Data Help Prioritize Drugs for Treating Epilepsy

BY ELIZABETH MECHCATIE
Senior Writer

The results of two large British trials that followed epilepsy patients for several years indicate that lamotrigine should be the drug of first choice for people with partial epilepsy and that valproate should be the drug of first choice for people with generalized and unclassifiable epilepsy, investigators reported.

The two Standard and New Antiepileptic Drugs (SANAD) studies were unblinded, randomized, controlled studies conducted in hospital-based outpatient clinics in the United Kingdom.

One study compared the established epilepsy drug carbamazepine with gabapentin, lamotrigine, oxcarbazepine, and topiramate in 1,721 patients with at least two clinically definite, unprovoked epileptic seizures in the previous year. The study included newly diagnosed patients, those who had failed monotherapy and those who had gone into remission but relapsed after treatment was stopped. Their mean age was 38-40 years, and they were followed for up to 6 years, wrote Dr. Anthony G. Marson of the University of Liverpool (England) and his associates.

Patients taking lamotrigine had significantly longer time to treatment failure for any reason (inadequate seizure control or unacceptable adverse events) than did those taking the standard treatment carbamazepine and the newer drugs gabapentin and topiramate, the authors reported. Lamotrigine had an advantage over oxcarbazepine, but it was not significant.

For time elapsed before achieving 12 months of remission, carbamazepine was significantly better than gabapentin. Their analyses suggested there was a nonsignificant advantage for carbamazepine over lamotrigine, topiramate, and oxcarbazepine for this end point. Lamotrigine, they noted, was considered "noninferior" to carbamazepine for 12-month remission from seizures, they added.

Two British trials point to lamotrigine for patients with partial epilepsy and valproate for those with generalized and unclassifiable epilepsy.

"Although there might be circumstances where other drugs are preferred (consideration of teratogenicity, bone health, drug interactions), the better tolerability seen in lamotrigine than carbamazepine, with noninferiority of longer-term efficacy outcomes, lends support to lamotrigine as first-choice treatment for most patients with partial epilepsy," the authors concluded (Lancet 2007;369:1000-15).

The second SANAD study enrolled 716 patients (mean age 22 years) with generalized onset seizures and seizures that were difficult to classify. Valproate, which the authors said is considered the standard treatment for these patients, was compared with lamotrigine or topiramate for up to 7 years.

Valproate was significantly more effective than topiramate for time to treatment failure, and significantly more effective than lamotrigine for 12-months remission. Based on these results, they concluded that valproate "should remain the first-line treatment for most patients with an idiopathic generalised epilepsy or seizures that are difficult to classify." But, they added, "there will always be some individual circumstances that would favour the choice of an alternative drug," such as family planning or drug interactions (Lancet 2007;369:1016-26).

In an accompanying editorial, Dr. Jacqueline French of the department of neurology, University of Pennsylvania, Philadelphia, said that the SANAD studies overcame many of the methodologic problems that have affected studies directly comparing newer antiepileptic drugs such as lamotrigine, topiramate, or levetiracetam with older drugs like carbamazepine or phenytoin. These studies "almost always" conclude that the newer drug is as effective but better tolerated than the older drug, she said (Lancet 2007;369:970-1).

The SANAD studies also are timely because many new drugs have been introduced over the past few decades, she added.

But she said that the question of whether it is possible to identify a drug as the treatment of first choice for patients with epilepsy remained.

Another concern she expressed was that designating a drug as first choice "may reduce the likelihood that a physician will make an effort to match the drug to the patient." An individualized approach would consider features of a drug that may not be addressed in trials like the SANAD studies, she said, citing as an example lamotrigine's side effect of insomnia, which may not make it the ideal choice for a patient with a sleep disorder.

"Simple is good, but overly simplistic may not provide the optimum benefit to our patients," Dr. French said.

"It might be wiser to conclude from SANAD that lamotrigine is the drug of first choice in patients with partial seizures, and valproate for patients with generalised or unclassified seizures in the absence of factors that would lead to an alternative choice." ■

Risk Score That Predicts Future Dementia Diagnosis Is Validated

BY JAMES BUTCHER
Contributing Writer

SALZBURG, AUSTRIA — A risk score that predicts the likelihood of a middle-aged person developing dementia within 20 years has been independently validated in an ethnically diverse population, according to data presented at an international conference on Alzheimer's and Parkinson's diseases.

