Evidence Backs Two Drugs for Epilepsy in Elderly

BY BRUCE JANCIN
Denver Bureau

BRECKENRIDGE, COLO. — Lamotrigine and gabapentin are the newly crowned, evidence-based first-line treatments for new-onset epilepsy arising in the elderly, according to the findings of a major new Veterans Affairs trial.

Both drugs significantly outperformed carbamazepine in VA Cooperative Study 428, a multicenter randomized double-blind clinical trial involving 593 veterans with new-onset seizures after age 60.

Lamotrigine showed a consistent trend for more favorable outcome measures compared with gabapentin, although many of these differences did not achieve statistical significance.

Both newer drugs significantly outperformed carbamazepine, Mark C. Spitz, M.D., reported at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

The study's primary end point was retention in the trial on the assigned drug after 12 months. The rates were 58% for patients randomized to lamotrigine, 49% for gabapentin, and 37% for carbamazepine.

The drugs were roughly equally effective at controlling seizures. Rather, the difference in outcome was due to disparities in tolerability.

Despite the fact that older veterans are a notoriously uncomplaining group that tends to stick with a problematic assigned treatment well beyond the point when others would bail out, more than 27% of the carbamazepine group dropped out of the trial due to intolerable side effects, compared with 17% on gabapentin and 10% on lamotrigine, noted Dr. Spitz, professor of neurology at the University of Colorado, Denver.

Target doses in the study were 150 mg/day of lamotrigine, 1,500 mg/day of gabapentin, and 600 mg/day of carbamazepine. Physicians were permitted to deviate from the standard titration schedules based upon a patient's signs and symptoms in a way that mirrored common clinical practice. This was done in 30% of cases.

There was a nonsignificant trend for less neurologic toxicities with the newer drugs. The significant differences in systemic toxicity involved weight gain and loss, water retention, and hypersensitivity-type skin rashes.

Skin rash occurred in 10% of patients on carbamazepine, 5% on gabapentin, and—to the great surprise of Dr. Spitz and the other investigators—in a mere 2.7% of lamotrigine-treated patients.

Three percent of carbamazepine-treated patients experienced skin rash requiring hospitalization, compared with none of the gabapentin group and 0.5% on lamotrigine. The sole death in the trial occurred in a patient on carbamazepine who developed Stevens-Johnson syndrome with multiorgan failure.

Because lamotrigine carries a black box warning about serious rashes including Stevens-Johnson syndrome, its titration schedule was more protracted than were those of the other agents. Patients started with 25 mg at bedtime for 2 weeks, then 25 mg b.i.d. for 2 weeks, followed by 50 mg b.i.d. for 2 weeks, and then 75 mg b.i.d.

The trial was designed a decade ago, at a time when investigators viewed carbamazepine as the best-proven antiepileptic drug for the elderly. The goal was to learn whether the then-new gabapentin and lamotrigine were clinically advantageous.

Today, phenytoin is the agent most often prescribed for epilepsy in the elderly. Indeed, a recent VA system-wide study showed 80% of veterans with epilepsy diagnoses are on phenytoin, a finding Dr. Spitz finds disconcerting because of the drug's narrow therapeutic range, complex pharmacokinetics, associated accelerated bone loss, and reduced hepatic clearance in the elderly.

The primary results of VA Study 428 will soon be published. The trial—one of the largest ever to focus on new-onset epilepsy in the elderly—includes numerous secondary end points expected to provide follow-up analyses for years to come.

The study has already provided data serving to debunk widespread misconceptions regarding the nature of seizure disorders arising in older people. ■

New-Onset Epilepsy Mimics Dementia in the Elderly

BY MARK BLOOM
Contributing Writer

BOSTON — Epilepsy in the elderly often presents as complex partial seizures that can resemble sudden-onset dementia, A. James Rowan, M.D., said at a meeting on epilepsy in the elderly sponsored by Boston University.

The incidence of new-onset seizures begins to climb when patients are in their 50s after a decline that begins in childhood and reaches a nadir around age 30, said Dr. Rowan, professor of neurology at the Mount Sinai School of Medicine in New York.

By age 60, the incidence of epilepsy reaches 40 new cases per 100,000 per year, Dr. Rowan said, citing data from W. Allen Hauser, M.D., professor of neurology and neuroepidemiology at Columbia University, New York. The incidence begins an almost exponential climb to age 75, when it hits 139 new cases per 100,000 per year, which is higher than the incidence of epilepsy in infants and children up to age 3.

