New Drugs, Devices Edge Toward Clinical Use

New antiepileptic drugs in the pipeline may provide enhanced safety, tolerability, or potency.

BY BETSY BATES

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN NEUROLOGICAL ASSOCIATION

SAN DIEGO – Several new antiepileptic drugs and devices aimed at preventing or suppressing seizure have achieved results with better management of side effects than is seen with existing therapeutic agents, according to Dr. Jacqueline A. French.

"You may hear many people saying that we have made no progress whatsoever" in epilepsy therapy, said Dr. French, professor of neurology and codirector of epilepsy research and clinical trials at New York University.

Indeed, about a third of patients were considered "treatment resistant" during the era of bromide therapy for epilepsy, and about the same proportion of patients are considered "treatment resistant" today, Dr. French said at the meeting.

However, she explained that far better management of side effects has been achieved, resulting in better overall management and fewer total seizures in today's patients.

One measure of that success is the increasingly challenging task of finding patients who experience four or more seizures a month, thereby qualifying for clinical trials, Dr. French noted.

In the pipeline today are what she called "evolutionary" drugs – new twists on mechanisms found in existing therapeutic agents that enhance their safety, tolerability, or potency – and "revolutionary" drugs characterized by novel mechanisms.

The following are among the potential options on the horizon for clinical practice.

Evolutionary Drugs

Clobazam, a benzodiazepine widely used in Canada and Europe, was approved by the Food and Drug Administration on Oct. 21 as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in adults and children 2 years of age and older. The drug will be marketed under the trade name Onfi. Dr. French said the agent is believed to produce less tachyphylaxis than others in its class.

Brivaracetam, an analogue of levetiracetam, is hoped to exceed the potency of its predecessor while reducing side effects of irritability and depression. The first study of the agent in a small group of expert sites was "extremely promising," but a second, global trial failed. A third trial is underway, Dr. French said, to clarify results.

Eslicarbazepine is a third-generation version of carbamazepine, "the drug we love to hate," she said. Approved in Europe, this agent has a short half-life and is dosed once daily. Its improved side effect profile is the main draw, especially with regard to body weight, cholesterol, glucose, and hepatic effects.

Revolutionary Drugs

Ezogabine (Potiga), a novel potassium channel blocker, selectively activates the KCNQ channel, resulting in "stabilization of hyperexcitable neuronal cells." In clinical trials in patients with partial-onset seizures, the drug showed "no plateau of efficacy," but adverse events have limited its dosage.

Perampanel is the first drug to be submitted to the FDA based on an excitation mechanism rather than membrane inhibition or stabilization. The drug is a highly selective, noncompetitive, antiglutamate receptor antagonist. "It's pretty close to getting to the clinic," she said at the meeting.

Drugs on the horizon for clinical practice build on existing mechanisms or operate through novel ones.

DR. FRENCH

VX-765 is "something completely different," said Dr. French: an interleukin-converting enzyme inhibitor developed at the behest of researchers based on their hypothesis that modulation of proinflammatory cytokines might play a major role in seizure suppression. One human proof-of-concept trial has been completed, and another trial will be launched soon. As in animal studies, seizures were reduced following a delay period in the initial human study, she said.

Devices

Medtronic's Deep Brain Stimulator, a device currently under FDA review, produces shocks at regular, timed intervals following implantation in the thalamus. "Patients can self-trigger the device if they feel a seizure coming on," she said. In studies of the Deep Brain Stimulator, both actively treated and sham groups had a reduction in seizures early on, but efficacy improved over time in the treated group, and the device is believed by proponents to be most efficacious as long as 2 years after implantation.

NeuroPace's Responsive Neurostimulator system, a "smart" device, countershocks the epileptic focus, and is similarly believed to lead to "better and better and better" seizure control over months of use, Dr. French said.

NeuroVista's Seizure Advisory System is another implantable device, this one acting on a complex algorithm of input from the brain to warn patients in advance of impending seizures. Should a patient receive a signal from the device, he or she might have an hour to prepare for a seizure, reducing safety concerns and heightening patients' sense of empowerment over the disease.

Dr. French is president of the Epilepsy Study Consortium, which receives funding and provides consultation to a large number of pharmaceutical companies, including those represented in her talk. As a nonprofit organization, the Epilepsy Study Consortium's members receive no personal compensation from pharmaceutical companies. ■

Authors Call for Earlier Referral

Seizures *from page 1*

some cases, the patient's next of kin. They asked about the occurrence of simple partial seizures (SPS), seizures with loss of awareness, and antiepileptic drugs taken. Median annual follow-up was 8 years. The researchers defined recurrence of seizures as outcome classification 3 on the outcome scale established by the International League Against Epilepsy.

Complete freedom from seizures or having only SPS was attained by an estimated 82% of patients at 1 year postop, 63% at 2 years, 52% at 5 years, and 47% at 10 years. Forty percent of patients had long-term complete seizure freedom after epilepsy surgery, and 11% had only SPS. No patient had substantial worsening of epilepsy.

Those who experienced SPS in the first 2 years after anterior temporal lobe surgery were 2.4 times more likely to experience subsequent seizures with impaired awareness than were those who experienced no SPS – a finding that has not been previously reported, the investigators said. This information "might affect the decision to taper or continue antiepileptic drugs," the researchers wrote.

But overall, individuals who underwent anterior temporal resection were more likely to be seizure free than were those who underwent resections in other parts of the brain.

Relapse was less likely the longer a person was seizure free. Conversely, remission was less likely the longer seizures continued. In 18 (19%) of 93 people, late remission was associated with introduction of a previously untried antiepileptic drug. Antiepileptic drugs were discontinued at the latest follow-up visit in 104 (28%) of 365 seizure-free individuals.

The researchers called for clinicians to refer appropriate patients sooner for possible surgery. But they also argued that the selection process and surgical methods need to improve because of "over-optimistic expectations" implied in some studies.

The study had several limitations to the assessment of outcomes in people with temporal lobe surgery, including "the small numbers [of patients], that the decision was not randomly assigned, and that patients with extensive disease and lesions close to the hippocampus were more likely to have anterior temporal resection than were other patients."

All but three of the authors disclosed relevant financial conflicts of interest with manufacturers of antiepileptic drugs or devices. ■

VIEW ON THE NEWS

Epilepsy Surgery Validated, but New Questions Raised

This study looks at surgical outcome for 19 years postop, making it the largest and longest prospective study of surgical outcomes for epilepsy. It also is unlike other epilepsy surgery studies in that it prospectively analyzed seizure freedom at successive annual visits in individual patients instead of only at the last follow-up visit.

The investigators found that 70% of patients were seizure free for the last year at any time, but only 51% were completely seizure free throughout the follow-up because each year there was a 3%-15% change within the different groups of patients.

Also, simple partial seizures that occurred within 2 years of surgery were a significant risk factor for the long-term recurrence of seizures. This finding has implications for the decision to discontinue antiepileptic drugs in patients with only simple partial seizures.

This study validates the long-term effectiveness of epilepsy surgery, but it raises important questions and challenges. It makes us wonder if there are equal benefits of being seizure free among patients who have had continuous remission and those who had later remission, as well as if we can improve selection and resection strategies to optimize long-term seizure control.

DR. AHMED-RAMADAN SADEK *of Southampton (United Kingdom) University Hospitals NHS Trust and* PROFESSOR WILLIAM PETER GRAY *of University of Southampton wrote their comments in an editorial accompanying the epilepsy surgery study (Lancet 2011;378:1360-2). They reported having no conflicts of interest.*