

## Deep Brain Stimulation in the Treatment of Epilepsy

Robert E. Gross, MD, PhD

Approximately 30 percent of patients with newly diagnosed epilepsy will continue to have seizures despite the best medical therapy and thus, are considered for surgical treatment. However, 50 percent will not be acceptable candidates for such treatment due to a variety of factors, such as multifocal or primary generalized onset of their seizures, which continue unabated. Vagal nerve stimulation (VNS) is an alternative that produces 50 percent or greater reduction in nearly 50 percent of patients, but many patients respond poorly and most desire greater seizure reduction. For this reason, alternative surgical treatments have been sought, and for many years, been pursued.

The role of the thalamus in seizure propagation in the primary generalized epilepsies has long been appreciated. On this basis, researchers have stimulated the nonspecific intralaminar nucleus (centromedian [CM]/parafascicular [Pfl]), which has widespread connections to the striatum and the cortex, and from which cortical recruiting responses can be elicited when stimulated. Benefits were obtained – greater for generalized than complex partial seizures – in uncontrolled trials in more than 50 patients with follow up from six months to 15 years. CM/Pf deep brain stimulation (DBS) has not been pursued further by other groups. Rather, on the basis of the anatomical circuitry and experimental work in rodent models of epilepsy, other subcortical DBS targets are being explored for epilepsy.

Preliminary research results of DBS of the basal ganglia, thalamus and hippocampus are promising enough to justify further experimental

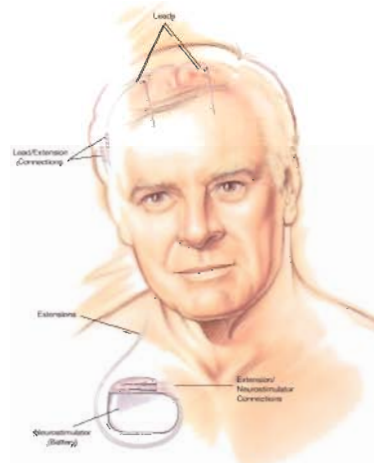
work in patients. Although the benefits would appear, with very few patients, to be in the range of VNS, which is less invasive, several points deserve emphasis. First, many patients experience poor seizure control with VNS and, ultimately may benefit from DBS. The overlap of patients that respond to each will be interesting to examine. Second, it is conceivable additive benefits from these two modalities

may be observed if they involve distinct neural pathways (as yet unknown). And third, if there is increased effectiveness, even if seizure freedom is not obtained, a modest (1.5 percent) rate of permanent neurological morbidity is justifiable, given the rate of significant morbidity/mortality associated with ineffectively treated epilepsy.

All of the DBS investigations have used continuous stimulation at various targets.

There is, however, some possibility intermittent

stimulation may be more effective. Even more promising is the specter of providing stimulation in advance or at the early stages of seizures (closed loop or contingent stimulation), which currently is being pioneered. The basis for this algorithm is the ability to detect seizures at an early stage, prior to clinical manifestations or even to predict seizures prior to electrographic onset. Contingent stimulation may block seizures either by invoking a seizure modulatory circuit or by desynchronization of the hypersynchronized brain electrical activity underlying seizures. The effectiveness of such a contingent system has not been demonstrated yet in animal models or patients but holds great promise for the future.



Source: Medtronic, Inc. (2005)

### OUR MISSION

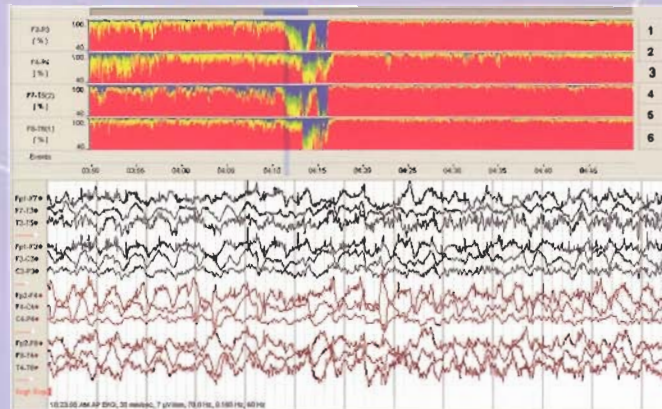
The Emory Epilepsy Center is dedicated to diagnosis, treatment and research to improve the lives of patients with epilepsy and seizures.

