Pharmacology Watch

Evidence-based updates in clinical pharmacology

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PCSK9 Drug Improves Heart Outcomes

In the mid-2000s, researchers discovered that variability in the activity of the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme produced wide-ranging effects on cholesterol levels in humans. Two monoclonal antibodies that inhibit PCSK9 were developed and were found to markedly reduce low-density lipoprotein (LDL) cholesterol. Evolocumab (Repatha) and alirocumab (Praluent) were approved in 2014 and 2015, respectively, to great anticipation. Although both drugs lowered LDL better than statins, evidence of cardiovascular benefit had been lacking — until now. The FOURIER trial was a randomized, double-blind, placebo-controlled trial comprised of 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of ≥ 70 mg per deciliter (1.8 mmol per liter) who already were taking a statin. Patients received evolocumab (either 140 mg every two weeks or 420 mg monthly) or matching placebo by subcutaneous injection. The primary outcome was a composite of cardiovascular death, myocardial infarction (MI), stroke, unstable angina, or coronary revascularization. The secondary outcome was the composite of cardiovascular death, MI, or stroke. After 48 weeks, evolocumab lowered LDL 59% from baseline compared to placebo. Both the primary and secondary outcomes were reduced significantly relative to placebo (primary outcome 9.8% vs. 11.3%; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.79-0.92; $P < 0.001$; secondary outcome 5.9% vs. 7.4%; HR, 0.80; 95% CI, 0.73-0.88; $P < 0.001$). Overall mortality was not different between the two groups. Evolocumab was well-tolerated except for injection site reactions. The authors concluded that patients with atherosclerotic cardiovascular disease benefit from lowering LDL below current targets (*N Engl J Med* 2017;376:1713-1722).

A new PCSK9 inhibitor, bococizumab, also showed benefit in reducing major cardiovascular events in high-risk patients, although the study ended early because of a high level of anti-drug antibodies (*N Engl J Med* 2017;376:1527-1539). Researchers halted further development of bococizumab in November 2016. Several other PCSK9 drugs are in development, including inclisiran, which is administered once every three months.

Association of Autism with Antidepressant Use During Pregnancy

Two new studies suggest that maternal use of antidepressants during pregnancy is not associated with autism. The first study, conducted in Canada, was a retrospective cohort study of 35,906 singleton births from 2002 to 2010, with the children followed until March 31, 2014, looking at the effects of serotonergic antidepressants. The absolute rate of autism was higher in the antidepressant group, but after sophisticated statistical analysis, the association was not significant (HR, 1.61; 95% CI, 0.997-2.59). The association also was not significant when exposed children were compared with unexposed siblings (incidence of autism spectrum disorder was 3.40 per 1,000 person-years vs. 2.05 per 1,000 person-years, respectively; adjusted HR, 1.60; 95% CI, 0.69-3.74). The authors suggested that although "a causal relationship cannot be ruled out, the previously observed association may be explained by other factors" (*JAMA* 2017;317:1544-1552).

In the second study, conducted in Sweden, first trimester maternal antidepressant use was evaluated with regard to offspring birth problems or neurodevelopmental problems. The records of nearly 1.6 million offspring were evaluated. First-trimester antidepressant exposure

was associated significantly with preterm birth (odds ratio, 1.3 in a sibling comparison analysis) but not with risk of being born small for gestational age or later autism spectrum disorder or attention-deficit/hyperactivity disorder (*JAMA* 2017;317:1553-1562).

An accompanying editorial reminds us that regardless of antidepressant treatment, children of mothers with depression remain at increased risk of developmental issues. Moving away from a focus on antidepressant medications alone will "disentangle" the effects of maternal mood disorders on the fetus vs. shared genetic predispositions to mental and neurodevelopmental disorders (*JAMA* 2017;317:1533-1534).

Testing the Effects of Statins on Muscles

How common are statin-related muscle symptoms? Perhaps not as common as many think, based on the results of a study from the Anglo-Scandinavian Cardiac Outcomes Trial. In a randomized, blinded trial, more than 10,000 patients were randomized to atorvastatin 10 mg per day or placebo for just over three years. Later, just under 10,000 patients were followed in a non-blinded, non-randomized study and assigned to atorvastatin 10 mg or no medication for about two years. In the blinded phase, when patients did not know if they were taking a statin, muscle-related events occurred at about the same rate in the treatment and placebo groups (HR, 1.03; 95% CI, 0.88-1.21; $P = 0.72$). Erectile dysfunction also occurred at about the same rate in both groups, while sleep disturbance actually was lower in the atorvastatin group. The rate of cognitive impairment was very low in both groups. In the unblinded study, when patients knew they were taking a statin, muscle-related adverse events were significantly higher in the statin group at 1.26% vs. 1.00% per annum (HR, 1.41; 95% CI, 1.10-1.79; $P = 0.006$). There was no difference in the rate of other side effects. The authors suggested that this study "should help counter the adverse effect on public health of exaggerated claims about statin-related side-effects." (*Lancet*. Published online May 2, 2017. Available at: http://bit.ly/2pg3Vyp. Accessed May 9, 2017.)

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FDA Actions

The FDA has approved a new human parathyroid hormone analog for the treatment of postmenopausal osteoporosis. Abaloparatide is a once-a-day subcutaneous injection similar to teriparatide. It is indicated for postmenopausal women who are at high risk of fracture (previous osteoporotic fracture, multiple risk factors for fracture, or have failed or are intolerant of other therapies). Approval was based on the results of the ACTIVE trial, which showed a relative risk reduction of 86% in new vertebral fractures and 43% in nonvertebral fractures over 18 months (absolute risk reduction of 3.6% and 2.0%, respectively). Similar to teriparatide, abaloparatide carries a warning about a potentially increased risk for osteosarcoma. The drug will be marketed under the trade name Tymlos.

The FDA has approved a generic version of ezetimibe/simvastatin (Vytorin) for the treatment of hypercholesterolemia. Simvastatin lost patent protection in 2006, and ezetimibe's patent expired in late April. At least two generic manufacturers have filed with the FDA to begin marketing the combination immediately.

The FDA has approved a second biosimilar to infliximab (Remicade), the popular TNF inhibitor used to treat several diseases, including rheumatoid arthritis, ulcerative colitis, and Crohn's disease. Under the FDA's naming convention for biosimilars, the new drug is called infliximab-abda and will be marketed as Renflexis. It is expected to be available later this year.

After almost two years of deliberation, the FDA is restricting the use of codeine and tramadol in children < 12 years of age. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain in children, but both drugs carry significant risks, including breathing problems that have led to a reported 24 codeine-related deaths and three tramadol-related deaths. The FDA is requiring labeling changes that indicate codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children < 12 years of age. Further, tramadol should not be used in children < 18 years of age to treat pain after tonsil and/or adenoid surgery. Codeine and tramadol should not be used in adolescents 12-18 years of age who are obese or have breathing issues such as obstructive sleep apnea or severe lung disease. Finally, codeine or tramadol should not be taken by a mother who is breastfeeding.

The FDA has approved valbenazine to treat tardive dyskinesia, the first drug approved for this indication. Valbenazine is a monoamine transporter 2-inhibitor that is indicated for adults with tardive dyskinesia. It is also under investigation as a treatment for Tourette's syndrome. Approval was based on a trial of 234 patients. After six weeks, those who received valbenazine demonstrated improvement in the severity of abnormal involuntary movements compared to those who received placebo. The drug may cause sedation and QT prolongation. Valbenazine will be marketed as Ingrezza. ■