PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Testosterone Replacement and Myocardial Infarction Risk

In this issue: Testosterone replacement and myocardial infarction risk; amyloid therapy and Alzheimer's disease; new guideline for menopausal symptoms; and FDA actions.

Testosterone replacement and MI risk

Testosterone replacement for men has come under scrutiny with the publication of a new study that suggests that men are at higher risk of myocardial infarction (MI) within 3 months of starting hormone therapy. In a cohort study of nearly 56,000 men who were started on testosterone therapy, the rate of MI was assessed in the first 90 days of therapy. The MI rates were compared to nearly 170,000 men started on sildenafil or tadalafil as comparators (similar age groups with similar complaints). In men ≥ 65 years of age, the relative risk (RR) for MI was 2.19 (1.27, 3.77) for testosterone therapy and 1.15 (0.83, 1.59) for sildenafil/tadalafil. The risk for MI with testosterone increased with age, with men > 75 years of age having the highest RR of 3.43. Men < 65 years of age only showed a risk for MI if they had preexisting heart disease. The authors suggest that with the "rapidly increasing use of testosterone therapy," there is urgency to perform clinical trials adequately powered to assess benefits and risks. In the meantime, physicians should include serious cardiovascular events in the discussion of side effects of therapy, especially for men with existing cardiovascular disease (*PLoS One*, published online January 29, 2014, DOI: 10.1371/journal.pone.0085805). ■

Amyloid therapy and Alzheimer's disease

Drugs targeted at amyloid deposits in the brain failed to produce cognitive improvement in two recent studies in *The New England Journal of Medicine*. In the first study, more than 2000 patients with mild-to-moderate Alzheimer's disease (AD) were randomly assigned to two different trials of the humanized monoclonal antibody solanezumab or placebo. Solanezumab preferentially binds soluble forms of amyloid and in preclinical trials promoted its clearance from the brain. After 80 weeks, there was no difference in any measure of cognitive function or functional ability (*N Engl J Med* 2014;370:311-321). In the second study, bapineuzumab, a humanized anti-amyloid-beta monoclonal antibody, was tested in two double-blind, randomized, placebo-controlled phase 3 trials involving patients with mild-to-moderate AD, about half with the APOE allele and half without. There was no significant difference in the primary outcomes after 78 weeks in any measure of cognitive change in either group (*N Engl J Med* 2014; 370:322-333). An accompanying editorial suggests that these studies have provided valuable information but have brought into question the value of some biomarkers in AD. These studies also point out that "we lack clarity on the roles that different forms of amyloid play in the disease" (*N Engl J Med* 2014;370:377-378). ■

New guideline for menopausal symptoms

The American College of Obstetricians and Gynecologists has published an updated guideline for the management of menopausal symptoms,

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the first update since 2001. The guideline recommends systemic hormone therapy, either estrogen alone or in combination with a progestin, as the most effective treatment for vasomotor symptoms, the most common menopausal symptom, affecting 50-82% of women. Low-dose or ultra low-dose estrogen is recommended for the shortest duration necessary, although most women experience vasomotor symptoms, especially hot flashes, for 4-10 years. Conjugated equine estrogen and medroxyprogesterone were found in the Women's Health Initiative Study to increase the risk of breast cancer and thromboembolic events. Transdermal estrogen appears to be safer than oral forms of the drug. The guideline also states that treatment can be extended past age 65 because vasomotor symptoms may persist. The guideline also recommends estrogen in combination with the recently approved selective estrogen receptor modulator (SERM) bazedoxifene in place of a progestin. For women who are unable or unwilling to take hormone-based treatments, selective serotonin reuptake inhibitors (SSRIs) may be helpful, although paroxetine is the only agent currently approved for this indication. SSNRIs, gabapentin, and clonidine may also be useful, but have not been evaluated by the FDA for treatment of vasomotor symptoms. Hormone-based therapy is also effective for vaginal dryness as is the recently approved SERM ospemifene (Osphena). There is not enough evidence to support the use of bioidentical hormones, phytoestrogens, herbal remedies, or even exercise (*Obstet Gynecol* 2014;123:202-216). ■

FDA actions

The FDA is advising clinicians to stop prescribing combination drugs containing more than 325 mg of acetaminophen as part of the policy to reduce liver injury from accidental overdose. The agency banned combination products with more than 325 mg of acetaminophen starting this year, but many drug combinations, including many commonly used pain medications (hydrocodone/acetaminophen and others), remain on the market for now. Over the last 10 years, the agency has seen increased liver injury and death from patients who took more than the prescribed dose of acetaminophen-containing products in 24 hours or took more than one combination product the same time. Alcohol also raises the risk of acetaminophen injury.

The FDA is proposing a study to assess safety outcomes in patients with atrial fibrillation treated with dabigatran (Pradaxa). The agency is asking for public input on the design of the study with particular focus on the risk of ischemic stroke, intracranial hemorrhage, and major extracranial hemorrhage compared to patients treated with warfarin. The study will utilize the FDA's Mini-Sentinel Distributed Database of multiple sources of adverse reactions with dabigatran and warfarin. The FDA stresses that this study does not indicate safety issues with the drug. However, similar studies have not been done with the two other novel oral anticoagulants, rivaroxaban and apixaban.

The FDA has approved dapagliflozin for the treatment of type 2 diabetes in adults. The drug is a sodium-glucose cotransporter 2 inhibitor that blocks the reabsorption of glucose by the kidney. It is the second drug in this class after canagliflozin (Invokana), which was approved 1 year ago. It is approved as monotherapy or in combination with other type 2 diabetes drugs. Dapagliflozin is not for use in type 1 diabetes or in patients with renal disease or a history of ketoacidosis. An increased number of bladder cancers were diagnosed among users of the drug in clinical trials. The drug can also cause dehydration and hypotension in susceptible patients, including the elderly and those on diuretics. The FDA is requiring postmarketing studies on the risk for cardiovascular disease and bladder cancer. Dapagliflozin in marketed by Bristol-Myers Squibb as Farxiga.

The FDA has approved the first treatment for non-24-hour sleep-wake disorder ("non-24") in totally blind individuals. Tasimelteon is a melatonin receptor agonist that helps regulate disrupted sleep/awake cycles in those individuals who can't perceive light well enough to establish a normal night sleep schedule. In clinical trials of 104 participants, tasimelteon resulted in significant improvement in non-24 disorder. The drug should be taken at the same time every night. Side effects may include impaired mental alertness, headache, elevated LFTs, nightmares, disturbed sleep, upper respiratory infections, or urinary tract infections. The drug was approved under the FDA's priority review process. Tasimelteon is marketed by Vanda Pharmaceuticals as Hetlioz. ■