Volume 18, Number 10

SHANDS at the University of Florida

November/December 2004

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met October 19, 2004. 2 drugs were added in the *Formulary* and 1 drug was deleted.

◆ ADDED

Adefovir
(Hepsera® by Gilead)

Salmeterol + Fluticasone
(Advair® by GlaxoSmithKline)

◆ DELETED

Rofecoxib (Vioxx® by Merck)

Adefovir is a nucleotide analogue used for the treatment of hepatitis B infections. It was evaluated for possible formulary addition because it is a high priority nonformulary drug.

Hepatitis B virus (HBV) infection is a major problem. If left untreated, it can lead to complications like chronic liver disease, cirrhosis, and hepatocellular carcinoma. Currently, there are 3 drugs with labeled indications for the treatment of HBV infections including interferon alpha, lamivudine, and adefovir. Recommendations from the American Association for the Study of Liver Diseases identify all 3 agents as plausible "first-line" agents. Before the addition of adefovir, only lamivudine was listed in the *Formulary*.

Adefovir has been shown to be effective in maintaining viral suppression in patients with chronic HBV infections. For hepatitis B e antigen (HBe Ag) negative and positive patients, adefovir provided histological improvements, improved necroinflammatory scores, and consistent reductions in viral loads when compared to placebo. Adefovir provided consistent reductions in viral activity and ALT

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NEWS

More head-to-head trials?

The P&T Committee uses an evidence-based approach to manage drug therapy at Shands at UF. Drugs are added and deleted from the *Formulary* and policies are established based on published evidence — as much as possible.

Decisions are easier to make when there is evidence to show that a drug is more effective or safer than alternatives. Unfortunately, often there is no evidence. This complicates the decision-making process.

The ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) trial reportedly cost nearly $80 million. However, it showed that the inexpensive diuretic was a viable option for many patients.

In the past, this void of information was filled by the promises of pharmacological features and benefits. These theoretical advantages stimulated some clinicians to favor a specific drug. Often these drugs were "me-too" products designed to have a specific pharmacological action, but for which there are no data to show that the product improved patient outcomes.

Now, with rising health care costs and pressure from the public, the government, and third-party payors, the demand for evidence that a product is superior is growing. More companies are undertaking comparative "head-to-head" trials with viable therapeutic alternatives. Some comparisons are designed to show equal efficacy (ie, noninferiority trial), which manufacturers then use to promote a convenience advantage (eg, less frequent dosing) or some theoretical safety advantage. Safety is often much more difficult to prove (or disprove) in a trial.

Head-to-head comparisons are still, however, rare. Drug companies have been reluctant to fund these trials because 2 of the 3 alternatives may hurt their product. If a product is found to be inferior, the marketing impact is obvious. If a product is found to be equal to a less expensive alternative, this too can have a negative marketing impact. Decisions are often made based on cost when therapies are equal. Only demonstrations of superiority are clear winners.

When head-to-head studies show inferiority or equivalency, these studies may never be published. This publication bias has been hotly debated in the lay media with the suppression of unfavorable results for antidepressants in children. This has led to the call for open access to all research results whether they are favorable to a sponsor or not. Recently, several major medical journals have announced that they will require the registering of clinical trials in order for the results to be eligible for publication. Unfortunately, an unintended consequence may be that this discourages drug companies from undertaking comparative trials.

Increasingly, there have been calls for federal funding of head-to-head comparisons. These large studies can be very expensive. For example, the ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) trial compared inexpen-

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for patients with lamivudine-resistant pathogens. Unfortunately, there are no direct comparisons of adefovir and lamivudine in patients. Questions left unanswered include durability of response, long-term safety, and resistance.

Adverse events were uncommon and are primarily gastrointestinal in nature. Nephrotoxicity is a concern for adefovir as it is with all nucleotide analogs. Monitoring for nephrotoxicity is necessary, especially when it is combined with other nephrotoxic agents.

Adefovir is expensive. It costs approximately $450 per month, which is roughly 3 times the cost of lamivudine. Since there are no data suggesting that adefovir is superior to lamivudine, it would be reasonable to reserve adefovir for patients who have lamivudine-resistant HBV infections.

Advair® is a combination product containing both salmeterol (Serevent®) and fluticasone propionate (Flovent®). Fluticasone propionate is a synthetic corticosteroid that has potent anti-inflammatory activity, and salmeterol is a long-acting selective $beta_2$-adrenergic agonist. Guidelines state that the preferred therapy for moderate persistent asthma is regular treatment with a long-acting inhaled $beta_2$-agonist plus low-to-medium doses of inhaled corticosteroids. Advair® combines these therapies making it easier for patients to receive both treatments.

