The Goal of Epilepsy Therapy: No Seizures, No Side Effects, as Soon as Possible

By Jerome Engel, Jr., MD, PhD

Epilepsy is a significant health problem. Ten percent of people living a normal lifespan will experience at least one epileptic seizure and one third will develop a chronic epileptic condition. At any given time, 0.5% to 1% of the world’s population has active epilepsy, amounting to over 40 million people. A World Health Organization-sponsored study determined that epilepsy accounts for 1% of the global burden of disease, measured as disability-adjusted life years equivalent to the global burden of lung cancer in men and to breast cancer in women. Disability-adjusted life years measure years of productivity lost as a result of disability or death, which is relatively high for epilepsy because this condition often begins in childhood. The cost of epilepsy in the United States has been estimated at $12.5 billion/year, and 80% of this cost is borne by the 30% of patients whose seizures are not controlled.

The cost of uncontrolled epileptic seizures to society, and to individuals with epilepsy and their families, is measured not only in economic terms, but also in terms of human suffering. In this month’s first article, Michael R. Sperling, MD, who has authored seminal papers on consequences of epilepsy, provides evidence that epilepsy is not a benign disorder; that early control of epileptic seizures is important to avoid irreversible disability due to the development of psychological and social disturbances and progressive cerebral dysfunction, as well as epilepsy-related death. The burden imposed on society and on individuals by uncontrolled epileptic seizures is all the more tragic because many suffer needlessly. For a significant number of adults who have had recurrent seizures since infancy, childhood, or adolescence, more aggressive early intervention might have rescued them from a lifetime of disability. Consequently, the goal of therapy today should be no seizures and no side effects, as soon as possible.

The remaining four papers address issues relevant to attaining this goal. This might often require early referral to an epilepsy specialist. In addition to the specialized medical and surgical therapies offered by an epilepsy center, admission to a telemetry unit may also be necessary to diagnose nonepileptic, particularly psychogenic, ictal events, a not uncommon cause of uncontrolled seizures.

Most epileptic seizures can be controlled with antiepileptic drugs (AEDs), and the optimal approach to the pharmacotherapy of epilepsy is to eliminate disabling epileptic seizures without introducing new, unacceptable side effects. This should be accomplished quickly, before adverse consequences of epilepsy become disabling. Physicians, patients, and parents should not be satisfied with a mere improvement in seizure frequency or severity if a more aggressive pharmacotherapeutic approach could eliminate disabling seizures completely, nor should they accept unwanted side effects if these could be relieved by a change in the therapeutic regimen. Quality of life is unnecessarily diminished when nothing is done to alleviate insidious drug-induced sedation, cognitive deficits, or behavioral disturbances, because they are erroneously attributed, particularly in children, to the underlying seizure disorder.

In the second article, Patrick Kwan, MD, PhD, and Martin J. Brodie, MD, who recently published a landmark study on responses to AEDs, will discuss approaches for determining the effect of drug regimens quickly and the concept of medical intractability. They present evidence suggesting that medical intractability can be predicted in many patients after only a few drugs have failed to control the epileptic seizures.

Surgical therapy is an alternative treatment for epilepsy which can eliminate disabling seizures in a high percentage of patients with surgically remediable epilepsy syndromes. These are disorders for which the pathophysiology and natural history are known, AEDs are often ineffective, and surgical intervention usually can eliminate disabling seizures. Patients with focal seizures due to well-localized, resectable, structural lesions of neocortex, and infants and young children with catastrophic secondary generalized epilepsy due to lesions limited to one hemisphere which can be removed or disconnected, have surgically remediable...
Introduction

The prototype of a surgically remediable syndrome, however, is mesial temporal lobe epilepsy (MTLE). MTLE, perhaps the most common form of epilepsy, is among the most medically intractable of epileptic conditions, but is also the epileptic disorder most easily treated surgically. The American Academy of Neurology recently published a practice parameter recommending surgical treatment for medically intractable MTLE.

In the third article, Samuel Wiebe, MD, who recently completed the only randomized controlled trial of epilepsy surgery, discusses the safety and efficacy of surgical intervention as a treatment for epilepsy.

