Recent Advances in Alzheimer’s Research Precede Annual Conference

Practitioners and scientists from around the world will converge this month in Washington, DC at the Alzheimer’s Association presents the first International Conference on Prevention of Dementia: Early Diagnosis and Intervention. Judging by the recent flurry of news stories about this condition, they’ll have a lot to talk about.

One of the most conversation-worthy ideas is the possibility of reviving beta-amyloid 1-42 as a vaccination for AD, an idea that was all but abandoned after a clinical trial was halted in 2002. According to data recently published in Neurology 2005;64:1553-1562, almost 20 percent of patients in the interrupted trial’s experimental group developed antibodies to beta-amyloid proteins during the one-year follow-up. MRI scans also revealed these immune responders had a decrease in brain volume, which researchers attributed to a reduction in plaque build-up, and performed slightly better on memory tests. However, this experimental treatment was halted due to reports of meningoencephalitis in six percent of subjects, especially since this condition occurred in those patients with higher levels of beta-amyloid antibodies.

Another experimental procedure, this one involving gene therapy, also shows promise. A Phase I study reported in Nature Medicine’s April 24, 2005 online edition found that, of eight patients in the early stages of AD who had nerve growth factor surgically implanted, one started to show new brain tissue growth. While this won’t cure AD, it may prove invaluable as a technique to delay the course for this and other progressive conditions if it proves feasible in future studies. Although the benefits may be elusive, no long-term adverse effects were reported at the 22-month follow-up.

Whatever course of action future research yields, making the decision to implement a preventive therapy will of necessity require first determining whether or not the patient is competent to make the choice, which certainly may not be easy. In Neurology 2005; 64:1494-1495, 1515-1519, psychiatrists at the University of Pennsylvania gauged the competence of 48 adults with very mild to moderate AD and found that only 40 percent made what were judged to be competent decisions on a hypothetical treatment based on the information they were given about its potential benefits and risks. These results tended to correlate with the patients’ MMSE scores, with those scoring 23 or higher far more likely to make a competent choice, while those below 19 were not.

These timely topics, along with the conference’s presentations on recent research on biomarkers, neuroimaging and lifestyle risk factors related to AD, will likely make for some interesting conversations at the Alzheimer’s Association meeting.

Aura of Believability. Those who suspect migraine and stroke are linked may have more support for this popular contention. Results reported in Neurology 2005;64:1573-1577 found that of the 12,740 subjects in the Atherosclerosis Risk in Communities Study, those with a history of migraine with aura were strongly associated with stroke symptoms (OR 5.46), TIA symptoms (OR 4.28), and verified ischemic stroke events (OR 2.81). The researchers said this could mean migraine with aura has an underlying physiology of blood flow that increases the risk of cerebrovascular incidents.

Crestor Caveat. Although statins are constantly getting attention because of their potential protective properties, one may confer more risks than its competitors. A study published in the June 14, 2005 online edition of Circulation found that patients taking rosuvastatin (Crestor) are eight times more likely to develop rhabdomyolysis, nephropathy, renal failure or proteinuria than those on pravastatin (Pravachol) and 6.5 times more likely than those taking atorvastatin (Lipitor). Crestor’s manufacturer, AstraZeneca, said it disagrees with the results of the study.

Ergot Monotherapy Isn’t Enough. Though sometimes considered an alternative to triptans for headache management, recent research suggests the ergot compound dihydroergotamine may not be an effective monotherapy for acute migraine. A systematic review found that this treatment did not represent a significant benefit over other options; also, patients on dihydroergotamine experienced nausea almost four times as often as those on other therapies. However, when combined with an antiemetic it was comparable to or (Continued on page 6)
Drug Approval and Post-Marketing Processes Now Under Increased Scrutiny

The standards for drug approval have endured a great deal of criticism of late, after the Bextra and Vioxx debacles left some wondering how objective the supporting data really were. Now, amid this environment of increased scrutiny, some observers are speculating that the pharmaceutical companies who sponsor clinical trials may wield too much influence in the research process.

In NEJM 2005;352:2202-2210, Michelle M. Mello, JD of the Harvard School of Public Health reported results of a survey showing 50 percent of academic research centers would allow a trial's sponsor to limit the investigators' role in making suggestions to the manuscript draft, 24 percent of schools would allow industry sponsors to insert their own statistical analysis into manuscripts, and 41 percent would allow sponsors to bar investigators from sharing data with third parties after the trial was over.

In her paper, Ms. Mello wrote this could lead some clinical trial sponsors could “forum shop” and conduct their studies in institutions that gave them control over the results.

Post-market research studies have also come under fire, particularly those that receive fast-track approval, as the promising but controversial new MS treatment Tysabri recently did. The FDA has been criticized by Senator Edward Markey (D-MA) for not collecting data from follow-up efficacy and safety studies on treatments that were brought quickly to the market. In many cases, the pharmaceutical companies did not follow up on the research, yet the FDA has never withdrawn approval. For example, AstraZeneca’s lung cancer drug gefitinib (Iressa) received an accelerated review but a later study found that patients on the medication did not live any longer than those who were not. Sen. Markey proposed new legislation that would require companies to inform patients when a treatment has received accelerated approval, require the companies to distinguish the difference on the product’s label, and have the FDA impose penalties on companies that do not conduct the studies with due diligence.

The FDA has publicly admitted there is a problem with its system. John Jenkins, MD, head of the FDA’s Office of New Drugs, said in a statement that the agency was working to improve its tracking system. Jeff Trehwitt, spokesman for the industry group Pharmaceutical Research and Manufacturers of America, says that three percent of all pharmaceuticals approved by the FDA were withdrawn before fast-tracking, and this ratio has not changed after fast-tracking. “The system works well, and the FDA is already pursuing some modest improvements,” he says. PN

**SHORT TAKES**

(Continued from page 5)

**B**etter than meperidine, valproate or ketorolac for pain, nausea and relapse outcomes. (Ann Emerg Med 2005;45:393-401)

**L**evel-Headed Approach. The conventional wisdom of elevating a stroke patient's head 30 degrees may do more harm than good. Researchers at the University of Texas at Houston used TCD to assess 20 patients with acute ischemic stroke with their heads held at various levels. They found that lowering the head-of-the-bed from 30 to 15 degrees, and then to 0 degrees, increased blood flow velocity in all patients. On average, a 20 percent increase occurred most while the head was lowered to 15 degrees. Three patients also showed an immediate improvement in neurologic function after their heads were lowered. (Neurology 2005;64:1354-1357)

**D**isheartening. A last-resort MS drug given to the most severe cases now has a new warning on its label, courtesy of the FDA. In May, the agency warned patients of possible heart damage from mitoxantrone after post-marketing reports linked it to diminished cardiac function early in the course of treatment. The new label also includes information about an elevated risk of developing leukemia while receiving the treatment. (Arch Neurol 2005;62:554-560, 533-536)

**B**rand New Brand Name. The popular Alzheimer’s medication galantamine hydrobromide now has a new brand name and dosing regimen. Originally released in 2001 under the name Reminyl, this cholinesterase inhibitor now goes by the name Razadyne ER. The new formulation contains twice the dose of Reminyl but only needs to be administered once daily and had an adverse effect profile similar to its predecessor in clinical trials, according to the manufacturer.