'Wait and See' Not Acceptable

TIAs *from page 1*

Brown University and the Rhode Island Hospital in Providence, R.I. "Those views are incorrect. Stroke and TIA are on a spectrum of serious conditions involving brain ischemia. Both are markers of reduced cerebral blood flow and an increased risk of disability and death. However, TIAs offer an opportunity to initiate treatment that can forestall the onset of permanently disabling injury."

TIAs have in the past been temporally defined as a focal cerebral ischemic event with symptoms lasting less than 24 hours. The new description defines TIA from a tissue-based stance, as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."

The tissue-based description is important, according to the recommendation committee, because distinguishing TIA by a time limit is misleading and can be inaccurate. "Time-based definitions unproductively focus diagnostic attention on the temporal course rather than the underlying pathophysiology. The key diagnostic issue in patients with cerebral ischemic events is not how long the event lasted, but rather the cause of the ischemia and whether cerebral injury occurred." A tissue-based definition also encourages the use of neurodiagnostic tests to identify brain injury and its cause, while the time-based definition encourages a "wait and see" approach, during which further ischemic insult may occur, they added.

Immediate evaluation not only offers the ability to discover the exact extent of any new infarct, but the chance to identify the TIA's cause. Testing should investigate whether there is any intracranial or extracranial vessel disease, and include a cardiac evaluation.

The committee recommended the following diagnostic evaluation, based on the new definition:

► Patients with TIA should undergo neuroimaging within 24 hours of symptom onset, preferably by MRI with diffusion-weighted imaging. If these are not available, computed axial tomography should be performed.

► The evaluation should include noninvasive testing of the cervicocephalic vessels.

► Noninvasive testing of the intracranial vessels is reasonable when the knowledge of transcranial vessel disease would alter management decisions. This may be done by carotid ultrasound/transcranial Doppler, magnetic resonance angiography, or computed tomography angiography.

► An electrocardiogram should be performed as soon as possible, especially in patients in whom the initial workup has shown no immediate cause of the TIA.

► Consider hospitalization of TIA patients if they present within 72 hours of the event with any of the following criteria: $ABCD^2$ score of 3 or higher; $ABCD^2$ score of 0-2 and uncertainty that a diagnostic work-up can be completed within 2 days; $ABCD^2$ score of 0-2 and other evidence that the TIA was caused by focal ischemia.

The statement will appear in the June issue of Stroke (doi:10.1161/STROKEAHA.108.192218).

Members of the writing committee disclosed having conflicts of interest with a number of pharmaceutical and medical device manufacturers. ■

Use of Antiepileptics Linked To Increase in Fracture Risk

BY SUSAN LONDON

SEATTLE — Older adults in the general population have an elevated risk of fractures related to osteoporosis if they take certain antiepileptic drugs, according to a population-based analysis.

"Prior studies have shown that antiepileptic drugs [AEDs] are associated with an increased risk of bone loss and fractures," presenting author Jane McChesney said at the annual meeting of the American Academy of Neurology. "However, population-based data assessing the association between AEDs and osteoporotic-related fractures are scarce."

"This study found that AEDs, except for fatty acid derivatives, are associated with an increased risk of osteoporotic-related fractures in men and women over age 50," Ms. McChesney said. "This is concerning as many of these AEDs are not only used to manage epilepsy, but are also widely used in older adults for the treatment of neuropathic pain, headaches, and psychiatric conditions, to name a few."

Ms. McChesney, a nursing student at the University of Calgary, Alta., and colleagues analyzed population-based data from the province of Manitoba for the years 1996-2004.

Individuals were included if they were at least 50 years of age and had continuous health care coverage during the study period. They were excluded if they had taken osteoprotective medications in the year before a fracture or were residents of long-term care facilities.

Fractures were ascertained from diagnostic codes and were limited to vertebral, wrist, and hip fractures that were not related to severe trauma, according to Ms. McChesney.

Using the fracture date as the index date, each older adult with a fracture was matched with three fracture-free older adults by age, sex, ethnicity, and number of comorbidities.

Use of AEDs, defined as dispensation of a prescription to the individual in the past 4 months, was assessed from a drug database containing virtually all pharmacy dispensations for the province.

Analyses were based on 15,792 older adults who had experienced a fracture and 47,289 older adults who had not, Ms. McChesney reported. Overall, 70% were female, 62% were aged 70 years or older, and 67% had three or more comorbidities.