"Epilepsy is, in fact, a disease of the very young and the very old," Dr. Rowan said.

Yet epilepsy in elderly patients is often quite different from that in children, who typically have generalized tonic-clonic seizures. In the elderly, complex partial seizures are the norm.

Dr. Rowan described the case of a 72-year-old woman whose treatable epilepsy was misdiagnosed as worsening dementia. She was about to be sent to a nursing home.

The woman was admitted to the hospital for a dementia evaluation. She reported having "fuzzy" periods. Her past medical history was unremarkable. A CT scan showed atrophy. ECG and lab results were negative. But in a neurologic consult, she said the "fuzzy" periods were intermittent. She kept asking, "What am I doing here?"

The neurologist felt that something did not fit, Dr. Rowan said.

A video EEG revealed a complex partial seizure. In the elderly the postictal state following a complex partial seizure may last up to 2 weeks. When she was treated with phenytoin, the symptoms resolved, and she went home. "It was a remarkable turnaround," he said.

If such patients are recognized as having seizures, they can be treated and may enjoy a vastly improved quality of life. Often, he added, they are misdiagnosed with altered mental status, confusion, dizziness, syncope, memory disturbance, or dementia.

Dr. Rowan noted that 50% of all new-onset seizures occur in patients 60 years or older. Although in younger patients the diagnosis of epilepsy is reserved for those who have had at least two seizures, the diagnosis can be made in the elderly after just one seizure; 90% of elderly patients who have had one seizure will have a second unless they are treated.

Among the other differences between epilepsy in the young and the elderly, he added, is that epilepsy in the elderly, while extremely common, is manifested by a low rate of seizures. Yet in the elderly the postictal state after complex partial seizures tends to be prolonged. The period of confusion can last up to 2 weeks, compared with a minute or so in infants and youngsters. ■

Symptom Scale Proves Superior In Finding Depression, Anxiety

BY DOUG BRUNK
San Diego Bureau

SAN DIEGO — A multisymptom scale identified elderly primary care patients with depression and anxiety symptoms who were missed by the standard 15-item Geriatric Depression Scale, results from a large pilot study have found.

The finding suggests that elderly patients may respond better to less-overt questions about depressive symptoms, Angela Hoth, Pharm.D., said in an interview during a poster session at the annual meeting of the American Association for Geriatric Psychiatry.

Elderly primary care patients are more likely to deny that they have depressive symptoms as defined by the standard 15-item Geriatric Depression Scale.

"We're finding that a lot of people will deny that they have depressive symptoms as defined by the GDS, or they don't associate those particular symptoms with what they're feeling," said Dr. Hoth, a clinical pharmacy specialist with the Iowa City VA Medical Center.

"If we asked them questions about symptoms, like 'How are you feeling physically over time?' and 'How is that affecting your overall quality of life?' we were able to pick up some patients that the standard GDS didn't pick up. We might be able to avoid missing some people in primary care by asking them more about their symptoms and relating that back to depression, rather than asking them the regular DSM-type of symptom questions," she explained.

The instrument used by the investigators is the Elderly Symptom Assessment Scale (ESAS), a measure developed to identify adverse drug events in VA patients. It contains six depression-related items (sadness, concentration, memory, fatigue, sleep, appetite) and three anxiety-related items (anxiety, irritability, and restlessness). Results are reported as a symptom count, with a range of 0-9. The ESAS contains 47 overall symptoms.

For the study, Dr. Hoth and her associates simultaneously administered the GDS and the ESAS to 351 cognitively intact VA outpatients. They categorized patients as depressed or nondepressed based on scores from both scales.

Of the 351 patients, 94 (27%) screened positive for depression by the GDS and 121 (34%) by the ESAS. The ESAS identified 64 depressed patients classified as nondepressed by the GDS. Dr. Hoth considered this the "greatest surprise" of the study.

"The other major finding was that patients who were very somatic had a lot more anxiety as part of their depression," she added. "This is not dissimilar from the medical literature, but in a veteran population that is significant, at least for how we're going to approach treating them, because a lot of them don't want to admit they're depressed. There's still a lot of stigma."

She and her associates plan to implement the scale in a depression clinic they are launching in the primary care division of the Iowa City VA Medical Center. ■