Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Researchers Find No Link Between Benzodiazepine Use and Dementia in Elderly Populations

Updated Antithrombotic Therapy Guidelines Released

The February issue of *Chest* includes the latest CHEST guideline on antithrombotic therapy for venous thromboembolism (VTE), representing the first installment in a series of updates of antithrombotic therapy. The guideline contains some significant changes from the previous CHEST guidelines. For patients with VTE and no cancer, long-term (3 months) therapy is recommended with one of the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) over vitamin K antagonists such as warfarin. But warfarin is recommended over low molecular weight heparin (LMWH). For VTE and cancer, LMWH is still the first choice. For deep venous thrombosis (DVT), compression stockings are not routinely recommended to treat post-thrombotic syndrome. Low-risk subsegmental pulmonary embolism without proximal DVT may be monitored without anticoagulation, although patients should be anticoagulated if they have a high risk of VTE. (*Chest* 2016;149:315-352. doi:10.1016/j.chest.2015.11.026)

Study: No Link Between Dementia, Benzodiazepine Use

Recent studies have suggested a link between benzodiazepine use and dementia in elderly populations. However, a new study refutes those findings, suggesting no link, even at high dose. In a prospective, population-based study, 3434 adults ≥ 65 years of age without dementia were followed for an average of 7.3 years. Researchers performed standard cognitive studies every 2 years and evaluated benzodiazepine prescriptions from pharmacy records. About 23% of patients developed dementia. For dementia, the adjusted hazard ratios associated with cumulative benzodiazepine use compared with non-use were 1.25 (95% confidence interval [CI]; 1.03-1.51) for low dose, 1.31 (CI, 1.00-1.71) for moderate dose, and 1.07 (CI, 0.82-1.39) for high dose. There was no difference when Alzheimer's disease was compared to other dementias. The authors concluded that the risk of dementia is slightly higher in people with minimal exposure to benzodiazepines but not with the highest level of exposure. These results do not support a causal association between benzodiazepine use and dementia. (*BMJ* 2016;352:i90) This study did not evaluate other significant adverse effects of these drugs in the elderly, including short-term cognitive changes and fall risk.

New Recommendations for Bisphosphonate Therapy

A new guideline provides recommendations on the duration of bisphosphonate therapy in postmenopausal women with osteoporosis. The Task Force of the American Society for Bone and Mineral Research recommends treating women with 5 years of oral therapy or 3 years of annual infusion therapy and then reassessing risk. For women at high risk (those with a low T score or high fracture risk score, those with a previous major osteoporotic fracture, or

those who fracture while on therapy), treatment may be extended up to 10 years for oral bisphosphonate or 6 years of yearly infusion bisphosphonate therapy. The guideline acknowledges that there is an increase in atypical fractures (but not osteonecrosis of the jaw) with continued therapy, but two studies have shown a significant reduction in major fractures in women at high risk with continued therapy. For women who are not at high risk after 3-5 years of bisphosphonate therapy, a drug holiday of 2-3 years may be considered. The same recommendations may be applicable to men with glucocorticoid-induced osteoporosis (*J Bone Miner Res* 2016;31:16-35, DOI 10.1002/jbmr.2708).

Promising Treatment Not Widely Available

Fecal microbiota transplantation (FMT) is a promising therapy for *Clostridium difficile* infection (CDI), but is often not readily available. A new study suggests that frozen FMT is as effective as fresh FMT in patients with recurrent or refractory CDI. In a randomized, double-blind, noninferiority trial, 232 adults with CDI were enrolled in six centers in Canada. Roughly half were given frozen FMT while the other half received fresh FMT via enema. The proportion of patients with clinical resolution was 83.5% for frozen FMT and 85.1% for fresh FMT ($P = 0.01$ for noninferiority). Similar results occurred in a modified intention-to-treat analysis. There were no differences in proportion of serious adverse events between treatment groups. The authors concluded that among adults with recurrent or refractory CDI, the use of frozen compared with fresh FMT did not result in worse proportion of clinical resolution of diarrhea (noninferior) (*JAMA* 2016;315:142-149. doi:10.1001/jama.2015.18098). The study is important because it validates the use of frozen/commercial FMT for use in CDI infections.

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Time to Limit Proton Pump Inhibitors?

Proton pump inhibitors (PPI) have been associated with bone loss, intestinal infections, and pneumonia. Now, a new study suggests the commonly used drugs may be associated with chronic kidney disease (CKD), especially at high doses. More than 10,000 participants with normal renal function were followed from the late 1990s to December 2011. Self-reported PPI use and prescription database PPI use was compared to use of an H2 blocker. The mean age was 63 years and 44% were male. PPI use was associated with an increased incidence of CKD in unadjusted analysis (hazard ratio [HR], 1.45; 95% confidence interval [CI], 1.11-1.90). When the analysis was adjusted for demographic, socioeconomic, and clinical variables, the HR was still 1.50 (CI, 1.14-1.96). PPI use was associated with CKD in all analyses, including time-varying in new-user design. Twice-daily PPI dosing was associated with a higher risk than once-daily dosing. The authors concluded that PPI use is associated with a higher risk of incident CKD and further research is needed to evaluate whether limiting PPI use reduces the risk (*JAMA Intern Med* 2016;176:238-246. doi:10.1001/jamainternmed.2015.7193). An accompanying editorial highlighted other risks of PPIs, including hypomagnesemia, infections, cardiovascular events, and fractures, and suggested patients and clinicians discuss the risks and benefits of long-term treatment (*JAMA Intern Med* 2016;176:172-174. doi:10.1001/jamainternmed.2015.7927). PPIs were added to the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults last October (doi: 10.1111/jgs.13702).

FDA Actions

The FDA has approved a new fixed-dose combination oral, once-daily pill to treat hepatitis C (HCV) genotypes 1 and 4. The new agent combines elbasvir in a NS5A inhibitor and grazoprevir in a NS3/4a protease inhibitor. The combination can be used in patients with chronic kidney disease and can be used with or without ribavirin, but does not require interferon. Researchers studied the safety and efficacy of the combination in 1373 participants with chronic HCV genotype 1 or 4 infections with and without cirrhosis. Ribavirin was added depending on the clinical setting, and patients were treated for 12 or 16 weeks. The overall sustained viral response ranged from 94-97% in genotype 1 patients and 97-100% in genotype 4 patients. It is recommended that patients with genotype 1a be screened for NS5A polymorphism prior to treatment to establish treatment duration and need for ribavirin. Liver enzyme tests should be monitored during treatment. Elbasvir/grazoprevir is marketed by Merck as Zepatier. The company sent a ripple through the hepatitis C community when it announced its price at $54,600 for 12 weeks, about half the cost of competitors Harvoni and Viekira Pak. ■