad of plans, all with slightly differing rules, leaves many seniors confused and frustrated. For example, the average patient in Alachua County has nearly 50 programs to choose from. Physicians fear scores of pharmacy calls requesting formulary switches resulting from the large increase in privately insured patients. Many politicians and opponents of the legislation believe manufacturers escaped this enormous switch from private to public healthcare unscathed.

Further, not all Medicare patients receive the same plan within the same insurance company. Patients with low incomes (less than 150% of Federal Poverty Guidelines) qualify for special plans that provide comprehensive coverage with low co-pays, low or no fees or deductibles, and no coverage gaps. Most recipients, however, will have a base plan that includes a monthly fee, $250 deductible, 25% co-pay up to a total of $2250 of coverage, followed by a coverage gap where they pay full price until they have a true out-of-pocket of around $3600 annually. The program then moves into catastrophic coverage where Medicare pays all except 5% of any prescription. Patients clearly benefit from controlling their prescription costs and staying out of the coverage gap or "doughnut hole."

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treat patients. For example, the various Medicare Part D programs and other third-party payers encourage the use of generics when they are available.

Escitalopram is the S-isomer of citalopram. Equivalent doses of citalopram are in the 2:1 to 4:1 range (ie, 20 mg to 40 mg of citalopram equals 10 mg of escitalopram).

Dexrazoxane is a cardioprotective agent used to avoid anthracycline-induced cardiac toxicity. It has a labeled indication for prevention of cardiotoxicity in women with advanced breast cancer receiving doxorubicin. It was reviewed for formulary inclusion as part of a comprehensive review of oncology agents.

Randomized controlled trials and meta-analyses show that dexrazoxane significantly reduces the incidence of anthracycline-induced congestive heart failure and adverse cardiac events in women with advanced breast cancer and adults with soft tissue sarcoma or small-cell lung cancer. These findings are regardless of whether the drug is given before the first dose of anthracycline or the administration is delayed until the cumulative doxorubicin dose is 300 mg/m^2.

The antitumor efficacy of anthracyclines is not altered by dexrazoxane use, but it does not improve progression-free or overall patient survival. The cardioprotective efficacy of dexrazoxane in patients with childhood malignancies is supported by limited data.

Dexrazoxane is generally well tolerated and has an adverse effect profile similar to that of placebo in cancer patients undergoing anthracycline-based chemotherapy, with the exception of a higher incidence of severe leukopenia.

Dexrazoxane costs approximately $500 to $800 per dose. Pharmacoeconomic evaluations suggest that the cost per patient is low in the prevention of life-threatening cardiotoxicity.

Since dexrazoxane is the only cardioprotective agent with proven efficacy in cancer patients receiving anthracycline chemotherapy, it was added in the *Formulary*. Dexrazoxane use is restricted to credentialed chemotherapy prescribers.

Fomepizole is a synthetic parenteral alcohol dehydrogenase inhibitor. It is the first treatment approved in the United States with labeled indications for the treatment of ethylene glycol and methanol poisonings. It was reviewed as part of a comprehensive review of antidotes listed in the *Formulary.* An alternative treatment for ethylene glycol and methanol poisonings is an ethanol infusion and dialysis. Most authoritative references list fomepizole as the drug of choice.

Although ethylene glycol and methanol poisonings are rare, serious morbidity and mortality can occur. Ethylene glycol is a highly toxic component of antifreeze, brake fluids, and automotive coolants. Ethylene glycol is normally converted to the toxic metabolite methanol by alcohol dehydrogenase. Methanol is a highly toxic alcohol commonly found in automobile windshield washer solvent, gas line antifreeze, copy machine fluid, fuel for small stoves, paint strippers, and as an industrial solvent.

There are limited published data on the efficacy and safety of fomepizole. Most of the data are from uncontrolled trials. However, these data suggest outcomes are at least as good as with ethanol. There are no similar published data about the efficacy of ethanol for ethylene glycol or methanol poisoning. There is no direct comparison with ethanol infusion; however, based on the infrequent incidence of ethylene glycol and methanol poisonings, the chance that a randomized controlled trial will be done is unlikely.