Although early control of epileptic seizures is important for preventing irreversible adverse consequences of these ictal events and a lifetime of disability, there is little published information to guide standards of practice as to when to discontinue additional trials of AEDs and refer a patient for surgical evaluation. Clearly, to be effective in preventing irreversible consequences of recurrent disabling epileptic seizures, epilepsy surgery can no longer be considered as a last resort. It would take more than a lifetime to prove that every available AED in every conceivable combination is ineffective. At present, however, patients are referred for surgical treatment an average of 18–22 years after onset of their epilepsy, and when they become seizure-free postoperatively, often it is too late for meaningful social rehabilitation. Patients who are disabled by epilepsy during periods of adolescence and young adulthood that are critical for acquiring interpersonal and vocational skills too often remain disabled after successful surgery at an older age, and are unable to live a full and independent life.

Next, Anne T. Berg, PhD, presents data from her recent revealing study that concluded that it takes an average of 9 years for patients with surgically remediable epilepsy syndromes to fail trials of two AEDs. She discusses the natural history of symptomatic focal epilepsy, the reasons why it can take so long to establish medical intractability in many patients, and what might be done to address this often detrimental delay.

In the fifth article, Kari Swartztrauber, MD, MPH, who has carried out important investigations into patient attitudes towards epilepsy and surgery, presents reasons that patients give for their reluctance to consider surgical treatment, another important factor in the failure of early surgical intervention, and will also discuss approaches that might help address their concerns.

The National Institute of Neurological Disorders and Stroke has recently funded a major multicenter clinical study, the Early Randomized Surgical Epilepsy Trial (ERSET), to address the question of whether aggressive optimal pharmacotherapy or surgical intervention, early in the course of MTLE, is more effective in eliminating disabling epileptic seizures and preserving quality of life. ERSET is not about epilepsy surgery, per se, but is about early effective therapeutic intervention, because it is unknown whether additional pharmacotherapy or surgical therapy is better at this stage of the disorder. Patients with MTLE, ≥12 years of age, who have rare or recent-onset disabling seizures will undergo a standardized comprehensive neurodiagnostic screening evaluation consisting of neuropsychological and psychiatric testing, magnetic resonance imaging, positron emission tomography, and inpatient video-electroencephalographic monitoring. Patients meeting criteria for surgery will be randomized either to 2 additional years of an optimal pharmacotherapy protocol designed by a panel of experts in the clinical pharmacology of AEDs, or to a standardized anteromesial temporal resection if they pass an intracarotid amobarbital test. Outcome measures at the end of 2 years will include percent of patients free of disabling seizures, health-related quality of life, a variety of social measures, neuropsychological function, morbidity, and mortality. In addition, follow-up magnetic resonance imaging and positron emission tomography will be used to determine whether there are progressive structural and functional changes in the temporal lobe in patients who continue to have seizures, but not in those who become seizure-free. At the end of the 2-year follow-up period, patients randomized to the medical arm who still wish to undergo surgical treatment, and who pass the intracarotid amobarbital test, will receive the standard operation as part of the study.

It is anticipated that recruitment will be a major challenge for completion of ERSET, because patients with MTLE this early in the course of their disorder are mostly under the care of general neurologists or primary care physicians, and not likely to come to the attention of the ERSET epilepsy centers. For this reason, a major campaign is being undertaken to make the medical community, and patients with epilepsy, aware of ERSET. Table 1 contains the inclusion and exclusion criteria for referral to ERSET and Table 2 lists the ERSET study sites. We hope that readers of CNS Spectrums will keep ERSET in mind when seeing new patients with epilepsy, and refer appropriate patients to the closest study site.

REFERENCES

TABLE 1. INCLUSION-EXCLUSION CRITERIA FOR ERSET REFERRAL*

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>212 years</td>
</tr>
<tr>
<td><strong>Recent seizure frequency</strong></td>
<td>22 days with seizures in the last 4 months prior to referral</td>
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<tr>
<td><strong>Epilepsy course</strong></td>
<td>Infrequent or recent-onset seizures</td>
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<tr>
<td><strong>Intractability</strong></td>
<td>Seizures despite adequate trials of at least two antiepileptic drugs, one of which must be either brand-name Dilantin, Tegretol, Carbarnol, or Trileptal</td>
</tr>
<tr>
<td><strong>Seizure type</strong></td>
<td>Complex partial seizures with or without auras or secondarily generalized seizures</td>
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<tr>
<td><strong>Seizure behavior</strong></td>
<td>Clinical seizures typical of mesial temporal lobe epilepsy will be evaluated at the ERSET site</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>None specified</td>
</tr>
</tbody>
</table>

* If you are uncertain whether a patient meets these criteria, contact your local site or refer and let the site investigators decide.

