DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

Antihypertensives and Dementia

Diabetes mellitus (DM) is an important risk factor for dementia; so is hypertension (HTN). Research has shown that 60% to 80% of patients with DM may also have HTN. Managing high blood pressure (BP) in patients with diabetes should help—but which antihypertensive is the right one? Guidelines have differed in their recommendations.

The researchers from the University of Houston, Houston, Texas; Baylor College of Medicine, Houston, Texas; Veterans Affairs Medical Center, Houston, Texas; the University of Texas Health Science Center, Memorial Hermann Hospital, Houston, Texas; and the South Central VA Mental Illness Research, Education and Clinical Center (MIRECC), Houston, Texas, conducted a study to test for an association between HTN and antihypertensive medications and the risk of dementia in elderly patients with DM. Using VA records of patients diagnosed with DM, the researchers analyzed data from 377,838 patients.

During the 2-year follow-up, 14,580 patients (4%) developed dementia. The incidence of dementia increased from 2.4% in the group aged 65 to 75 years to 8.3% in the group aged > 85 years. Patients aged 75 to 85 years had more than double the risk of dementia compared with patients aged 65 to 75 years. People aged > 85 years had more than triple the risk. About 82% of the patients also had HTN, which was significantly associated with dementia. Increasing years with DM and higher comorbidity were each associated with a higher incidence of dementia. A 1-unit increase in the comorbidity score was associated with a 36% higher risk of dementia.

Angiotensin receptor blockers (ARBs) offered the most protection against dementia: about a 24% lower risk. By comparison, the risk was 14% with diuretics, 11% with angiotensin-converting enzyme (ACE) inhibitors, 7% with calcium channel blockers (CCBs), and 4% with β-blockers. Patients taking statins, oral hypoglycemics, and digitalis had a lower incidence of dementia than did patients who were not taking those medications. Patients taking insulin and nonopioid analgesics had a higher incidence of dementia compared with those not taking those medications.

In the subgroup of patients without HTN, the researchers found that only ACE inhibitors and ARBs were protective for dementia. The findings, they say, might reflect that both of those drug types act on the renin-angiotensin system. They point to other research that showed patients with albuminuria treated with ACE inhibitors or ARBs had lower odds of cognitive decline, although the results were not always statistically significant. The researchers suggest that those drugs may have a protective effect against dementia apart from the antihypertensive effects.

Source: Johnson ML, Parikh N, Kunik ME, et al. *Alzheimers Dement.* 2012;8(5):437-444. doi: 10.1016/j.jalz.2011.05.2414.

New Option for Irritable Bowel Treatment

With the recent approval of once-a-day linaclotide for adults with chronic idiopathic constipation and IBS with constipation (IBS-C), patients have another alternative in treatment.

In 2 double-blind, multicenter clinical trials, 1,605 patients with IBS-C were randomly assigned to take 290 µg of linaclotide or placebo for up to 26 weeks. The 2 trials were identical for the first 12 weeks; thereafter, Trial 1 included a 4-week, randomized withdrawal period, and Trial 2 continued for 14 more weeks of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take other types of laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation.

Linaclotide was more effective in reducing abdominal pain and increasing the number of complete spontaneous bowel movements (CSBMs). Improvements began to show in the first week; maximum effects were seen at weeks 6 to 9 and maintained throughout the study. One endpoint for responders was to have at least a 30% reduction in mean abdominal pain from baseline and an increase of at least 1 CSBM per week, for at least 6 of 12 weeks. Roughly half of patients taking linaclotide met that endpoint, versus about one-third of patients taking placebo.

In 2 other multicenter studies of patients with chronic idiopathic constipation, 1,272 patients were randomly assigned to linaclotide 145 µg, 290 µg, or placebo for 12 weeks. Again, patients on linaclotide had more CSBMs compared with patients on placebo (20% vs 3% in the first trial and 16% vs 6% in the second). (The higher dose of linaclotide was not approved because the studies indicated it was no more effective than the lower dose.)

Diarrhea, sometimes severe, was the most common adverse effect. Five percent of patients taking linaclotide stopped treatment due to diarrhea

compared with 1% of patients taking placebo. The majority of diarrhea cases were reported within the first 2 weeks of treatment. Patients should be counseled to stop taking linaclotide and get medical help immediately if they have severe diarrhea or unusual or severe abdominal pain.