Since fomepizole is used for ethylene glycol or methanol poisonings, it is difficult to associate adverse effects with fomepizole, instead of the ingested poison. In general, fomepizole is thought to have few adverse effects. The most common adverse effects listed in the official labeling are headache, nausea, dizziness, drowsiness, and bad/metallic taste. Undiluted injections of fomepizole have caused venous irritation and phlebosclerosis.

Fomepizole is expensive. It costs over $1100 per day for treatment. However, ethanol infusions can also be expensive and are associated with additional monitoring costs not needed with fomepizole. It is anticipated that the use of fomepizole will be extremely rare.

Fomepizole may help avoid hemodialysis in some patients or decrease ICU or hospital stay. There are also the theoretical benefits of avoiding renal failure and/or death. However, these advantages have not been proven in formal evaluations.

Fondaparinux is a synthetic anticoagulant used to prevent and treat thromboembolic disorders. It indirectly inhibits Factor Xa by selectively binding to antithrombin III.

Fondaparinux has labeled indications for the prevention of deep venous thrombosis/pulmonary embolism (DVT/PE) in orthopedic surgeries (hip and knee replacements and repair of hip fractures) and in abdominal surgery patients. It also has labeled indications for the treatment of DVT and PE.

There are limited published data about fondaparinux use in patients with a history of heparin-induced thrombocytopenia (HIT) for either prophylaxis or therapeutic anti-coagulation. There are also limited data about off-labeled use for acute coronary syndrome (ACS), as an anticoagulant for percutaneous coronary interventions (PCI), and DVT prophylaxis in general medicine patients.

The labeled prophylaxis dosage for fondaparinux is 2.5 mg subcutaneously daily. Higher dosages are used for therapeutic anticoagulation depending on the size of the patient (ie, 5-10 mg SC daily). Use is contraindicated in patients with severe renal dysfunction (creatinine clearance less than 30 mL/min) because fondaparinux is primarily eliminated renally. Fondaparinux is also contraindicated in patients less than 50 kg.

There are many published trials for fondaparinux, including several trials comparing fondaparinux to low molecular weight heparins (LMWHs). Although results for DVT prophylaxis shows that fondaparinux is slightly more effective than LMWHs for orthopedic surgery indications, its use has been slow to catch on because of the perception that the risk of bleeding is higher. The current ACCP guidelines recommend fondaparinux as an alternative to LMWHs and warfarin for DVT prophylaxis in orthopedic surgeries.

Current data do not show superiority for fondaparinux over UFH or LMWHs for general surgery or general medicine DVT prophylaxis. There are limited data about off-labeled indications. Although these data may support use in patients with HIT who require therapeutic anticoagulation (eg, ACS or PCI), the shorter duration of effect for argatroban and lepirudin makes these agents safer for therapeutic anticoagulation.

Bleeding is the major adverse effect for fondaparinux. Although fondaparinux is an alternative for patients with HIT, thrombocytopenia is reported and platelet counts must be monitored. Fondaparinux has the same black-boxed warning found on LMWHs for epidural or spinal anesthesia or spinal puncture.

Fondaparinux is considerably more expensive than UFH, but costs similar to LMWHs.

Fondaparinux is restricted to use in patients who have been approved by the Hematology Service. Anticipated use will be for prophylactic anticoagulation in patients with a documented or suspected history of HIT until a definitive diagnosis can be made.

Lepirudin is a direct thrombin inhibitor that has required Hematology's approval for use. This restriction was lifted by the P&T Committee.

Lepirudin has a labeled indication for anticoagulation in patients with HIT and associated thromboembolic disease in order to prevent further thromboembolic complications. It has also been used as an anticoagulant in other clinical situations (eg, cardiopulmonary bypass surgery) in patients with a history of HIT.

POLICIES AND PROCEDURES

Standardized insulin concentration facilitates dosage titrations

The P&T Committee passed a policy that established a single standardized insulin concentration for intravenous infusions. Only a 0.5 unit/mL insulin infusion will be available at Shands at UF. A single insulin concentration for intravenous infusions was selected to decrease the risk of medication errors.