Advancing  
the  
Possibilities

# Continuous EEG Monitoring in the ICU

Suzette LaRoche, MD

Patients in the intensive care unit (ICU), particularly neurological patients with underlying brain injury, are at risk for secondary brain injury from various insults including seizures and/or ischemia. These patients have many physiological variables that are being continuously monitored including blood pressure, EKG, pulse oximetry and intracranial pressure. Cerebral activity, one of the most important measures of neurological function, however, typically is not monitored. Routine EEG studies often are used but provide a very limited view of brain function and may not detect changes and events that are intermittent or fluctuating over time.



Because the majority of ICU patients are comatose, neurological exam is limited and detection of early ischemia may not be possible until irreversible changes are seen on brain imaging. In addition, subclinical seizures are increasingly recognized as an important cause of continued coma in critically ill patients, particularly neurological patients with a history of epilepsy, CNS infection, brain tumors or recent neurosurgical intervention. Only recently has technology allowed for efficient use of continuous EEG monitoring to assess and record cerebral function. Continuous EEG monitoring is not only useful for detection of ischemia and subclinical seizures but also can aid in assessment of sedation level, determination

of prognosis and characterization of paroxysmal movements or posturing that may be suspicious for seizure activity.

Digital acquisition of EEG has allowed for collection of large amounts of data that can be displayed in various representations. In addition, software programs now are available that use Fast Fourier Transform to display relative changes in frequency, amplitude and variability that occur over time (also called compressed spectral arrays). This technology allows for compression of several hours of data that can be displayed on a single screen for rapid visual analysis. The use of these so-called data trends in combination with automated spike and seizure detection highlight areas of interest where raw EEG data must be reviewed and interpreted in further detail. Furthermore, the use of video monitoring can be added for more accurate distinction of artifacts and to correlate clinical or behavioral changes with EEG.

At Emory University, continuous EEG monitoring is used frequently in the management of acutely ill neurological and neurosurgical patients. Epileptologists and EEG technical staff work closely with the critical care team to communicate results and correlate EEG findings with clinical changes. Many treatment decisions are influenced by these findings and favorably impact the outcome as well as length of ICU stay.

For more information regarding continuous EEG monitoring in the ICU at Emory Hospital, please contact Dr. Suzette LaRoche at 404-778-5943.

# Considerations in Treating Women with Antiepileptic Drugs During Reproductive Years

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Antiepileptic drugs (AEDs) are used for the treatment of epilepsy, but are even more frequently prescribed for other neuropsychiatric disorders such as migraine headaches, chronic pain, tremors, and mood/bipolar disorders. There were more than 56 million prescriptions written last year in the United States alone, and AEDs are considered one of the most frequent chronic teratogen exposures. This must be considered when prescribing AEDs to women in their reproductive years.

Prescribing AEDs to women during their reproductive years requires maintaining a precarious balance between control of illness and minimizing fetal exposure to harmful medication effects. The fetal anticonvulsant syndrome consists of various combinations of the following features: minor anomalies, major congenital malformations, intrauterine growth retardation, cognitive dysfunction, microcephaly and infant mortality.

Certain general treatment paradigms are accepted to improve both maternal and fetal outcomes. These standards include the use of folic acid, avoiding the use of AED polytherapy and maintaining best possible seizure control for the mother with epilepsy. Harmful consequences of seizures can include maternal and fetal hypoxia and acidosis, fetal bradycardia, poor neurodevelopmental outcome, fetal intracranial hemorrhages, miscarriages and stillbirths. Control of other neuropsychiatric illnesses during pregnancy with these compounds is more controversial. However, given more than 50 percent of pregnancies are unplanned in the U.S., and often not diagnosed until after critical periods of organogenesis, these same risks are of concern when prescribing AEDs to any woman of reproductive age.

Even more women on AEDs have unplanned pregnancies because of the interaction between many AEDs and contraceptive medications.

Important results recently have been released from the North American AED Pregnancy Registry: two widely prescribed AEDs have a much higher risk of birth defects than previously believed. Specifically, these two drugs – valproate and phenobarbital – show up to a five times greater risk for women to have babies with major birth defects.

These types of birth defects include spina bifida, heart abnormalities and cleft lip, among others. Many women and their healthcare providers may not be aware of the newly emerging data and potential consequences to their offspring.

These recent findings and concerns about their impact led to the Epilepsy Foundation Women's Health News Media Event, held in New York City June 22, 2005. The Epilepsy Foundation, in cooperation with medical experts and several relevant voluntary health organizations, developed Call to Action steps to empower women to reduce the risks associated with AEDs. These included

working with their healthcare providers to find the medication that works best, taking folic acid, and staying on top of emerging information about antiepileptic drugs. Details soon will be available at [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org). Further information on this topic also can be found on the Web sites of the American Academy of Neurology ([www.aan.org](http://www.aan.org)), the North American Pregnancy Registry ([www.aedpregnancyregistry.org](http://www.aedpregnancyregistry.org)) and the American Epilepsy Society ([www.aesnet.org](http://www.aesnet.org)).