ERSET=Early Randomized Surgical Epilepsy Trial.


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**TABLE 2. ERSET SITES**

- **Baylor Neurological Institute**
  - Telephone: 602-406-6282
  - Fax: 602-406-6299
  - E-mail: SSSChung@cch.harvard.edu

- **Bayfront Medical Center Comprehensive Epilepsy Program**
  - Telephone: 727-824-7135
  - Fax: 727-824-7169
  - E-mail: mrich@tampabay.rr.com

- **The Cleveland Clinic Foundation**
  - Telephone: 216-445-2990
  - Fax: 216-445-6205
  - E-mail: sjohnson@ccf.org

- **Columbia Comprehensive Epilepsy Center**
  - Telephone: 212-305-1742
  - Fax: 212-305-1450
  - E-mail: uck33@columbia.edu

- **Emory Epilepsy Center**
  - Telephone: 404-778-3772
  - Fax: 404-778-5904
  - E-mail: jean_montgomery@emoryhealthcare.org

- **Johns Hopkins Epilepsy Center**
  - Telephone: 410-955-2621
  - Fax: 410-955-0751
  - E-mail: akemi@jhu.edu

- **Massachusetts General Hospital Epilepsy Service**
  - Telephone: 617-726-3311
  - Fax: 617-726-9250
  - E-mail: lda@partners.org

- **Minnesota Comprehensive Epilepsy Program Epilepsy Care**
  - Telephone: 952-525-4500, Ext. 5000
  - Fax: 952-525-1560
  - E-mail: minneapolis@mncomp.com

- **Northwestern Memorial Hospital**
  - Telephone: 312-695-0632
  - Fax: 312-695-3166
  - E-mail: jstogut@northwestern.edu

- **Stanford Comprehensive Epilepsy Center**
  - Telephone: 650-725-6648
  - Fax: 650-498-6326
  - E-mail: mcallanan@stanfordmed.org

- **Swedish Medical Center—The Epilepsy Center**
  - Telephone: 206-386-3880
  - Fax: 206-386-3882
  - E-mail: georgia.galvin@swedish.org

- **Thomas Jefferson University**
  - Telephone: 215-955-6666 or 955-1222
  - Fax: 215-955-4060
  - E-mail: michael.sperling@jefferson.edu

- **University of California, Los Angeles**
  - Telephone: 310-825-5745
  - Fax: 310-206-8461
  - E-mail: SDewar@mednet.ucla.edu

- **University of Michigan Epilepsy Program**
  - Telephone: 734-936-7310
  - Fax: 734-936-5520
  - E-mail: dmhinman@umich.edu

- **University of New Mexico Comprehensive Epilepsy Program**
  - Telephone: 505-272-3344
  - Fax: 505-272-6692
  - E-mail: jshih@bodas.unm.edu

- **University of Rochester—Strong Epilepsy Center**
  - Telephone: 585-275-0599
  - Fax: 585-275-8113
  - E-mail: georgia.galvin@swedish.org

- **University of Texas Southwestern Medical Center**
  - Telephone: 214-648-6880
  - Fax: 214-648-6132
  - E-mail: dminecan@utsouthwestern.edu

- **Vanderbilt University Epilepsy Program**
  - Telephone: 615-936-0209
  - Fax: 615-936-0225
  - E-mail: diana.coleman@vanderbilt.edu

- **Washington University Comprehensive Epilepsy Center**
  - Telephone: 314-747-0559
  - Fax: 314-747-0225
  - E-mail: diana.veath@utsouthwestern.edu

ERSET=Eary Randomized Surgical Epilepsy Trial; NIH=National Institutes of Health.

* More information can be obtained for physicians at www.erset.org and for patients at www.erset.net.