Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Possible Link Between Acetaminophen Use During Pregnancy and Later ADHD Development

Prenatal exposure to acetaminophen may be a risk for attention-deficit/hyperactivity disorder (ADHD) in offspring, according to a new study. Data from the Norwegian Patient Registry of nearly 123,000 offspring included 2,246 patients with ADHD. Maternal use of acetaminophen during pregnancy and paternal use prior to pregnancy were evaluated. After adjusting for maternal use of acetaminophen before pregnancy, familial risk for ADHD, and indications for acetaminophen use, the researchers observed a modest association between any prenatal use of acetaminophen in one trimester (hazard ratio [HR], 1.07; 95% confidence interval [CI], 0.96-1.19), two trimesters (HR, 1.22; 95% CI, 1.07-1.38), and three trimesters (HR, 1.27; 95% CI, 0.99-1.63) and ADHD. The HR for > 29 days of maternal acetaminophen use was 2.20 (95% CI, 1.50-3.24), while use for < 8 days was associated negatively with ADHD. Acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR, 6.15; 95% CI, 1.71-22.05). Paternal use prior to pregnancy for ≥ 29 days was as strongly associated with ADHD as maternal use. The authors concluded that long-term maternal use of acetaminophen during pregnancy was associated substantially with ADHD, even after adjusting for indications of use, familial risk of ADHD, and other potential confounders. However, given that paternal use of acetaminophen also was associated with ADHD, the causal role of acetaminophen can be questioned. (*Pediatrics* 2017 Nov;140(5). pii: e20163840. doi: 10.1542/peds.2016-3840)

Lowering Dementia Risk in Atrial Fibrillation Patients

Oral anticoagulants may reduce the risk of dementia in patients with atrial fibrillation (AF), according to a new study from Sweden. A retrospective registry study looked at 444,106 patients with AF. Patients on anticoagulant treatment at baseline demonstrated a 29% lower risk of dementia than patients without anticoagulation (hazard ratio, 0.71; 95% confidence interval, 0.68-0.74). For those who started anticoagulation earlier and stayed on anticoagulation longer, the benefit was nearly a 50% reduction in the incidence of dementia. There was no difference in risk reduction between vitamin K antagonists (warfarin) and non-vitamin K oral anticoagulants. There was more benefit in patients with higher CHA_2DS_2-VASc scores, suggesting that microembolization may be the cause of dementia in AF patients. The authors concluded that the risk of dementia is higher in AF patients without oral anticoagulation, suggesting that "early initiation of anticoagulation treatment in patients with AF could be of value in order to preserve cognitive function." (*Eur Heart J* 2017 Oct 24. doi: 10.1093/eurheartj/ehx579)

Monitoring Bleeding Risks Associated With Non-vitamin K Oral Anticoagulants

The non-vitamin K oral anticoagulants (NOACs) are used for the treatment of nonvalvular atrial fibrillation (AF), in part because they are seen as more convenient and safer alternatives to warfarin. But NOACs (e.g., rivaroxaban, dabigatran, and apixaban) produce important drug-drug interactions, as noted in a new study from Taiwan. In a retrospective cohort study, the records of more than 91,000 AF patients who had received at least one NOAC were reviewed. There were nearly 5,000 major bleeding events during almost 450,000 person-quarters with NOAC prescriptions. The most common drugs administered concurrently with NOACs were atorvastatin, diltiazem, digoxin, and amiodarone. Of that group, only amiodarone was

associated with a significantly higher risk of bleeding. Other drugs that increased bleeding risk were fluconazole, rifampin, and phenytoin. Concurrent use of atorvastatin, digoxin, and erythromycin or clarithromycin lowered bleeding rates, while verapamil, diltiazem; cyclosporine; ketoconazole, itraconazole, voriconazole, or posaconazole; and dronedarone produced no effect. The authors suggested that among patients taking NOACs for AF, concurrent use of amiodarone, fluconazole, rifampin, and phenytoin was associated with increased risk of major bleeding. (*JAMA* 2017;318:1250-1259)

