PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medication Nonadherence is Common in Primary Care

In this issue: Medication nonadherence is common; statins for venous ulcers; price concerns over hepatitis C drug; new atrial fibrillation guideline; antibiotics and risk of arrhythmia and death; and FDA actions.

Medication nonadherence is common

Medication nonadherence is widespread among patients, according to a new study from Canada. In a cohort of nearly 16,000 patients in a primary care network, primary adherence (defined by not filling a prescription) was monitored between 2006 and 2009. Overall, 31.3% of more than 37,000 prescriptions were not filled within 9 months. The most expensive drugs were the least likely to be filled (odds ratio, 1.11; 95% confidence interval [CI], 1.07 to 1.17) as were topicals, gastrointestinal drugs, and autonomic drugs compared with anti-infectives. Older patients were more likely to fill their medications as were patients with no prescription copay. Patients who saw their primary care physician more frequently were also more likely to fill their prescription. The authors conclude that primary nonadherence is common (as much as one-third of prescriptions) and may be improved by lower drug costs and lower copayments as well as close follow-up (*Ann Intern Med* 2014;160:441-450). ■

Statins for venous ulcers

Statins may improve healing of venous leg ulcers, according to a recent study. In a small, double-blind, placebo-controlled trial of 66 patients with uninfected ulcers smaller than 10 cm, half were randomized to simvastatin 40 mg and the other half to placebo. Overall, 72% of ulcers in simvastatin-treated patients healed vs 32% healed in the control group. Smaller ulcers had a better response rate. The authors conclude that simvastatin 40 mg daily, in addition to standard wound care and compression, was associated with a significant improvement in healing rate and healing time compared to placebo in the management of venous ulcers (published online *Br J Dermatol*, doi: 10.1111/bjd.12883). The authors postulate that statins inhibit pro-inflammatory cytokines, which may help wound healing. The benefit was seen in patients regardless of cholesterol levels. ■

Price concerns over hepatitis C drug

Sofosbuvir (Sovaldi) has become the 800-pound gorilla in the hepatitis C wars. The drug has better cure rates than other drugs on the market and it allows for interferon-free regimens for some hepatitis C genotypes. But Gilead Sciences, which manufactures and markets sofosbuvir, has come under fire for pricing the drug at about $84,000 for a 12-week course ($1000/pill). According to *The New York Times*, Democratic members of the House Energy and Commerce Committee are demanding that Gilead justify the price. Patient advocacy groups and pharmacy benefit management companies are also critical of the pricing. With 3-4 million Americans infected with hepatitis C virus, the drug is destined to be a blockbuster. Most analysts feel the Republican-controlled House will not act on price controls, rather opting to let the market regulate prices. There are new

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drugs coming onto the market within a year that may provide some competition in pricing. ■

New atrial fibrillation guideline

The American Heart Association, American College of Cardiology, and Heart Rhythm Society in collaboration with the Society of Thoracic Surgery have published an updated atrial fibrillation (AF) guideline. The new guideline has several important changes, including: New oral anticoagulants join the treatment options — along with warfarin, new options include dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). At the same time, the role of aspirin is reduced in the new guideline. The guideline also recommends a more comprehensive scoring system for AF risk, with the CHA2DS2-VASc scoring algorithm replacing the older CHADS2 scoring system. The newer scoring system gives points for congestive heart failure, hypertension, diabetes, vascular disease, age 65-74 years, and female sex, with two points for age ≥ 75 and prior stroke/TIA/thromboembolism. Catheter ablation has a more prominent role in the new guideline, especially as primary therapy in very symptomatic individuals. The use of radiofrequency ablation has become more commonplace since the last guideline in 2006. The new guideline was published simultaneously online in the *Journal of the American College of Cardiology* and *Circulation* (doi: 10.1016/j.jacc.2014.03.021). ■

Antibiotics and risk of arrhythmia and death

Another study has demonstrated that the commonly used antibiotics azithromycin and levofloxacin raised the risk of arrhythmia and death when compared to amoxicillin. In a retrospective cohort study of 1.8 million U.S. veterans (mean age 56.8 years), antibiotic use was linked to death rate and serious arrhythmias. The average use of azithromycin was 5 days, while levofloxacin and amoxicillin were generally used for 10 days. Azithromycin was associated with a hazard ratio for death of 1.48 (95% CI, 1.05-2.09) and serious arrhythmia 1.77 (95% CI, 1.20-2.62) compared to amoxicillin users. The hazard ratios for levofloxacin were 2.49 for death (95% CI, 1.7-3.62) and 2.43 for serious arrhythmia (95% CI, 1.56-3.79). The higher rates of events dropped off quickly after the drugs were discontinued (*Ann Fam Med* 2014;12:121-127). The FDA issued a warning regarding azithromycin and fatal heart arrhythmias in May 2013. The risk for levofloxacin may be just as significant. ■

FDA actions

The FDA has approved apremilast for the treatment of psoriatic arthritis. The drug is a phosphodiesterase-4 inhibitor that is taken orally, the first non-steroid oral drug available for this indication. The drug was approved on the basis of three clinical trials of nearly 1500 patients with psoriatic arthritis which showed that the drug improved the signs and symptoms of psoriatic arthritis. Common side effects included weight loss, diarrhea, nausea, and headache. The drug was also associated with an increase in depression. Apremilast is marketed by Celgene Corporation as Otezla.

The FDA has approved apixaban (Eliquis) for prophylaxis of deep vein thrombosis in patients who have undergone knee or hip replacement. The drug is already approved for stroke prevention in patients with non-valvular atrial fibrillation. The new indication was based on results of the ADVANCE trial in which apixaban was compared to enoxaparin in 11,000 postoperative joint patients. Apixaban joins rivaroxaban as the second novel oral anticoagulant with this indication.

The FDA has approved an auto-injector formulation of naloxone for the treatment of suspected opioid overdoses. The product is designed for caregivers and family members and is small enough to be carried in a pocket or stored in a medicine cabinet. Once turned on, the auto-injector provides verbal instructions on how to deliver the drug, similar to defibrillators. The drug is formulated to be given intramuscularly or subcutaneously. Repeat doses may be needed since many opioids have a longer half life than naloxone. Medical care should be sought after administration. Naloxone auto-injector is manufactured by kaleo Inc. as Evzio.

FDA Commissioner Margaret A. Hamburg has issued a Statement on Prescription Opioid Abuse to address "misuse, abuse, addiction, and overdose of opioid analgesics" as well as assuring appropriate prescribing. Among a number of recommendations that include education, more research, and better labeling, the commissioner again suggests that hydrocodone-containing combination products move from Schedule III to the more restrictive Schedule II. This would require a handwritten, non-tamper proof prescription for some of the most widely used pain relievers including Vicodin and Norco. ■