PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Statins Cause Cognitive Changes? Not So Fast

In this issue: Statins and changes in cognition; fluoroquinolones and retinal detachment; diabetic nephropathy and ACEIs/ARBs; tamsulosin and hypotension risk; and FDA actions.

Statins and changes in cognition

Do statins cause changes in cognition? The FDA required new labeling in 2012 regarding the risk of reversible cognitive changes with statins. But a new study suggests that statins are no worse than other commonly used drugs when it comes to cognitive changes. Researchers reviewed 27 studies in a meta-analysis of statins and cognitive function. They found that among statin users, low-quality evidence suggested no increased incidence of Alzheimer's disease and no difference in cognitive performance related to procedural memory, attention, or motor speed. Moderate-quality evidence suggested no increased incidence of dementia or mild cognitive impairment or any change in cognitive performance related to global cognitive performance scores, executive function, declarative memory, processing speed, or visuoperception. They also reviewed FDA postmarketing surveillance databases and found that the rate of cognitive-related adverse events reported with statins was similar to the rates seen with other commonly prescribed medications such as losartan or clopidogrel. They conclude that better studies are needed to draw unequivocal conclusions about the effects of statins on cognition, but current published data do not suggest an adverse effect, although the strength of evidence is limited (*Ann Intern Med* 2013;159:688-697). It is doubtful the FDA will change required labeling based on this study, but it may be reassuring for the millions of patients who take statins daily. ■

Fluoroquinolones and retinal detachment

Fluoroquinolones such as ciprofloxacin, levofloxacin, and moxifloxacin have been associated with retinal detachment since the publication of the large, case-control study in 2012. A new study challenges that finding, suggesting fluoroquinolones do not increase the risk of retinal detachment. The new study was a nationwide, register-based cohort from Denmark from 1997-2011 that included nearly 750,000 episodes of fluoroquinolone use, the majority of which was ciprofloxacin. The study looked at recent and past use of the drugs up to 180 days prior. They found that "fluoroquinolone use was not associated with an increased risk of retinal detachment." This included current users, recent users (past month), or past users of the drugs (up to 6 months). Almost 90% of the participants in the study used ciprofloxacin, so the results are primarily applicable to that drug (*JAMA* 2013;310:2184-2190). ■

Diabetic nephropathy and ACEIs/ARBs

Patients with diabetic nephropathy do not benefit and may be harmed by dual angiotensin converting-enzyme inhibitor (ACEI)/angiotensin-receptor blocker (ARB) therapy, according to new research. In a Veterans Affairs' study, 1448 patients with type 2 diabetes and albuminuria were randomized to losartan 100 mg per day or

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losartan plus lisinopril (10 to 40 mg per day). The primary endpoints were decline in glomerular filtration rate, end-stage renal disease, or death. The study was stopped early after a median follow-up of 2.2 years when it was found that the dual therapy group had a rate of acute kidney injury that was 1.7 times higher than the monotherapy group (12.2 vs 6.7 events per 100 person years, $P < 0.001$). Combination therapy also significantly increased the risk of hyperkalemia. The authors conclude that "the use of combination therapy with an ACE inhibitor and an ARB in patients with proteinuric diabetic kidney disease does not provide an overall clinical benefit" (*N Engl J Med* 2013;369:1892-1903). In an editorial titled, "The End of Dual Therapy with Renin-Angiotensin-Aldosterone System Blockage?" Dr. de Zeeuw states that "dual RAAS blockade for the treatment of patients with diabetes cannot currently be recommended" (*N Engl J Med* 2013;369:1960-1962). ■

Tamsulosin and hypotension risk

Despite being a "selective" alpha blocker, tamsulosin (Flomax) carries a significant risk of severe hypotension in middle-aged and older men being treated for benign prostatic hyperplasia (BPH), according to a new study. Data were reviewed from the IMS Lifelink database of the records of nearly 400,000 new users of either tamsulosin or a 5-alpha reductase inhibitor (finasteride [Proscar] or dutasteride [Avodart]) used as comparators. Severe hypotension requiring admission to the hospital was higher with tamsulosin (42.4 events/10,000 person years) vs 5ARIs (31.3/10,000 person years). The rate was much higher within the first 8 weeks of initiation of tamsulosin or for 8 weeks if the drug was stopped and then restarted. The authors suggest that patients should be warned about the alpha blocker "first-dose phenomenon" with tamsulosin. The authors also point out that the selective alpha blockers doxazosin, prazosin, and terazosin all have black box warnings regarding severe hypotension and syncope whereas tamsulosin only has a standard warning regarding hypotension (*BMJ* 2013;347:f6320). ■

FDA actions

The FDA has approved two new drugs for the treatment of chronic hepatitis C virus infections. Simeprevir was given the green light in late November and sofosbuvir was approved 2 weeks later. Simeprevir is a protease inhibitor similar to currently available protease inhibitors (boceprevir and telaprevir) and is indicated for adults, in combination with peginterferon-alpha and ribavirin, for adults with compensated liver disease, including cirrhosis, who have not received previous treatment or for whom previous treatment has not been effective. In both groups, about 80% achieved sustained virological reponse. Simeprevir is marketed by Janssen Pharmaceuticals as Olysio. Sofosbuvir is a nucleotide analog inhibitor, a new class of anti-hepatitis C drugs. It was approved with the "breakthrough therapy" designation. It is the first drug to be approved for use without interferon for certain hepatitis C infections, although it should be used with ribavirin and interferon for most indications, including all three common genotypes. Sofosbuvir is marketed by Gilead Pharmaceuticals as Sovaldi.

The FDA has approved obinutuzumab for use in combination with chlorambucil for the treatment of chronic lymphocytic leukemia (CLL) in previously untreated patients. The drug is the first agent to be approved under the FDA's new "breakthrough therapy" designation — an expedited approval process for drugs that treat serious or life-threatening conditions that may be granted if the drug potentially offers substantial improvement over available therapies. Obinutuzumab's approval was based on a study of 356 patients in an open-label trial of the drug plus chlorambucil vs chlorambucil alone, which showed that the two drugs resulted in progression-free survival of 23 months vs 11.1 months for the single agent. Obinutuzumab is marketed by Genentech as Gazyva.

The FDA has approved generic rabeprazole (Aciphex). This is the fourth generic proton pump inhibitor (PPI) to be approved following omeprazole (Prilosec), omeprazole/sodium bicarbonate (Zegerid), pantoprazole (Protonix), and lansoprazole (Prevacid). Generic rabeprazole is indicated to treat gastroesophageal reflux in adults and adolescents aged 12 years and older. Like the branded version, generic rabeprazole is provided in a 20 mg delayed-release version that is dosed once daily. Five generic manufacturers have received FDA approval to market the drug. ■