The 0.5-unit/mL standard was selected in order to make titrating dosages more precise. More concentrated solutions (eg, 1 unit/mL) did not allow infusion pumps to be adjusted based on patients' measured blood glucose concentrations. In the past, some intensive care units were using a 1-unit/mL concentration for insulin infusions. This concentration will no longer be available. Orders written for any concentration other than 0.5 unit/mL will need to be changed.

Better serum glucose control has been associated with better outcomes for patients. More precise dosage titrations should result in better glucose control.

MEDICATION ERROR PREVENTION

Preventing medication errors in HIV patients

Even among HIV clinicians, the complexities of highly active antiretroviral therapy (HAART) can be challenging. Consequently, physicians who infrequently treat HIV-positive patients may be more prone to prescribing errors. In years past, hospitals contained wards designated for the treatment of patients with HIV/AIDS. Health professionals who cared for these patients on a daily basis were, therefore, familiar with their complex drug therapy. Currently, fewer patients with HIV/AIDS are being admitted to the hospital because their care is provided in the outpatient setting. With this transition, inpatient healthcare providers have a greater risk of being unfamiliar with the complexities of managing HIV/AIDS patients once they are admitted to the hospital.[1]

The primary goal in the management of HIV infection is maximal suppression of viral replication, thereby slowing or stopping the progression of disease and the subsequent destruction of the immune system. Assuring proper use of HAART is critical, which is difficult considering the increasingly complicated regimens. Making sure these regimens are correct and promoting proper adherence are the responsibilities of all healthcare providers. The risk of medication errors is increased in patients with HIV/AIDS, and knowledge deficit is recognized as an important cause. Studies consistently show that the majority of medication errors concerning antiretroviral therapy occur during prescribing and administering medications. The most common prescribing errors are due to inappropriate dosing, and the most frequently reported reasons for mistakes in all areas are due to lack of experience and understanding.[1]

Because of the enormous risk of resistance and virological failure in patients with HIV/AIDS, it is extremely important for every healthcare provider to take ownership of patient care. Physicians must pay close attention to detail when writing all orders for patients on HAART. Each order should include instructions for use.

Nursing staff also plays an important role. HAART regimens typically

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News, from page 1

Catastrophic coverage is perhaps the most compelling reason Medicare recipients should strongly consider wading through their many options and enrolling in an optional Part D plan. The best source of information regarding plan choices can be found on the Medicare web site www.medicare.gov. There is even a function that allows patients or their caretakers to enter their prescription drugs into a plan finder for the programs that best suit their medication profile (ie, Formulary Finder). Unfortunately, many seniors do not use computers and will need assistance in this process. Patients can call 1-800-MEDICARE (ie, 1-800-633-4227) for assistance. Providers are forbidden from recommending any particular plan to patients, according to the rules of the program. Experience so far in our outpatient areas suggest that accurate evaluation of any plan will be very difficult before Medicare Part D actually begins this month.

From the providers' perspective, an unsettling result of Part D implementation is the loss of some forms of dual eligibility. Previously, many state, local (eg, The Shands Charity Care Program), and manufacturer-sponsored programs served to cover prescription drugs for Medicare recipients. For the most part, these programs will no longer exist for Medicare patients.

Effective January 1, 2006, the Shands Charity Care program will no longer cover patients with Medicare Part D eligibility. Shands believes that patients will be best served long-term with participation in Part D. Allowing patients dual eligibility will discourage them from signing up for Part D. After May 15, 2006, there will be financial penalties for applying late. The hospital has already received letters from manufacturers that support the Charity Care Program stating they will no longer provide drugs for Medicare recipients. The loss of manufacturer support would necessitate significant changes to the *Charity Care Formulary,* thereby reducing the utility of the program for all eligible patients. While most patients will benefit from the new program, a few, particularly those with incomes not quite low enough to qualify for special coverage under Part D, may struggle. Time will tell whether safety net institutions, like Shands at UF, will need to provide supplemental support for these patients.

