Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Alzheimer's Drug Proven Ineffective

The neuropathologic hallmarks of Alzheimer's disease (AD) include plaques containing amyloid beta and neurofibrillary tangles, along with synaptic and neuronal loss. These pathologic findings lead to hope that solanezumab, a monoclonal antibody that potentially clears amyloid beta from the brain, would help AD patients. Early studies with the drug in advanced AD patients were disappointing, but there was hope that intervention early in the disease may help. Based on this, researchers conducted a double-blind, placebo-controlled, Phase III trial involving patients who exhibited mild AD with amyloid deposition shown on PET scan or seen in spinal fluid analysis. Patients were randomized to solanezumab or placebo intravenously every four weeks for 76 weeks. The outcome was a standardized Alzheimer's assessment score. At 80 weeks, there was no statistical mean difference in three baseline cognitive scores between the two groups (difference, -0.80; 95% confidence interval; -1.73 to 0.14; $P = 0.10$). No significant adverse effects were observed. The authors stated that solanezumab did not significantly affect cognitive decline in patients with mild AD (*N Engl J Med* 2018;378:321-330). This study is a huge disappointment for AD researchers, patients, and families who have been looking for a cure. Solanezumab joins a long list of failed drugs, and there is very little in the pipeline for those seeking a cure.

One of those failed drugs is idalopirdine, a selective 5-hydroxytryptamine-6 receptor antagonist, which was tested in patients with mild to moderate AD who were taking cholinesterase inhibitors.. Idalopirdine was studied in three randomized, clinical trials that included 2,525 patients. Each study lasted 24 weeks. The three studies used three different doses of the drug compared to placebo. None of the three doses improved cognition based on standardized cognitive testing. The authors concluded that these findings do not support the use of idalopirdine for the treatment of AD (*JAMA* 2018;319:130-142).

Fish Oil for Heart Patients?

Should clinicians recommend omega-3 fatty acid supplements to our patients to prevent heart disease? The answer is no, according to a new meta-analysis that found omega-3 fatty acid supplements are of no value for patients with a history of coronary disease. Researchers from the United Kingdom combined data from 10 large randomized, clinical trials that included nearly 78,000 individuals (61.4% men; mean age, 64 years). There were nearly 6,300 coronary heart disease events among this group over a median of 4.4 years. Randomization to omega-3 fatty acid supplementation (eicosapentaenoic acid dose range, 226-1800 mg/d) had no significant associations with coronary heart disease death (relative risk [RR], 0.93; 95% confidence interval [CI], 0.83-1.03; $P = 0.05$), nonfatal myocardial infarction (RR, 0.97; 95% CI, 0.87-1.08; $P = 0.43$), or any coronary heart disease events (RR, 0.96; 95% CI, 0.90-1.01; $P = 0.12$). Omega-3 fatty acid supplements also had no effect on vascular events (RR, 0.97; 95% CI, 0.93-1.01; $P = 0.10$), regardless of the patient's risk group. The authors concluded that omega-3 fatty acids "had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of

coronary heart disease" (*JAMA Cardiol* 2018 Jan 31. doi: 10.1001/jamacardio.2017.5205. [Epub ahead of print]). The American Heart Association currently recommends omega-3 fatty acid for prevention of heart disease in high-risk patients.

Oral Medications for Toenail Fungus

Which oral medication works best for toenail fungus? The winner seems to be terbinafine (Lamisil), based on a recent clinical evidence review. Researchers studied 48 trials that included more than 10,000 patients over 30 years. Terbinafine was compared to placebo and other oral antifungals, including the azole antifungals (ketoconazole, itraconazole, and fluconazole) and Griseofulvin. All three oral antifungal groups (terbinafine, azoles, and Griseofulvin) demonstrated higher cure rates than placebo, but terbinafine outperformed both the azoles and Griseofulvin in clinical and mycologic cure rates. Terbinafine also was associated with a lower recurrence rate than the other drugs. Terbinafine and the azoles were well-tolerated compared to placebo, but patients treated with Griseofulvin experienced more adverse events than terbinafine or the azoles. Although both terbinafine and the azoles are considered effective treatments, only 31-57% of patients achieved clinical cure, while 43-76% achieved mycological cure (*JAMA* 2018;319:397-398).

FDA Actions

The FDA is proposing limiting packaging of loperamide (Imodium) to prevent the risk of abuse. Loperamide, used to treat diarrhea, is available over the counter and also as a prescription medication. In the last two years, the FDA has received reports of serious cardiac problems and even death associated with self-administration of high doses of the drug in an attempt to treat opioid withdrawal or even achieve a feeling of euphoria. High-dose loperamide has been associated with QT prolongation, torsades de pointes, or other ventricular arrhythmias, syncope, and cardiac arrest. The agency is working with manufacturers to use blister packs or other single-dose packaging and to limit the number of doses in a package. Currently, loperamide is available in bottles of 60 or 100 pills.

The FDA has approved olaparib for the treatment of metastatic breast cancer in patients with the BRCA mutation. Olaparib is the first poly (ADP-ribose) polymerase (PARP) enzyme inhibitor approved to treat breast cancer. Patients must undergo an FDA-approved genetic test called the BRACAnalysis CDx to qualify to receive the drug. Olaparib also is approved to treat advanced, BRCA-mutated ovarian cancer. Approval for BRCA-mutated breast cancer indication was based on a randomized, clinical trial of 302 patients with HER2-negative metastatic breast cancer with a germline BRCA mutation, in which the median progression-free survival for patients taking olaparib was seven months, compared to 4.2 months for patients taking chemotherapy only. Olaparib was given priority review. It is marketed as Lynparza.

The FDA has changed the indication on opioid cough and cold medications to stop their use in children < 18 years of age. Products containing codeine and hydrocodone can no longer be prescribed to children because of the potential for serious side effects, including respiratory depression and death. The agency also noted that exposure of young children to opioids may be contributing to the ongoing opioid epidemic. Last year, the FDA also banned the use of codeine for pain in children < 12 years of age. Opioid-containing cough and cold medicines also will carry a new boxed warning cautioning adult users about the risks for misuse, abuse, addiction, overdose, death, and slowed or difficult breathing.

The FDA will allow nurse practitioners (NPs) and physician assistants (PAs) to prescribe and dispense buprenorphine-containing drugs approved for opioid addiction. A trial program was launched in 2016 as part of the Comprehensive Addiction and Recovery Act (CARA), of which about 5,000 NPs and PAs participated. The agency believes that some 25,000 NPs and PAs will complete the 24 hours of training required to receive the special FDA license required to prescribe buprenorphine. Most states still will require physician supervision. The FDA believes the new rule will help more people with opioid use disorder in rural areas, which generally are underserved by addiction specialists.

Plecanatide (Trulance) has received a new indication to treat irritable bowel syndrome with constipation (IBS-C) in adults. The drug is marketed for the treatment of adults with chronic idiopathic constipation. Approval was based on two Phase III, randomized, 12-week, double-blind, placebo-controlled trials that evaluated the efficacy and safety of plecanatide in more than 2,100 adults with IBS-C. Plecanatide was superior to placebo in relieving symptoms, defined as a ≥ 30% reduction in worst abdominal pain and an increase of ≥ 1 complete spontaneous bowel movements from baseline in the same week for at least 50% of the 12 treatment weeks. Diarrhea was the most common side effect. ■

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