# Release Date Remains Uncertain

**Pregabalin** *from page 1*

placed, but the company expects it to be included in a category with lower potential for misuse or abuse.

She told CLINICAL NEUROLOGY NEWS that the company does not know how long the investigation will take nor when the drug will be released. "We're hopeful it will be available by the end of this year," she said in an interview. Once the drug is on the market for adults, Pfizer will begin pediatric studies, Ms. Hamm said.

Dr. Holmes noted that patients who continue to have seizures despite polypharmacy "can be a very difficult group of patients; only about 70% of adults with partial seizures become seizure-free on any of the current medications, so it's very nice to have another we can try, to continue to offer some hope."

A pivotal pregabalin trial included 287 patients at 45 centers worldwide; 51% were on two antiepileptic drugs at baseline, and 30% were on three. Of the patients taking the highest dose of pregabalin, 43% experienced at least a 50% reduction in seizures, compared with those taking placebo (Epilepsia 2004;45:20-7).

For epilepsy, the recommended starting dosage will be 150 mg/day, given in two or three doses. Dosage may be increased to a maximum of 600 mg/day. Dizziness and somnolence are the most common side effects.

Pregabalin also has antianxiolytic properties. In 2004, Pfizer sought approval for an antidepressant indication, which the FDA denied. But its antidepressant action, and the slight feelings of euphoria some patients experience when taking it, may actually be a benefit to some epilepsy patients, Dr. Homes said. "A lot of our patients have comorbid depression, so I would think the drug could also be helpful in that respect," he said.

Pregabalin, an alpha-2-delta ligand, is chemically related to gabapentin (Neurontin), but is more rapidly absorbed, with peak concentrations occurring within 1 hour. Pregabalin has a bioavailability of about 90% irrespective of dosage level. Gabapentin bioavailability decreases from 60% to 30% as the dose increases, according to a paper by Pfizer researchers D. Wesche and H. Bockbrader presented at the 2005 annual meeting of the American Pain Society.

Other researchers are investigating its use in generalized anxiety disorder, school phobia, and pain associated with fibromyalgia. ■

# *Counsel Patients About Epilepsy Surgery's Possible Risks, Benefits*

BY BRUCE JANCIN
*Denver Bureau*

BRECKENRIDGE, COLO. — Recent research findings enable physicians to counsel patients with drug-refractory temporal lobe epilepsy much more effectively about the risks and benefits of resective surgery, Lauren C. Frey, M.D., said at a conference on epilepsy syndromes sponsored by the University of Texas at San Antonio.

"Chronic seizures carry their own risks. If you ignore that, you're really missing the boat in trying to decide whether or not to offer someone epilepsy surgery," said Dr. Frey, a neurologist at the University of Colorado, Denver.

Investigators at the University of Göteborg (Sweden) performed formal neuropsychologic testing in 36 adults with a mean age in their early 30s who had long-time, drug-resistant partial epilepsy and in a healthy control group matched for age, gender, and education level, said Dr. Frey. Cognition at baseline was worse in patients with intractable epilepsy than controls. At follow-up testing 5 years later, patients showed further significant declines in general cognition and verbal memory (Epilepsy Behav. 2004;5:677-86).

Dr. Frey said that probably the best study to date addressing the question of mental decline in patients with uncontrolled epilepsy involved 147 adults with a mean age in their early 30s at baseline with surgically and 102 with medically managed temporal lobe epilepsy evaluated longitudinally at the University of Bonn (Germany).

Neuropsychologic testing conducted at baseline and at 1, 2, and 10 years' follow-up showed progressive cognitive loss, particularly in memory, in those patients with continued seizures despite surgery or medical management. Surgery, whether successful or not, caused cognitive deficits in the short run, but these deficits were often reversed in those patients who became seizure free (Ann. Neurol. 2003;54:425-32). Seizures stop in some patients, who also may regain the deficits caused by surgery. A few patients still have seizures, progressive cognitive loss, and acceleration of the deficits due to surgery, she explained. ■

## IMAGE OF THE MONTH

Magnetoencephalography (MEG) measures magnetic fields that are produced by small electrical currents that arise from neuronal activity in the brain. Through analysis of the spatial distribution of the magnetic fields, MEG enables physicians to localize epilepsy-induced abnormal electrical activity within the brain. This information is then overlaid on a magnetic resonance (MR) image, which provides anatomical detail. Both functional and structural information about the brain is visible in the combined image.

MEG has a number of advantages over other imaging modalities, beginning with its noninvasive nature. "We don't have to inject anything into the patient," unlike some nuclear imaging techniques, said Eduardo M. Castillo, Ph.D., of the University of Texas in Houston. Patients aren't subjected to radiation or strong magnetic fields. Tests can be repeated without safety concerns, making MEG an especially attractive option for children and infants.

While functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), and single-photon emission computed tomography (SPECT) assess brain function indirectly, MEG takes direct measurement of the brain's electrical function in real time.

With its high temporal resolution, MEG can be used to measure events lasting only milliseconds. fMRI, PET, and SPECT have much longer time scales. MEG also has excellent spatial resolution, localizing sources of activity with millimeter precision.