Prescribers can prepare for the formulary changes many of the Part D programs will mandate by organizing or streamlining their prescription refill processes. Most changes will be relatively simple switches among drugs in a particular class (eg, ACE inhibitors), prior authorizations for expensive medications, or requests for step therapy. Prescribing generics will circumvent most formulary issues for all the plans, as the CMS guidelines for the creation of these formularies encouraged generic medication use. Many newer and very useful generics, such as ace inhibitors, calcium channel blockers, diuretics, SSRIs, antibiotics, and antidiabetics are now available in their generic forms. A list of generic medications is available on the Shands intranet for prescriber use.

Like all other insurance plans, Medicare Part D will work best with participation in the program by both healthy and unhealthy individuals. Encouraging patient participation in the new Medicare Part D will help ensure success of the program. Patients who are healthy must be made aware of the health risks of aging and the benefits of catastrophic coverage afforded under Part D. The dutiful use of generic drugs will help both patients and the healthcare system, which will continue to be a target because of rising healthcare costs and today's political climate. Questions about Medicare Part D can be directed to HARBIJW@shands.ufl.edu, or upon request, a pharmacy representative can provide a Medicare Part D inservice for your division. Change begins in the examination room and at the pharmacy counter. All providers are encouraged to participate.

By Bill Harbilas, PharmD

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Medication error prevention, *from page 3*
consist of at least 3 medications, and treatment regimens require close adherence, which further complicates therapy. Prompt and proper administration of medications is essential due to the risk of resistance. Issues that must be considered include timing of administration, number of units per dose, and consideration of drug and food interactions (including tube feedings). Medication administration records (MARs) can aid in proper administration. These computer-generated medication lists provide the nursing staff with time of administration, specific instructions, and a consistent form to document when and if medications are given. MARs are generated by the Pharmacy Department, but they reconcile the medication records of Nursing and Pharmacy.

Another obstacle is the lack of continuity in reconciling home medication therapy when a patient is admitted to the hospital. It is often difficult to determine medications patients are taking on an outpatient basis. Obtaining a current list of home medications is important to continuity of care. Upon admission to the hospital, a list of medications should be obtained from the patient and verified by the patient's outpatient pharmacy or primary care physician. This list should remain in the patient's chart throughout the hospital stay and should be reconciled at discharge to ensure that the patient is discharged on appropriate regimens.

Providing appropriate care to patients on HAART is extremely important because of the risk and incidence of HIV infection. In the United States, approximately 900,000 people are currently infected with HIV and 40,000 new cases present each year. Over 400,000 deaths associated with AIDS were reported to the CDC as of 1998. In 90% of the cases, death is due to an opportunistic infection.[2]

The pathogenesis of HIV disease has been studied intensively over the past 20 years. This research led to the development of HAART and is intended to decrease morbidity and mortality. The first HAART medication was approved in 1987, and since that time, more than 20 antiretrovirals have proven to be effective in suppressing viral load, with proper use. Treatment with HAART and prophylaxis for opportunistic infections in patients with HIV/AIDS have decreased the death rate by 80% in North America and Europe.[3]

Complex treatment is necessary to suppress the replication of HIV. Approximately 10 billion copies of HIV can be generated in a single day in untreated persons, and because the HIV reverse transcriptase lacks "proofreading capacity," an average of 1 mutation occurs during each replication cycle.[4] Resistance to antiretroviral agents and, in particular, the increasing levels of transmitted resistant virus could offset the substantial gains won with potent antiretroviral therapy. Lapses in treatment and ineffective regimens contribute to the development of resistance.[5]

Even though HAART is challenging, it is possible for each healthcare provider to play a part in decreasing medication errors in the HIV/AIDS patient population. Educational materials are available both online and through the Pharmacy Department. Information on HIV and AIDS is available online at www.aidsinfo.nih.gov. In addition, a quick-reference pocket card is available to practitioners to guide antiretroviral therapy in both adult and pediatric patients. These pocket cards are available through the Shands Pharmacy Department. This pocket card and other HIV/AIDS related information can be also found online at www.faetc.org.

By Laura Smith, PharmD

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