PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

New Oral Anticoagulants Are Safe for Treating Acute VTE

In this issue: Rivaroxaban, Apixaban for Acute VTE; Benzodiazepine Use and Risk of AD; Patients More Adherent to Generic Statins; and FDA Actions.

Rivaroxaban, Apixaban for Acute VTE

When treating acute venous thromboembolism (VTE), the new oral anticoagulants are safe and effective alternatives to low-molecular-weight heparin (LMWH) followed by warfarin, according to a new study. The gold standard for treating acute VTE is LMWH followed by warfarin, but this regimen is often unwieldy for patients and requires frequent lab tests and follow-up. The new oral factor Xa inhibitors rivaroxaban (Xarelto) and apixaban (Eliquis) are both approved for initial treatment of VTE, but many physicians have safety concerns. The direct thrombin inhibitor dabigatran (Pradaxa) is also approved for VTE, but only after an initial course of LMWH. Using warfarin + LMWH as a comparator, eight different anticoagulation options were reviewed in a large meta-analysis. The regimens included LMWH plus dabigatran and the new agent edoxaban, as well as rivaroxaban and apixaban alone. Treatment outcomes were similar with all regimens except for unfractionated heparin with warfarin, which had the highest VTE recurrence rate. Bleeding rates were lowest with rivaroxaban and apixaban (hazard ratio, 0.55 and 0.31, respectively). The authors conclude that all regimens were of similar efficacy with the new Xa inhibitors rivaroxaban and apixaban associated with the lowest rate of bleeding (*JAMA* 2014;312:1122-1135). This study may help change standard treatment for many emergency physicians who are looking to avoid cumbersome injection therapies for new diagnoses of VTE. ■

Benzodiazepine Use and Risk of AD

Patients may be asking about a recent study linking benzodiazepine use to Alzheimer's disease (AD). Researchers from Canada performed a case-control study of nearly 1800 people with first-diagnosis AD along with nearly 7200 matched controls. Patients were followed for at least 6 years. Benzodiazepine ever-use was associated with a 50% increased risk of AD (adjusted odds ratio [OR], 1.51; 95% confidence interval [CI], 1.30-1.69). After adjustment for anxiety, depression, and insomnia, the OR was 1.43 (95% CI, 1.28-1.60) There was an increase in the association for exposure density, including number of prescribed daily doses and longer drug half-life. The authors conclude that benzodiazepine use is associated with increased risk of AD, with a stronger association with long-term use (*BMJ* 2014;349:g5205). The authors addressed and feel they avoided "reverse causal bias" — the possibility that pre-dementia patients may be more likely to take a benzodiazepine due to anxiety or insomnia. They do not, however, suggest a mechanism whereby these drugs possibly cause permanent cognitive damage and suggest more research is needed. ■

Patients More Adherent to Generic Statins

Low-cost generic statins improve compliance and clinical outcomes compared to their brand-name

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counterparts. Those are the findings of a recent study of Medicare beneficiaries who were on the cholesterol-lowering medications. Researchers reviewed the records of 90,000 statin users of which 93% took a generic and 7% took a branded version. The mean age was 75 years and about 60% were women. The average out-of-pocket cost was $10 for the generic statin vs $48 for the brand-name product. Adherence (as measured by proportion of days covered) was 77% in the generic group and 71% in the brand name group ($P < 0.001$). The generic group also saw an 8% reduction in the composite outcome of hospitalization for acute coronary syndrome, stroke, or all-cause mortality compared to the brand-name group (HR, 0.92; 95%CI, 0.86-0.99). The authors conclude that "compared to those initiating brand-name statins, patients initiating generic statins were more likely to adhere and had a lower rate of a composite clinical outcome." (*Ann Intern Med* 2014;161:400-407). An accompanying editorial points out that this study was looking at generic vs brand-name drugs "but the operating factor for patients is affordability." ■

FDA Actions

The FDA has approved a once-weekly injectable GLP-1-receptor agonist for the treatment of type 2 diabetes. Dulaglutide is an ultra long-acting agent that can be used as monotherapy or in combination with other antidiabetic drugs including metformin, sulfonylureas, thiazolidinediones, or insulin. Approval was based on six clinical trials in more than 3300 patients with type 2 diabetes in which the drug improved blood sugar control and lowered HbA1c levels. As with other GLP-1 agonists, dulaglutide has been linked to thyroid C-cell tumors in rodents. Dulaglutide is marketed by Eli Lilly and Company as Trulicity.

An FDA panel has recommended limiting indications for use of testosterone supplements to specific medical conditions that impair testicular function. The Bone, Reproductive and Urologic Drugs Advisory Committee to the FDA voted overwhelmingly to limit use of the increasingly popular prescription testosterone products, recommending against use for age-related low testosterone levels. The panel also recommended research to study the cardiovascular risks of prescription testosterone products. If approved by the FDA later this year, the new rule would limit marketing and promotion of prescription testosterone products for otherwise healthy men with "low T," a multibillion dollar market. Last year, 2.3 million men were prescribed testosterone with the majority being younger than the age of 65. The new rule may change the way health plans cover prescription testosterone as well. The FDA generally approves the recommendations of their advisory committees.

The FDA has revised the safety label for the smoking cessation drug varenicline (Chantix) after new studies indicate that it may not carry the risk of suicidality and other psychiatric disorders as previously thought. A meta-analysis of more than 1900 patients in five randomized trials found no increase in suicidality compared to placebo. Another large meta-analysis found no increase in mood disorders, including anxiety or depression. There has also been no evidence of increased neuropsychiatric hospitalizations. The FDA placed a black box warning on varenicline more than 5 years ago when initial data suggested an increase in neuropsychiatric problems with the drug. Pfizer, the drug's manufacturer, is petitioning the FDA to remove the black box warning altogether, although the agency has not ruled on this yet.

The FDA has approved naloxegol for the treatment of opioid-induced constipation in adults. The drug is a peripherally acting opioid receptor antagonist that is available as a once-daily oral tablet. Safety and efficacy were established in two trials of 1352 participants with opioid-induced constipation in which 41-44% of patients experienced some relief compared to 29% improvement with placebo. Naloxegol is marketed by AstraZeneca as Movantik.

The FDA has approved a new combination of two older drugs — naltrexone and bupropion as a fixed-dose, extended-release formulation for the treatment of obesity in addition to a reduced-calorie diet and physical activity. It is approved for those with a body mass index (BMI) ≥ 30 kg/m^2 with no risk factors or a BMI ≥ 27 kg/m^2 associated with hypertension, type 2 diabetes, or dyslipidemia. The approval was based on several clinical trials of about 4500 obese and overweight patients in which the drug was associated with a weight loss of 4.1% over 1 year compared to placebo. Because the combination includes bupropion, there is a boxed warning regarding suicidal thoughts and behaviors associated with antidepressants. It should be avoided in patients with uncontrolled blood pressure and eating disorders. Naltrexone is an opioid antagonist, so the combination should be avoided in those taking opioids. Bupropion/naltrexone is marketed by Takeda Pharmaceuticals as Contrave. Contrave is the third drug approved for this indication after phentermine/topiramate (Qsymia) and lorcaserin (Belviq). Both drugs were approved in 2012 but have seen scant use in the United States. ■