Source: U.S. Food and Drug Administration. FDA approves Linzess to treat certain cases of irritable bowel syndrome and constipation [news release]. U.S. Food and Drug Administration website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317505.htm. Updated August 30, 2012. Accessed October 18, 2012.

Linzess [package insert]. St. Louis, MO: Forest Laboratories, Inc; 2012.

When Does Niacin Work Best?

Extended-release (ER) niacin is popular in clinical use, but it might not be doing the job it is expected to do. Researchers from the University of Pennsylvania, Philadelphia, Pennsylvania; Einstein Medical Center, Philadelphia, Pennsylvania; and York Hospital, York, Pennsylvania, suggest that, when taken before bedtime, ER niacin runs out of steam before it is needed—that is, to suppress triglycerides (TGs) after the next meal, normally breakfast. They conducted a study to find out whether changing the dosing time would make a difference.

In the study, 22 healthy volunteers took 2 g ER niacin or matching placebo after a 12-hour overnight fast. After 1 hour they drank heavy cream. The researchers sampled blood hourly for 12 hours. Subjects crossed to alternative treatment after at least 1 week.

Extended-release niacin reduced postprandial TG by 33% compared with placebo. This is in contrast to earlier research that found ER niacin failed to suppress postprandial TGs when dosed the night before a fat meal.

The findings underscore their hypothesis that the recommended dosing strategy for ER niacin misses the mark, the researchers believe. They suggest that niacin has an acute pharmacodynamic effect, and bedtime dosing may have an "opportunity cost," in that the rapid decrease in free fatty acid is long gone by the next meal. Further, they point out that bedtime dosing risks the patient's having breakfast during the free fatty acid rebound, which interferes with the benefit. Indeed, the researchers note, bedtime dosing boosts fasting free fatty acids "well into the next morning," which may promote very low density lipoprotein production and undermine TG suppression.

African Americans did not respond to the niacin—the researchers say this is the first study to demonstrate significant inefficacy of ER niacin in African Americans. They note that that population has lower fasting TGs and postprandial TGs; moreover, their study subjects were healthy and fit.

One reason for prescribing bedtime dosing of ER niacin is to "time the disagreeable dermal response with sleep," the researchers acknowledge. They propose, however, that after developing tolerance to the latter, bedtime dosing is neither obligatory nor advantageous.

Source: Usman MH, Qamar A, Gadi R, et al. *Am J Med.* 2012;125(10):1026-1035. doi: 10.1016/j.amjmed.2012.03.017.

Lead Poisoning From Ayurvedic Treatment

High levels of lead in their patient's blood puzzled doctors until they discovered that the patient had been taking daily Ayurvedic therapy for diabetes.

The patient, a 56-year-old man, was admitted to the emergency department at Winthrop University Hospital in Mineola, New York, with diffuse abdominal pain—which he had had for 3 months—reduced oral intake, and constipation. His hemoglobin had dropped to 9.7 g/dL from a baseline of 14 g/dL a year earlier. Serum iron, transferrin, haptoglobin, vitamin B_{12}, and folic acid were within normal limits, other laboratory and examination results were unremarkable. However, a peripheral blood smear showed prominent basophilic stippling within the erythrocytes. That alerted the clinicians to measure the blood lead level, which was markedly high, as were urine porphyrins. After emergency chelating, the patient was discharged with oral succimer for 2 weeks.

Ayurvedic formulations often contain large quantities of heavy metals, according to case reports. It is possible, the authors note, that the minerals are added intentionally after the formulations have been "detoxified." When they sent their patient's Ayurvedic powder for chemical analysis, they learned the lead content was 62% by weight. In Ayurvedic medicine, lead is considered an aphrodisiac, the authors say. Their patient may have been taking it to counter the impotence associated with diabetes.

Lead toxicity from Ayurvedic medicine used for diabetes has rarely been reported. Still, their case underlines the need to specifically ask patients whether they're taking complementary or unconventional treatments, since patients may not offer the information on their own.

Among the many dangerous complications from lead poisoning is encephalopathy. This case highlights the value of basophilic stippling as a red flag, the authors say.

Source: Desai A, Staszewski H. *Am J Med.* 2012;125(10):e3-e4. doi. 10.1016/j.amjmed.2012.04.002.