Pharmacology Watch

Evidence-based updates in clinical pharmacology

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New Study Compares Leading Atrial Fibrillation Treatments

A new head-to-head study compared dabigatran (Pradaxa) and rivaroxaban (Xarelto) for the treatment of non-valvular atrial fibrillation (AF), and it appears that dabigatran may be the winner. Dr. David Graham and his team at the FDA's Center for Drug Evaluation and Research performed a retrospective, new-user cohort study of nearly 120,000 patients with AF, ≥ 65 years of age who started dabigatran (150 mg twice a day) or rivaroxaban (20 mg once daily) for stroke prevention. Rivaroxaban was associated with a nonsignificant reduction in thromboembolic stroke (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.65-1.01; *P* = 0.07; adjusted incidence rate differences [AIRD] = 1.8 fewer cases/1,000 person-years), but a statistically significant increase in intracranial hemorrhage (ICH) (HR, 1.65; 95% CI, 1.20-2.26; *P* = 0.002; AIRD = 2.3 excess cases/1,000 person-years) and major extracranial bleeding (HR, 1.48; 95% CI, 1.32-1.67; *P* < 0.001; AIRD = 13.0 excess cases/1,000 person-years), including major gastrointestinal bleeding (HR, 1.40; 95% CI, 1.23-1.59; *P* < 0.001; AIRD = 9.4 excess cases/1,000 person-years), and with a statistically nonsignificant increase in mortality (HR, 1.15; 95% CI, 1.00-1.32; *P* = 0.051; AIRD = 3.1 excess cases/1,000 person-years). Mortality was statistically higher for rivaroxaban-treated patients ≥ 75 years of age or with a $CHADS_2$ score > 2. The authors concluded that rivaroxaban use for AF was associated with significantly higher rates of ICH and major extracranial bleeding, including major gastrointestinal bleeding and possibly increased mortality in the elderly or those with higher risk of stroke compared to dabigatran (*JAMA Intern Med*. Published online Oct. 3, 2016. doi:10.1001/jamainternmed.2016.5954). There was no mention of use of idarucizumab (Praxbind) as a reversal agent for dabigatran during the study period.

New Erectile Dysfunction Data Counter Previous Studies

A new study suggests that the 5-alpha reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart) are not associated with an increased risk of erectile dysfunction (ED), countering the findings of previous studies. Researchers from the United Kingdom examined the records of 90,000 men with benign prostatic hypertrophy (BPH) or alopecia on a 5-alpha reductase inhibitor alone or with an alpha-blocker, or an alpha-blocker alone. The main outcome was diagnosis of ED or a prescription or procedure for ED. In the BPH group (n = 71,849), the risk of ED was not increased with 5-alpha reductase inhibitor alone (incident rate ratio [IRR], 0.92; 95% confidence interval [CI], 0.85-0.99; odds ratio [OR], 0.94; 95% CI, 0.85-1.03) or in combination with an alpha-blocker (IRR, 1.09; 95% CI, 0.99-1.21; OR, 0.92; 95% CI, 0.80-1.06) compared with alpha-blocker only. Duration of BPH was a risk factor for ED regardless of drug exposure. For alopecia (n = 12,346), 1 mg of finasteride was not associated with ED compared to men with alopecia who were not treated (IRR, 1.03, 95% CI, 0.73-1.44; OR, 0.95; 95% CI, 0.64-1.41). The authors concluded that 5-alpha reductase inhibitors do not seem to increase the risk of ED, regardless of the indication for use (*BMJ* 2016; 354 doi: http://dx.doi.org/10.1136/bmj.i4823). This study will be a relief for men who take 5-alpha reductase inhibitors, since previous studies suggested ED may be a significant problem with these drugs.

Experts Withdraw Support for Codeine in Children

Codeine is no longer recommended for use in children. After years of debate, the American Academy of Pediatrics (AAP) has issued a Clinical Report recommending against the use of codeine for cough or pain in children, regardless of age. The recommendation from the AAP's Section on Anesthesiology and Pain Medicine, Committee on Drugs, notes that codeine is a prodrug of morphine, and the conversion occurs in the liver. There is substantial genetic variability in the activity of the responsible hepatic enzyme leading to significant individual variation in the effect of codeine. Some children experience no effect at all, while others are ultrarapid metabolizers, which may result in high serum morphine levels. The FDA has received multiple reports of respiratory depression and death after receiving codeine in children, many of whom were subsequently found to be rapid metabolizers. Children with sleep apnea seem to be at particularly high risk. The FDA and the World Health Organization are considering similar warnings. Despite these concerns, codeine continues to be commonly prescribed, with more than 800,000 prescriptions for children < 11 years of age in 2011. Unfortunately, other opioids have similar safety concerns, precluding their use as an alternative, leaving nonsteroidal anti-inflammatory drugs and acetaminophen as options (*Pediatrics* Sep 2016, e20151648; doi: 10.1542/peds.2016-2396). An FDA advisory panel met last December and by an overwhelming majority recommended that the use of codeine is contraindicated for the treatment of cough in children ≤ 18 years of age; however, the FDA has not yet acted on the recommendation.

FDA Actions

In a mixed vote, an FDA advisory committee has voted to remove the black box warning from varenicline (Chantix). The warning was placed in 2009 after the FDA received reports of neuropsychiatric events, including depression and thoughts of suicide. But a company-funded trial published in April did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30272-0/abstract). Although some at the FDA criticized the study design, 10 of the 19 committee members voted to remove the warning. Of the dissenters, several voted to amend the current warning, while others voted to keep the current warning as is. This is the second time varenicline's manufacturer has petitioned the FDA to remove the warning, after an unsuccessful attempt in 2014.

The FDA has approved the first biosimilar to adalimumab (Humira). Adalimumab-atto is approved for the same indications as adalimumab, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, and juvenile idiopathic arthritis in children ≥ 4 years of age. The approval was based on structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrate adalimumab-atto is biosimilar to adalimumab. Adalimumab-atto is marketed as Amjevita.

The FDA has issued a warning regarding direct-acting antiviral drugs used to treat hepatitis C (HCV) and the risk of reactivation of hepatitis B (HBV) in patients co-infected with HBV and HCV. The FDA has identified 24 cases of HBV reactivation in the last three years, of which two patients died and one required a liver transplant. The drugs implicated include the most commonly used HCV drugs, including (by tradename) Harvoni, Sovaldi, Daklinza, Viekira Pak, and Zepatier. The FDA recommends testing patients for HBV prior to initiating therapy for HCV, and monitoring patients for HBV reactivation during and after treatment. The FDA also added a boxed warning to all direct-acting antivirals to treat HCV warning about HBV reactivation.

In a controversial decision, the FDA has approved the first drug to treat the most common childhood form of muscular dystrophy. Eteplirsen has been the subject of intense lobbying by patient advocacy groups for years, but evidence for effectiveness has been marginal. Approval was based on one study of 12 boys with Duchenne muscular dystrophy, of whom all were treated (no control group). The approval also was based on a surrogate endpoint without evidence of improvement in motor function. The drug was not recommended for approval by the agency's expert panel, but the FDA overruled that decision and approved the drug on a close vote. The drug also was granted fast-track approval and orphan designation, which is used to accelerate approval and provide financial incentives to companies to develop drugs for rare conditions. Eteplirsen is marketed as Exondys 51. Eteplirsen is expected to cost about $300,000 per year. ■

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