Rivaroxaban Plus Aspirin for Secondary Prevention

Which is best for patients with stable cardiovascular disease: aspirin, rivaroxaban, or both? The combination may be more beneficial for secondary prevention — but could carry an increased bleeding risk, according to a new study. Researchers randomized more than 27,000 patients with stable atherosclerotic vascular disease to rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg daily), rivaroxaban alone, or aspirin alone with the primary outcome a composite of cardiovascular death, stroke, or myocardial infarction (secondary prevention). The study was ended early (after 23 months) when researchers noted the superiority of rivaroxaban plus aspirin. The primary outcome occurred less frequently in the rivaroxaban-plus-aspirin group compared to the aspirin alone group (4.1% vs. 5.4%; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66-0.86; $P < 0.001$), but major bleeding was more common in the combination group (3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40-2.05; $P < 0.001$). There was no significant difference in intracranial or fatal bleeding between these two groups. The death rate was lower in the rivaroxaban plus aspirin group (3.4% vs. 4.1%; HR, 0.82; 95% CI, 0.71-0.96; $P = 0.01$; threshold P value for significance, 0.0025). Rivaroxaban alone was no better than aspirin alone but was associated with more major bleeding events. The authors concluded that among patients with stable cardiovascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin experienced better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban alone was no better than aspirin. (*N Engl J Med* 2017; 377:1319-1330)

FDA Actions

The FDA has approved the second herpes zoster vaccine for adults ≥ 50 years of age. The new vaccine is delivered in two intramuscular doses, with the second dose between two and six months following the first. The vaccine is a non-live, recombinant subunit vaccine that has shown 90% efficacy across all age groups in the prevention of shingles. Approval was based on safety and efficacy trials of more than 38,000 adults, which showed 90% efficacy over a four-year follow-up. The vaccine also reduced the overall incidence of postherpetic neuralgia. The new vaccine is marketed as Shingrix. On Oct. 25, the CDC's Advisory Committee on Immunization Practices voted to recommend the new vaccine for those ≥ 50 years of age. The other shingles vaccine, Zostavax, is recommended only for those > 60 years of age. However, the committee, on a close vote, agreed to recommend Shingrix over Zostavax for all age groups. The committee also recommended Shingrix for patients who have received Zostavax already — as long as there was a minimum of eight weeks between vaccines.

The FDA has approved the second gene therapy for cancer, this time for the treatment of adults with certain types of large B-cell lymphoma who have failed or relapsed after at least two other types of therapy. Axicabtagene ciloleucel is a chimeric antigen receptor T-cell therapy in which the patient's T cells are extracted and genetically modified to include a new gene that targets and kills the lymphoma cells once reinfused into the patient. Safety and efficacy were shown in a trial of more than 100 adults with refractory or relapsed large B-cell lymphoma. The complete remission rate with the new treatment was 51%. The drug also is approved for the treatment of primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma. Axicabtagene ciloleucel is marketed as Yescarta, with an announced price of $373,000 per patient.

To curb health fraud, the FDA is issuing warning letters to four companies marketing cannabidiol (CBD, a component of marijuana) who claim their product treats or cures serious diseases, especially cancer. CBD is not FDA approved in any drug product for any indication. It is marketed as oil drops, capsules, syrups, teas, topical lotions, and creams. Along with claims that CBD prevents, reverses, and cures cancer, there also are claims that the drug treats Alzheimer's disease and other chronic conditions. Recipients of the warning letters were Greenroads Health, Natural Alchemist, That's Natural! Marketing & Consulting, and Stanley Brothers Social Enterprises, LLC, makers of more than 25 products that claim to "combat tumor and cancer cells," "make cancer cells commit suicide without killing other cells," prevent cancer cells from growing, and treating breast cancer. CBD is promoted as a "non-psychoactive cannabinoid." ■

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