Fractures most commonly occurred in the wrist (52%), followed by the hip (26%) and vertebrae (22%).

After adjustment for social and demographic characteristics, home care, and comorbidities known to affect fracture risk, older adults had elevated odds of fracture if they used carbamazepine (odds ratio, 1.9), clonazepam (1.3), gabapentin (1.6), phenobarbital (2.2), and phenytoin (2.1). In contrast, their odds were not elevated if they used valproic acid.

It remains unknown if osteoprotective agents are beneficial in this context, she acknowledged, and that would be an important focus of additional research.

Ms. McChesney reported that she had no disclosures to make in relation to the study. ■

Pramipexole Has Antidepressant Effects in Parkinson's Patients

BY SUSAN LONDON

SEATTLE — Pramipexole reduces depressive symptoms in patients with Parkinson's disease, largely independent of its effect on motor symptoms, according to the results of a randomized trial.

An estimated 45% of patients with Parkinson's disease (PD) have a depressive disorder, said Dr. Paolo Barone, a neurologist at the University of Naples "Federico II" in Italy. Evidence suggests that depression is not simply reactive in this population, but occurs independently of motor symptoms and may be related to dysfunction in limbic dopaminergic circuits.

"Generally speaking, there are very few placebo-controlled studies of depression in Parkinson's disease," he noted. "We have several open-label studies showing that dopaminergic agents, pramipexole [Mirapex] in particular, are able to reduce [or] improve depressive symptoms in Parkinson's disease." Pramipexole is approved by the Food and Drug Administration for the treatment of the signs and symptoms of idiopathic Parkinson's disease and moderate-to-severe primary restless legs syndrome.

Patients in the trial were 30 years or older and had idiopathic PD with stable motor function; a score of 5 or greater on the Geriatric Depression Scale score; a score of 2 or greater on part I, question 3 (depression) of the Unified Parkinson's Disease Rating Scale (UPDRS); and a score of 24 or greater on the Mini-Mental State Examination, Dr. Barone reported at the annual meeting of the American Academy of Neurology.

They were allowed to continue on other medications for PD, depression, and comorbidities at constant doses.

In the 12-week study, 152 patients were randomly assigned to placebo and 144 were assigned to pramipexole, with optional titration up to a dose of 1.0 mg three times a day.

Evidence suggests depression is not simply reactive, but occurs independently of motor symptoms and may be related to dysfunction in limbic dopaminergic circuits.

Rates of trial completion were 88% and 86%, respectively.

The patients were 67 years old on average, and 53% were female. The mean duration of PD was 4 years, and 77% of patients had a modified Hoehn and Yahr stage of 2 or 3. Ninety percent were receiving concomitant therapy for their PD.

The baseline total score on the Beck Depression Inventory (BDI) was 19.2 in the placebo group and 18.7 in the pramipexole group, corresponding to moderate depression, he said. By week 12, the respective scores were 15.0 and 13.1. The adjusted mean difference in the change in scores between groups—the trial's primary end point—was 1.9, significantly favoring the active treatment.

Compared with placebo, pramipexole was also associated with significantly greater improvements in Geriatric Depression Scale score (adjusted mean difference, 0.8), UPDRS II score (adjusted mean difference, 1.2), and UPDRS III score (adjusted mean difference, 2.2).

Control of depression and control of PD motor symptoms were only poorly correlated, Dr. Barone reported, with a correlation coefficient between the BDI score and UPDRS III score of 0.088 for placebo-treated patients and 0.215 for pramipexole-treated patients.

In addition, a path analysis showed that 80% of the treatment effect on depressive symptoms was accounted for directly by BDI score, whereas only 20% was accounted for by the indirect effect of UPDRS III score.

Patients in the pramipexole group had higher rates of dizziness (11% vs. 6%, respectively), somnolence (10% vs. 8%), and dyskinesia (7% vs. 3%), Dr. Barone observed. The rate of serious adverse events was 4% in each group.

Establishing an effective treatment for depression could lead to a reduction in the number of medications needed to effectively manage PD symptoms, said Dr. Barone, who reported receiving research support and consulting fees from Boehringer Ingelheim Pharmaceuticals Inc., the manufacturer of Mirapex. ■