Three trials compared Advair® to alternative therapies in asthmatic patients not controlled with inhaled corticosteroids. All of the trials showed significant improvements in forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), and supplemental albuterol use in patients receiving salmeterol + fluticasone combination therapy. The rates of adverse events were not significantly different from other asthma therapies (medium-dose fluticasone, triamcinolone, and low-dose fluticasone and montelukast). It is, however, important to note that high doses or overdoses of salmeterol can lead to clinically significant QT prolongation, which can produce ventricular arrhythmias.

In patients with chronic obstructive pulmonary disease (COPD) the combination of salmeterol + fluticasone produced significant improvements in FEV_1, PEF, and decreased supplemental albuterol use compared to salmeterol alone, fluticasone alone,and placebo. There are questions about whether these differences are clinically significant, however.

The adverse effects seen with the salmeterol + fluticasone combination product was similar to those seen with the individual products.

Rofecoxib was not listed in the *Formulary,* however, it was occasionally requested through the nonformulary request process. Since it was voluntarily removed from the market on September 30, 2004, it will now be nonformulary and not available. Celecoxib (Celebrex®) remains the COX-2 inhibitor listed in the *Formulary,* while valdecoxib (Bextra®) remains nonformulary and not available.

The manufacturer of rofecoxib, Merck, "voluntarily" withdrew it from the market based on increasing evidence that it was associated with an increased risk for cardiovascular events (ie, myocardial infarction and stroke).

The cardiovascular safety of rofecoxib was first questioned in 2000 based on the findings in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial in over 8000 patients. This study found a decreased risk for gastrointestinal adverse effects compared with naproxen, but an increased risk for cardiovascular events, including heart attacks and strokes. These results led to labeling changes that reflected the increased risk of heart attack and stroke found in the VIGOR trial.

Subsequently, an FDA researcher led a large observational study in 1.4 million patients with Kaiser Permanente of California taking NSAIDs (including COX-2s). This case-control study found a greater than 3 times higher exposure to COX-2s compared with traditional NSAIDs in patients with cardiovascular adverse events, which supported the findings of the VIGOR trial.

The final blow that led to the withdrawal of rofecoxib was the reporting of the results of a long-term (3 year), placebo-controlled trial of rofecoxib in 2600 patients for the treatment of familial adenomatous polyposis (FAP). This study, known as the APPROVe trial (Adenomatous Polyp Prevention on Vioxx), showed a roughly 2-fold higher incidence of cardiovascular events in the rofecoxib-treated patients, which was detectable after 18 months of treatment.

The withdrawal of rofecoxib casts doubt on the safety of the other COX-2 inhibitors on the market. However, the data from the Kaiser case-control study also looked at celecoxib and did not find an increased risk of cardiovascular effects associated with the use of celecoxib. This makes keeping celecoxib in the *Formulary* a reasonable option — at least for now.

The lack of data on valdecoxib and data showing an increased cardiovascular risks with valdecoxib's investigational parenteral prodrug, parecoxib, supports the position of keeping this agent nonformulary and not available.

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sive generic diuretics (chlorthalidone) with an angiotensin converting enzyme inhibitor (lisinopril), a calcium channel blocker (amlodipine), or an alpha-blocker (doxazosin). Although this study reportedly cost nearly $80 million, it showed that the inexpensive diuretic was a viable option for many patients. It also showed that doxazosin had a higher incidence of combined coronary vascular events, particularly heart failure, compared with chlorthalidone. If diuretics are used as first-line therapy, the government, which is the payor for many patients with hypertension (eg, Medicaid, the Veterans Administration, and soon Medicare), would easily recoup the cost of this expensive study.

Other similar studies are onging. The National Institute of Mental Health (NIMH) funded a study (Clinical Antipsychotic Trials of Intervention Effectiveness or CATIE) that will provide comparative information on the efficacy of the atypical antipsychotic agents (ie, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone). This study is no longer recruiting patients and the results are pending. Hopefully, this study will provide some evidence to help make decisions about the use of atypical antipsychotic drugs.

Head-to-head comparisons will help fill a knowledge void. They will help differentiate among "me-too" agents and could promote cost-effective therapy. However, not all head-to-head comparisons are helpful. These comparison must be a "fair fight."

For example, equipotent doses must be used. When esomeprazole (Nexium®) was developed to replace omeprazole (the old "purple pill"), some comparisons used much higher doses of esomeprazole (ie, esomeprazole 40 mg versus omeprazole 20 mg). Drug-company-funded comparison trials must be carefully examined to make sure the comparisons are fair.

Hopefully more government funded head-to-head trials will be forthcoming. With the government poised to pay for more pharmaceutical expenditures, there will be a strong incentive for more NIH funding of head-to-head trials.

