Pharmacology Watch

Evidence-based updates in clinical pharmacology

By William T. Elliott, MD, FACP

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Is There a Connection Between Breast Cancer and Hormonal Contraceptives?

Women may be asking about birth control pills and the risk of breast cancer after publication of a highly publicized study. Researchers from Denmark reviewed the records of 1.8 million women over about 11 years (19.6 million person-years), during which 11,517 cases of breast cancer occurred. Compared to women who had never used hormonal contraception, the relative risk (RR) of breast cancer among all current and recent users of hormonal contraception was 1.20 (95% confidence interval [CI], 1.14-1.26). The risk increased with duration of usage from a RR of 1.09 with less than one year of hormonal contraceptive use to 1.38 with > 10 years of usage. The risk remained higher after discontinuation if contraception was used for > 5 years. Interestingly, the intrauterine progestin-only system also was associated with a higher risk of breast cancer (RR, 1.21; 95% CI, 1.11-1.33). The increase in breast cancer risk associated with hormonal contraception calculates to about one extra breast cancer for every 7,690 women using hormonal contraception for one year. The authors concluded that while the risk is small, there was a higher risk of breast cancer among women who currently or recently used contemporary hormonal contraceptives than among women who had never used hormonal contraceptives. Also, this risk increased with longer use (*N Engl J Med* 2017; 377:2228-2239).

The authors of an accompanying editorial noted that the 20% higher risk of breast cancer associated with hormonal contraceptives found in this study is about the same observed in other large studies. The difference is that the new study used more modern formulations of oral contraceptives. But the low risk of breast cancer must be combined with the low incidence of cancer in younger women, along with the protective effects of oral contraceptives against other cancers, including ovarian, endometrial, and colorectal cancers, later in life. Still, the search for a hormonal contraceptive that does not raise the risk of breast cancer must continue (*N Engl J Med* 2017;377:2276-2277).

No Association Between Vitamin D, Calcium Supplements and Fracture Prevention in Older Adults

Older community-dwelling adults do not benefit from calcium, vitamin D, or both regarding fracture prevention, according to a large new meta-analysis. Researchers combined 33 randomized, clinical trials that included more than 51,000 participants ≥ 50 years of age to determine whether calcium supplements, vitamin D, or the combination affected fracture incidence. The risk ratios (RR) vs. placebo were 1.53 for calcium alone, 1.21 for vitamin D alone, and 1.09 for the combination. No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements or the incidence of nonvertebral, vertebral, or total fractures. The results were consistent regardless of the dose of vitamin D or calcium, sex, fracture history, dietary calcium intake, or baseline serum 25-hydroxyvitamin D concentration. The authors concluded that "these findings do not support the

routine use of these supplements in community-dwelling older people." (*JAMA* 2017;318:2466-2482). Current practice guidelines recommend calcium and vitamin D, but with mounting evidence of no benefit and potential harm (coronary artery disease, kidney stones, etc.), those guidelines may change.

FDA Actions

The FDA has approved a fourth sodium-glucose cotransporter-2 (SGLT2) inhibitor for the treatment of type 2 diabetes. Ertugliflozin is approved as an adjunct to diet and exercise for treating adults with type 2 diabetes. It was approved as monotherapy and in combination with sitagliptin and with metformin. Like other SGLT2 inhibitors, the drug blocks reabsorption of glucose by the kidney, resulting in increased excretion of glucose in the urine. Ertugliflozin is marketed as Steglatro as monotherapy, as Steglujan in combination with sitagliptin, and as Segluromet in combination with metformin.

The FDA has approved an angiotensin II injection for the treatment of shock (septic or other distributive shock). Angiotensin II raises blood pressure in adult patients who are unable to maintain blood flow to vital tissues. Approval was based on a trial of 321 patients with shock and critically low blood pressure in which significantly more patients responded to treatment with angiotensin II compared to those treated with placebo. The drug effectively increased blood pressure when added to conventional treatments used to raise blood pressure. Angiotensin II can cause arterial and venous clotting, requiring prophylactic anticoagulation. The drug received priority review. The injection is marketed as Giapreza.

The FDA has approved a follow-on version of insulin lispro injection. Generally, a follow-on drug is defined as a drug with a similar chemical structure or the same mechanism of action as a drug that is already marketed, in this case insulin lispro (Humalog). The new version of the short-acting insulin is approved to control blood sugar in adults and children ≥ 3 years of age with type 1 or type 2 diabetes. The FDA is striving to increase competition in the prescription drug market to facilitate the entry of lower-cost alternatives, and insulin lispro is a drug "taken by millions of Americans every day for a patient's lifetime to manage a chronic disease," according to FDA Commissioner Scott Gottlieb, MD. The new insulin was cleared through an abbreviated approval pathway called 505(b)(2), which may rely on the previously approved drug's published literature. The FDA notes that potassium levels should be monitored in patients who are at risk for hypokalemia. The new insulin lispro injection is marketed as Admelog.

The FDA is launching a new website to assist clinicians with antibiotic selection. The website will list critical updates regarding which bacterial or fungal infections are likely to respond to a specific drug, allowing for "more informed prescribing decisions that will both benefit their patients and prevent the spread of resistant bacteria." Previously, each drug manufacturer updated its drug labeling with new susceptibility information, which had to be reviewed and approved by the FDA. The new system bypasses the approval process and shares information in a timelier manner. The new site can be accessed at: www.FDA.gov/STIC.

Pfizer has announced it is launching a generic version of sildenafil citrate (Viagra). The new version will be white rather than blue and will cost about half the $65-a-pill branded version. Generic manufacturer Teva also plans to market a version of sildenafil citrate, while other manufacturers plan to follow by next summer. Used to treat male erectile dysfunction, sildenafil has been one of the most popular (and lucrative) drugs since its launch in 1998.

The FDA is removing the boxed warning from long-acting beta-agonists (LABAs) in combination with inhaled corticosteroids (ICS) regarding asthma-related death. Previously, ICS/LABA inhalers were thought to be higher risk than ICS inhalers alone. In 2011, the FDA required ICS/LABA manufacturers to conduct several large, randomized, double-blind, 26-week trials to assess the risk of serious asthma-related events when LABAs were used in fixed-dose combination with an ICS, compared to ICS alone, in patients with asthma. More than 41,000 patients were enrolled. The results showed that the fixed-dose combinations did not result in a significant increased risk of serious asthma-related events, even in subgroup analyses for gender, adolescents 12-18 years, and African-Americans. ICS/LABA combinations also were more efficacious than ICS alone in reducing asthma exacerbations. However, LABAs used alone still carry the boxed warning. ■

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