## The Emory Epilepsy Center

It is estimated more than 40 million people in the world suffer from epilepsy. The condition affects all ages – children, adults and seniors. Epilepsy is a genetic condition for some patients, but epilepsy also can be caused by stroke, brain tumor, infectious disease, head injury and many other types of brain injury. For many individuals with epilepsy, the cause cannot be found. The Emory Epilepsy Center, however, offers effective treatment that has resulted in seizure control for more than two-thirds of affected patients.

The Emory Epilepsy Center in Atlanta, Georgia is one of the nation's leading institutions in the study and treatment of epilepsy, providing diagnostic services, therapy and surgical treatment. The Center cares for both adults and children. The pediatric epilepsy specialists are specifically trained to manage childhood seizures and to address particular challenges of childhood educational and behavioral difficulties that often are byproducts of seizure disorders. The adult epilepsy specialists have expertise in controlling seizures without excessive adverse effects of medication and in addressing the occupational and social problems younger adults experience, as well as the memory and quality of life issues older adults with epilepsy face.

The Emory Epilepsy Center is part of the Emory University School of Medicine, globally recognized for medical

research and physician training, and EMORY HEALTHCARE, one of the nation's leading healthcare systems. These resources support the neurologists and neurosurgeons of the Emory Epilepsy Center in applying the latest innovations in treatment. In addition, our neuropsychologists work with patients to manage the emotional and psychological stresses that often are experienced by those with seizure disorders.

The Emory Epilepsy Center staff consults with and treats more than 3,000 patients each year from around the nation. Our comprehensive services include diagnostic testing and the latest treatments for the management of all forms of epilepsy.

Our Center also is a leader in research and clinical trials, searching for new answers to the origins of epilepsy and new treatments that will improve the lives of patients with these disorders.



**Referrals to the Emory Epilepsy Center** EMORY HEALTHCARE offers our referring physicians the knowledge, advanced technology and medical innovations only available from an academic-based healthcare system.

To make referrals quickly and easily to our Center, please call the Emory Physician Consult Line at 404-778-5050 or 1-800-22-EMORY (3679) between 7 a.m. and 7 p.m. Monday through Friday.

# Clinical Trials at the Emory Epilepsy Center

The following clinical trials currently are being conducted through the Emory Epilepsy Center. For more information about our clinical trials or to refer a patient, please contact the Epilepsy Research Department at 404-778-5943.

**E2007 Study** – A multi center, randomized, placebo-controlled parallel group study of the experimental anti-epilepsy drug E2007 as adjunctive therapy in patients with refractory partial seizures.

**Early Randomized Surgical Epilepsy Trial (ERSET)** – NIH-sponsored clinical trial of anterior temporal lobectomy versus prolonged medical management of temporal lobe epilepsy, early in the course of refractory temporal lobe seizures.

**Effects of Age, Gender and Race on the Metabolism of Antiepileptic Drugs** – A pharmacokinetic and pharmacoepidemiology study of antiepileptic drugs in the elderly. This project also includes investigation of genetic and racial factors.

**Excretion of Lamotrigine into Human Breast Milk: Determining Nursing Infant Daily Dose** – A two-center study of pharmacokinetics and pharmacodynamics of lamotrigine in breastfeeding mother-child pairs and in newborns exposed to lamotrigine in-utero (neonatal clearance).

**Progesterone Therapy for Women with Epilepsy** – A multi-center, randomized, placebo-controlled trial evaluating the efficacy and safety of adjunctive progesterone therapy in women with refractory epilepsy.



**Retrospective Study of In-Utero Antiepileptic Drug Effects on Neurodevelopment (RetroNEAD Study)** – A multi-center retrospective parallel group study to determine if in-utero exposure produces differential antiepileptic drug (AED) effects on subsequent cognitive abilities and behavioral abnormalities in children.

**SP754 Study** – A randomized, placebo-controlled multi-center clinical trial of adjunctive therapy of patients with partial epilepsy, with or without generalization.

**Specialized Center of Research (SCOR) on Sex and Gender Factors Affecting Women's Health** – Involves pharmacokinetic modeling of AED and psychotropic medications during pregnancy and lactation: defining fetal/neonatal exposure and influence on obstetrical outcome. Study participation is up to one year postpartum.

**Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE)** – A phase II study of chronic, intermittent, high-frequency electrical stimulation of the anterior thalamic nuclei in patients with partial epilepsy, previously found refractory to multiple other treatments.

# Neuropsychological Services in the Evaluation and Treatment of Temporal Lobe Epilepsy

Anthony Y. Stringer, PhD, ABPP/CN, CPCRT

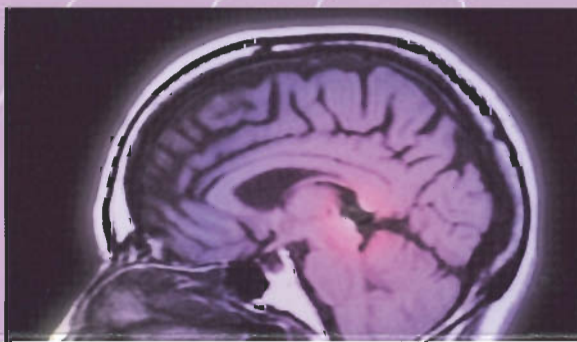
Intractable seizures originating in the mesial temporal lobe have a well-known, chronically debilitating effect on memory. Less appreciated are the affects of temporal lobe epilepsy on other areas of cognition, including attention, perceptual ability, language, reasoning and executive functioning. Such widespread cognitive changes may be due to the pathways along which mesial temporal seizures propagate or other unknown mechanisms. Importantly, these changes in cognitive function can appear before or in the absence of neuropathological signs in MRI or PET scans. Nonetheless, the cognitive deficits can impede patient performance and safety at home, school, work and other community settings beyond the direct impact of the seizures themselves.

At Emory University, neuropsychological diagnostic and treatment services play a vital role in the evaluation and management of temporal lobe epilepsy (TLE). All patients who are being considered for surgical treatment of TLE undergo a comprehensive, eight-hour neuropsychological examination, administered in one of three neuropsychological testing laboratories. Each laboratory is equipped with more than sixty current, standardized and normed neuropsychological tests administered by

patients regarding the potential risks and benefits of temporal lobe surgery. For cases in which the surgical resection might encroach upon eloquent cortex, the neuropsychologist and neurologist will conduct a cortical mapping examination using brief electrical stimulation to map language areas in the brain. This allows the surgeon to tailor the resection to maximize seizure control while minimizing the risk of post surgical aphasia. Historically, an obstacle with validating results in these examinations has been the necessity to use the same test materials across hemispheres or cortical stimulation sites. Emory neuropsychologists have pioneered the development of standardized Wada and Language Mapping protocols that use unique tests, matched for item difficulty, across hemispheres or stimulation sites. This permits valid assessment without risk of confounding practice effects. Emory remains one of very few sites nationally that has incorporated this innovation.

Even with careful assessment and counseling, some patients will experience a mild, sometimes transient, decrease in

memory after surgery. Neuropsychological testing at the six-month follow-up visit identifies patients with persisting memory changes. A program of cognitive rehabilitation



trained technicians under the supervision of a board-certified neuropsychologist. Testing permits a precise delineation of both the areas of



is offered to these patients to teach them compensatory strategies that permit better functioning at home, work and school

cognitive impairment and their severity. Results are used in conjunction with other neurological and radiological data obtained by the Emory Epilepsy Center's team of physicians to localize seizure onsets, determine candidacy for surgery and delineate the risk of postsurgical cognitive disability.

To further minimize risk of cognitive disability, candidates undergo an Intracarotid Amobarbital (Wada) Test prior to being cleared for surgery. While each hemisphere is briefly and independently anesthetized, the Emory neuropsychologist tests for language lateralization and the capacity of each hemisphere to mediate memory functions. This permits more precise counseling of

despite memory impairment. Using an evidence-based medicine approach, Emory has developed a cognitive rehabilitation program with demonstrable efficacy in improving patient functioning. This program, referred to as Ecologically-Oriented Neurorehabilitation, currently is only available at Emory.

For more information or to make a referral for neuropsychological services, please contact the Division of Neuropsychological and Behavioral Health of the Emory School of Medicine at 404-712-5667.

# Would You Like Us to Visit YOUR Office?

At the Emory Epilepsy Center, we are committed to ensuring you have all the information you need about our services and that you are able to access these services. If you would like a physician from the Emory Epilepsy Center to visit your office, we will be happy to plan a visit tailored to your needs. For more information or to schedule an appointment, please call 404-778-2300.

