Pharmacology Watch

Evidence-based updates in clinical pharmacology

By William T. Elliott, MD, FACP

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FDA Approves Drug to Prevent Delayed Phase Chemotherapy-induced Nausea

Liraglutide Effective for Weight Loss in Diabetics

Liraglutide helps patients with type 2 diabetes lose weight, according to a new study. In a 56-week, randomized, double-blind, placebo-controlled trial, 846 adults with type 2 diabetes who were overweight or obese were randomized to once-daily subcutaneous liraglutide 3 mg (n = 423), liraglutide 1.8 mg (n = 211), or placebo (n = 212). Patients were also on a calorie-restricted diet and counseled on engaging in more physical activity. Baseline weight was similar in all three groups. Weight loss was 6% with liraglutide (3 mg), 4.7% with liraglutide (1.8 mg), and 2% with placebo ($P < 0.001$ for both doses). Weight loss of 5% or more occurred in 54.3% of patients on the higher dose, 40% on the lower dose, and 21.4% on placebo. Weight loss of more than 10% occurred in 25% of patients on the higher dose, 18.5% on the lower dose, and 12.4% of placebo patients. Measures of weight-related quality of life significantly improved with the 3 mg dose of liraglutide, but not with the 1.8 mg dose. Gastrointestinal symptoms were more common with liraglutide compared to placebo, but no cases of pancreatitis were seen. The authors concluded that among overweight and obese participants with type 2 diabetes, use of subcutaneous liraglutide (3 mg) daily compared with placebo resulted in weight loss over 56 weeks (*JAMA* 2015;314:687-699). Liraglutide as Victoza (0.6 mg to 1.8 mg) is approved for treatment of type 2 diabetes, while liraglutide as Saxenda (0.6 mg to 3 mg) is approved for long-term treatment of obesity.

Chronic Sinusitis Recognized as Inflammatory Disease

Researchers from Canada have reviewed available data on the treatment of adult chronic sinusitis in a systematic review published in the *Journal of the American Medical Association*. Chronic sinusitis is defined by persistent symptomatic inflammation of the sinonasal cavities lasting longer than 3 months. Previously thought to be entirely infectious in etiology, chronic sinusitis is now recognized as an inflammatory disease of the upper airways analogous to asthma in the lower airways. Evidence supports daily high-volume saline irrigation along with topical corticosteroids as first-line therapy (A-1 grade). A short course of systemic corticosteroids, short-course doxycycline (3 weeks), or a leukotriene antagonist may be considered in patients with nasal polyps. Three months of macrolide antibiotics may be considered for patients without polyps (*JAMA* 2015;314:926-939).

Aspirin and NSAIDs Reduce Colorectal Cancer Risk

A new case-control study from Denmark confirms low-dose aspirin and nonsteroidal anti-inflammatories (NSAIDs) reduce the risk of colorectal cancer. Several previous epidemiologic studies have shown an inverse association between regular aspirin use and colorectal cancer risk. In this new study, patients with first-time colorectal cancer were compared with population-controlled participants for use of low-dose aspirin or NSAIDs. Among more than 10,000 case patients and

more than 100,000 controlled participants, those with continuous long-term use of low-dose aspirin had an odds ratio (OR) of colorectal cancer of 0.73 (27% reduction; 95% confidence interval [CI], 0.54-0.99). High-intensity long-term use of NSAIDs was associated with a substantial reduction in risk of 43% (OR, 0.57; CI, 0.44-0.74). Data were not available for over-the-counter use of aspirin or NSAIDs. The authors concluded long-term continuous use of low-dose aspirin and long-term use of non-aspirin NSAIDs was associated with reduced colorectal cancer risk. They suggest a reduction of prostaglandin production via inhibition of COX enzymes is the likely mechanism for the antineoplastic effect of the drugs (*Ann Intern Med* 2015;163:347-355).

FDA Actions

The FDA has approved the first drug to treat hypoactive sexual desire disorder in premenopausal women. Flibanserin is a serotonin 1A agonist and a serotonin 2A antagonist, although the mechanism by which the drug improves sexual desire and is related to stress is unknown. Given orally once daily at bedtime, 100 mg of flibanserin was evaluated in three 24-week, double-blind, placebo-controlled trials in about 2400 premenopausal women with an average age of 36. In the trials, women counted the number of satisfying sexual events, reported sexual desire over the preceding 4 weeks, and reported distress related to low sexual desire. On average, flibanserin increased the number of satisfying sexual events by 0.5-1 additional event per month over placebo. Sexual desire scores and sexual distress scores both improved. The drug comes with a boxed warning regarding the risk of severe hypotension and syncope, especially in women who drink alcohol or take a CYP3A4 inhibitor during treatment with flibanserin. The use of alcohol is contraindicated while taking the drug. The approval comes with the requirement for a risk evaluation and medication strategy due to the interaction with alcohol. The FDA is also requiring manufacturers to conduct three well-designed studies in women to understand the risk of the combination of flibanserin with alcohol. Because of the risk, the drug will only be available through certified pharmacies and may only be prescribed by certified prescribers. Flibanserin is marketed by Sprout Pharmaceuticals as Addyi. The cost of the drug has not been announced, but company officials have noted the cost will be roughly the equivalent of a month's supply of male erectile dysfunction pills — speculated to be approximately $400 per month.

The FDA has approved rolapitant to prevent delayed phase chemotherapy-induced nausea and vomiting. It is approved for use in combination with other antiemetic agents. Rolapitant is a P/neurokinin 1 (NK-1) receptor antagonist with a plasma half-life of about 7 days. Approval was based on three randomized, double-blind, controlled trials where rolapitant was used in combination with granisetron and dexamethasone in patients receiving highly and moderately emetogenic chemotherapy. The use of rolapitant vs granisetron and dexamethasone alone resulted in greater reduction in vomiting and use of rescue medication during the delayed phase (24-120 hours). The most common side effects are neutropenia, hiccups, anorexia, and dizziness. Rolapitant joins aprepitant (Emend) as the second NK-1 antagonist approved for this indication. Rolapitant is marketed by Tesaro Inc as Varubi.

The DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin) used to treat type 2 diabetes may cause severe and disabling joint pain, according to the FDA. There have been 33 cases of severe arthralgia reported to FDA's Adverse Event Reporting System from 2006-2013. About one-third of the patients required hospitalization for disabling pain. Arthralgia onset ranged from 1 day to years after imitation of a DPP-4 inhibitor. Symptoms generally resolved within a month after discontinuing medication. The FDA has added a new warning and precaution about this risk to the labels of all DPP-4 medications (www.fda.gov/Safety/MedWatch/).

The FDA has approved evolocumab, the second PCSK9 inhibitor to lower LDL cholesterol in adults with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease for whom current therapy options aren't sufficient. Like alirocumab (Praluent), evolocumab is a monoclonal antibody that inhibits PCSK9, which augments LDL clearance through the liver. The drug is given by subcutaneous injection once or twice a month. Efficacy and safety were shown in one 52-week, placebo-controlled trial and eight 12-week, placebo-controlled trials, where evolocumab resulted in an average 60% lowering of LDL cholesterol compared to placebo. Side effects included upper respiratory infection symptoms and back pain. Neither evolocumab nor alirocumab have been shown to reduce the risk of cardiovascular disease; however, clinical trials are ongoing. Evolocumab is marketed by Amgen as Repatha. The drug is expected to cost more than $14,000 per year. ■

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Customer Service: (800) 688-2421
Email Address: jonathan.springston@ahcmedia.com
Website: AHCMedia.com

Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.