Changes in electrical activity in the brain affect the associated magnetic fields. These changes in the magnetic fields are captured by the MEG machine's array of superconducting detectors and amplifiers, said Dr. Castillo.

The equipment is housed in a specially shielded room to isolate the sensor from external noise produced by vibration and from electrical devices that produce magnetic fields.

In this case, MEG provided two types of information on the location of the abnormal electrical activity (i.e., epileptiform activity) and location of his speech centers, both of which were necessary for planning the boy's epilepsy surgery.

The yellow triangles in the image on the left located the site of interictal epileptiform electrical activity. For measurement of interictal epileptiform activity, the boy was placed in the helmet-shaped sensor, resting with his eyes closed. MEG measurement of interictal epileptiform activity was done in tandem with EEG to zero in on the abnormal activity, said Dr. Castillo.

The second type of information (indicated by red dots in the image on the right) is functional activity, recorded while the child listened to a series of words, to locate language function within the brain. When mapping functional activity, such as the ability to recognize words, the patient is subjected to repetitions of specific stimuli. Brain activity is averaged across all of the repetitions, which filters out any background brain activity that is not related to the task. The language function measurement takes about 30 minutes—long enough to repeat the task twice.

Typically children older than 5 years don't need to be sedated, but younger children do in order to remain still for the duration of the test.

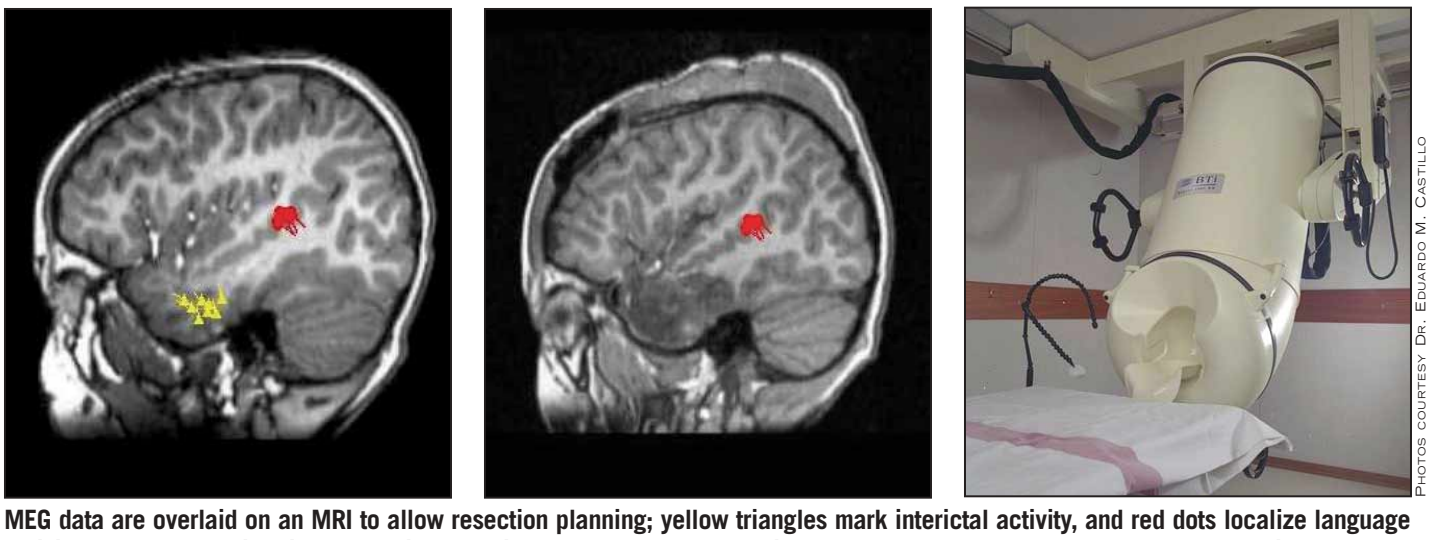
After the MEG-derived map of the epileptogenic zone was intraoperatively confirmed, the area was resected, sparing areas of the eloquent cortex within the dominant hemisphere language-specific cortex. The postsurgery map on the right shows that the boy's language-specific cortex was spared by the surgeon. After surgery his linguistic skills were intact, and he is currently seizure free, said Dr. Castillo. In addition, the boy has regained some of the cognitive abilities he had lost.

MEG also is used currently to map cognitive and sensory functions prior to surgery to remove brain tumors. In addition, the technique is being investigated to track the effect of different interventions following stroke, when the brain reorganizes the location of functions to compensate for the areas lost due to stroke. "We try to track changes in the organization of functions in the brain after stroke and understand how different types of interventions can modulate those changes," said Dr. Castillo.

The group at the University of Texas in Houston is also conducting research into dyslexia and ADHD using MEG. Other groups are using MEG to better understand the progression of Alzheimer's disease.

Currently there are nine facilities in the United States that are using MEG clinically to prepare for surgery due to epilepsy or brain tumors, said Dr. Castillo.

**—Kerri Wachter**



PHOTOS COURTESY DR. EDUARDO M. CASTILLO

**MEG data are overlaid on an MRI to allow resection planning; yellow triangles mark interictal activity, and red dots localize language activity (left). Postsurgical image confirms sparing of language cortex (middle). The sensor array covers the head only (right).**