Writing outpatient prescriptions

Tending to your patients is difficult even without the burden of unwanted pages and telephone calls about problem prescriptions. It has been estimated by the Institute for Safe Medication Practices (ISMP) that unclear or unreadable prescriptions lead to 150 million calls a year from pharmacists to physicians. The following information will help you make sure your outpatient prescriptions contain the proper information…and hopefully avoid some of those unwanted phone calls. These suggestions should also decrease the chances that your patients will have to wait while a problem is resolved or, in some cases, suffer the consequences of delays in starting vital treatments.

State and federal laws mandate that specific elements be included in all prescriptions. A prescription must have the patient's name, drug and strength, quantity, directions for use, number of refills (except for Schedule II controlled substances, which cannot be refilled), prescriber's name, prescriber's address, prescriber's telephone number, and prescriber's DEA number (for controlled substances). Often the number of refills is omitted. If no refills are intended, the prescriber should write "no refills." Calling prescribers for refills is a common issue for pharmacists.

The prescriber's name, address, telephone number, and DEA number are on all pre-printed prescription blanks provided to residents and fellows by Shands. Problems arise, however, when the pre-printed blanks are not used or when prescription pads are borrowed. New pre-printed prescription blanks are ordered through the Department of Pharmacy Services by faxing a Prescription Pad Order Form to 338-9849. Please allow at least 2 weeks for new blanks to be printed. A signed signature card must be on file for the prescription pads to be released.

Controlled substances, particularly Schedule II controlled substances (eg, morphine, methylphenidate), have additional requirements and tend to generate more phone calls. All controlled substance prescriptions require the patient's address in addition to all the other elements required for any prescription. Also, the prescription must be written and signed in ink or indelible pencil to prevent alteration.

A prescription for a Schedule II controlled substance cannot legally be written on the same prescription with another prescription for a controlled substance from a different schedule. Nonscheduled prescriptions also cannot be on the same prescription order with a controlled substance.

Another problem noted with controlled substance prescriptions is postdating. The date the Schedule II prescription is written *must* appear on the prescription. However, prescribers can add a "Do-not-fill-before date" on the face of the prescription. The prescription then cannot be filled before the "Do-not-fill-before" date. This facilitates prescriptions for chronic, stable medications.

Florida Law now requires that prescribers must write the quantity of all prescription drugs in numerals and words to prevent adulteration (ie, #10 [ten]). This can help prevent patients from changing the quantity of controlled substance prescribed.

There are additional steps you can take for all prescriptions that will help you avoid problems. Pharmacies, especially community pharmacies not affiliated with Shands, need to be able to obtain information about prescribers to successfully bill third-party payors and public assistance programs. This includes the DEA number, including the appropriate extension for housestaff members. Housestaff use the Shands DEA number plus their doctor number. Although a DEA number is technically needed only for controlled substances, its use for billing purposes makes it essentially a requirement for all prescriptions.

Another suggestion to avoid medication errors associated with outpatient prescriptions is to include the indication on the prescription. Although not a legal requirement, doing so can help avoid dispensing the wrong drug when drug names look similar (and there are legibility problems). It also helps pharmacists counsel patients.

Early refills are a problem for your patients and the pharmacists that fill their prescriptions. For controlled substances, this raises the questions of overuse or diversion. For regular prescriptions, it can be a problem for third-party payors. Payors may not authorize payment if the refill request is to soon. The patient may have to wait to get their medication or pay large out-of-pocket expenses. If the directions for use change, it is important to phone in a new prescription. For example, if a patient's requirement for a pain medication increases and you instruct your patient to take more than the labeled amount, call the pharmacy with a new prescription (or write a new prescription if it is a Schedule II controlled substance).

Finally, legible handwriting is critical. A legible signature and/or printed name of the prescriber is important, especially when pre-printed prescription blanks are not used. Patients may not remember the name of the prescriber, particularly a housestaff member, which can result in significant delays when a problem prescription needs to be clarified.

Legibility of prescriptions has become such a prominent issue that the Florida Legislature passed a law in 2003 requiring legible printing on typed prescriptions. The prescription must be "capable of being understood by the pharmacist filling the prescription." This requires that the "quantity of the drug be prescribed in both textual and numeric formats" and that "the month [be] written out in textural letters." Dates like "11/15/2004" are not acceptable. "November 15, 2004" must be written.

The number of outpatient prescriptions continues to rise. Workload demands for prescribers are also increasing. By including the proper information on written prescriptions, both prescribers and pharmacists will have more time to take care of their patients. Patients will also be safer.

Quotable Quotes

"…it is essential to determine whether the cardiovascular risk [with COX-2 inhibitors] is or is not a class effect. The burden of proof now rests with those who claim that this is a problem for rofecoxib [Vioxx®] alone and does not extend to other coxibs. We must remember that the absence of evidence is not the evidence of absence."

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Coxibs and cardiovascular disease. N Engl J Med 2004;351:1709-11.

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 18, No.10 Nov./Dec. 2004

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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Shands HealthCare's Publication Svcs.

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