The Cardiovascular Risk Factors, Aging and Dementia (CAIDE) risk score originally was created using data from the CAIDE study, a population-based study of 1,409 individuals in a Finnish population in the 1970s (mean age 50.4 years). When the Finnish subjects were reexamined in 1998, 61 of the subjects were diagnosed with dementia.

Study participants with dementia were found to be older at the midlife examination (mean age 53.4 years vs. mean 50.2 years) and less well educated (6.7 years of formal education vs. 8.7 years), and they had more vascular risk factors—such as high blood pressure, high total cholesterol, and high body mass index, as well as a history of smoking—present at midlife than did participants without dementia.

Dr. Miia Kivipelto of the Aging Research Center at the Karolinska Institute, Stockholm, used the data from the CAIDE study to create a score that could predict the risk of developing dementia in later life.

The CAIDE dementia score uses age, years of formal education, sex, systolic blood pressure, total cholesterol, body mass index, and physical activity to determine an individual's likelihood of developing dementia within 20 years. The risk of dementia was found to be 1% for those with a score of 0-5; 1.9% for a score of 6-7; 4.2% for a score of 8-9; 7.4% for a score of 10-11; and 16.4% for a score of 12-15 (Lancet Neurol. 2006;5:735-41).

"When the cutoff was set at 9 points or more, the sensitivity was 0.77, the specificity was 0.63, and the negative predictive value was 0.98," said Dr. Kivipelto at the conference.

Rachel Whitmer, Ph.D., an epidemiologist working at the Kaiser Permanente Division of Research, Oakland, Calif., validated the CAIDE dementia risk score in a sample of 9,480 long-term members of Kaiser Permanente's integrated health care delivery system, of whom 1,011 developed Alzheimer's disease or vascular dementia. The study sample was ethnically diverse (474 Asian, 1,401 black, and 7,605 white), and included people from a wide demographic range.

In addition, Dr. Whitmer added more variables to the score, including obesity, smoking, pulmonary function, and depression, but found that these did not improve the score's predictive value.

However, the addition of diabetes as a variable improved the predictability of the score for Asian patients, but not for black or white study patients.

"It seems like we're really onto something here," said Dr. Whitmer.

"It replicated really well and is so predictive in such a different population." ■

Eradication of H. pylori *Modifies Idiopathic Parkinsonism Syndrome*

SALZBURG, AUSTRIA — Eradication of *Helicobacter pylori* in patients with idiopathic parkinsonism modified the syndrome but did not arrest it, according to interim results from a randomized controlled trial presented at an international conference on Alzheimer's and Parkinson's Diseases.

Dr. Sylvia Dobbs presented an interim analysis of a 5-year trial of 30 patients with early disease who were either not on medication or were taking stable, long half-life antiparkinsonism medication. Patients using levodopa were excluded.

All the participants had biopsy-proven *H. pylori* infection. The researchers randomly and blindly assigned the patients to 1 week of triple therapy to eradicate *H. pylori* infection or placebo. The antimicrobials used in eradication were chosen according to in vitro sensitivity tests.

Unblinding occurred at 1 year or if the disease had progressed quickly and the researchers thought the patient's lifestyle was unsustainable. Patients on placebo who were breath-test positive at 1 year were given active treatment.

Dr. Dobbs of the Institute of Psychiatry, King's College London, reported follow-up to a mean of 468 days after unblinding. The primary outcome measure was time trend in mean stride length at free-walking speed.

"If you use global scores, which are very insensitive, you require huge numbers of patients," Dr. Dobbs said in an interview. "If you objectively measure the outcome criteria, you require small numbers. If you do time trends in the outcome criteria, you require even smaller numbers."

Protocol analysis on the primary outcome showed a clinically relevant effect in favor of biopsy-proven successful, blinded active eradication over placebo (7.3 cm/yr increase in mean stride length [95% confidence interval 1.4,13.2], P less than .01). The presence or absence of antiparkinsonism medication did not affect the results, she said.

Patients in the placebo group who received treatment to eradicate their *H. pylori* infection unblinding also improved in the primary outcome measure (9.5 cm/yr increase in mean stride length [95% confidence interval 1.2, 20.1], $P = .04$).

"We have some prima facie evidence pointing to a direct or surrogate but not necessarily unique, response to [*H. pylori* eradication]," said Dr. Dobbs. "The effect was sustained in the following year."

—James Butcher