The Neurology REPORT

Selected Reports from the 8th European Congress on Epileptology and the 62nd Annual Meeting of the American Epilepsy Society

Joan A. Conry, MD
Guest Editor

CONTINUING MEDICAL EDUCATION: 2 CREDITS AVAILABLE

This activity is supported by an educational grant from Eisai Inc.
Selected Reports from the
8th European Congress on Epileptology and the
62nd Annual Meeting of the American Epilepsy Society

Joan A. Conry, MD
Guest Editor

Introduction 3
Joan A. Conry, MD
George Washington University and the Children’s National Medical Center, Washington, DC

New Insights into Childhood Absence Epilepsy 5
Mackenzie C. Cervenka, MD
Johns Hopkins Hospital, Baltimore, Maryland

Immune-Mediated Epileptic Encephalopathies in Children 11
Rani K. Singh, MD
Children’s National Medical Center, Washington, DC

Raising Expectations in the Management of Partial Onset Seizures 17
Sarah Hopkins, MD, MSPH
Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

What Type of Data Makes You Pick Your Drug? 22
Bernhard Suter, MD
Baylor College of Medicine, Houston, Texas

Rufinamide: A Clinical Update 25
Thomas Gann, MD
University of Alabama at Birmingham Epilepsy Center, Birmingham, Alabama

When Monotherapy for Epilepsy Fails 31
Vikram Bhise, MD
SUNY Downstate Medical Center, Brooklyn, New York

CME Post Test and Evaluation 38
Rationale and Purpose
This edition of The Neurology Report examines in depth some of the many issues confronting neurologists who diagnose and treat patients with epilepsy, including the management of pediatric seizure disorders and treatment failures in patients of all ages. It is based upon presentations delivered at the 8th European Congress on Epileptology (ECE), held September 21–25, 2008, in Berlin, Germany, and the 62nd Annual Meeting of the American Epilepsy Society, held December 5–9, 2008, in Seattle, Washington. The authors examine the possibility that autoimmunity may contribute to epilepsy, particularly in children, and review what we know of childhood absence epilepsy, taking special note of its genetic components, presentation, relationship to other medical conditions, and response to common antiepileptic drugs (AEDs). The use of just one AED to treat seizure disorders would be ideal; however, this strategy too often is less than successful. The authors discuss how failure of monotherapy may be defined, whether it is wiser to add another AED or substitute a different AED for the one originally used, when and which surgical procedures may be tried, and why the results of animal studies of combination therapy may not translate well to the clinical setting. The authors also look at what type of data makes us choose one drug over another and explore recent additions to the armamentarium of AEDs. One of the newest, rufinamide, represents a novel medical therapy to address Lennox-Gastaut syndrome, a particularly devastating and difficult-to-treat seizure disorder that strikes in early childhood and lasts a lifetime. The treatment of some other seizure types often transcends the results of clinical trials, and measures of quality of life may assist in evaluating the effects of particular therapies and making crucial therapeutic decisions.

The articles in this issue, written from the academic perspective of physicians in training at leading medical institutions, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders, under the direction of CME LLC, to meet a perceived educational need to provide neurologists and other physicians with diagnostic and therapeutic strategies to help them perform their medical roles.

Learning Objectives
After studying this issue of The Neurology Report, participants in this educational activity should be able to:

• Understand the genetic and immunologic bases of some types of epilepsy and the use of various antibodies as prognostic markers of different seizure disorders.
• Review current knowledge about the role of encephalopathy in prompting seizures and the role of immunotherapy in treating affected patients.
• Discuss findings on types of clinical trials and quality-of-life assessments used to evaluate patients with epilepsy.
• Recognize the pharmacodynamic and pharmacokinetic features of AEDs and the value of adjuvant therapy in managing patients with refractory partial seizures.
• Examine the results of clinical trials of various AEDs, used alone and in combination, and the promise of new AEDs now being tested.
• Appreciate the various cognitive and neuropsychological effects of childhood absence seizures.
• Comprehend the challenges of managing Lennox-Gastaut syndrome and the potential role of rufinamide in its treatment.

Target Audience
Neurologists and other physicians significantly involved in the diagnosis and management of epilepsy should find participation in this educational activity valuable.

Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of CME LLC and Direct One Communications, Inc. CME LLC is accredited by the ACCME to provide continuing medical education for physicians.

Faculty Disclosures
In compliance with the ACCME’s Standards for Commercial Support, any person who was in a position to control the content of this CME activity was required to disclose all relevant financial relationships that created conflicts of interest. CME LLC has identified and resolved all conflicts of interest prior to the publication of this educational activity. All faculty have been offered a modest honorarium for their participation in this activity.

Joan A. Conry, MD, is Professor of Neurology, George Washington University and the Children’s National Medical Center, Washington, DC. Dr. Conry has served as a speaker for and advisor/consultant to Eisai and Ovation Pharmaceuticals and has received research support from both companies. Mackenzie C. Cervenka, MD, an Epilepsy and Clinical Neurophysiology Fellow in the Department of Neurology, Johns Hopkins Hospital, Baltimore, Maryland, has nothing to disclose. Rani K. Singh, MD, a Fellow in Child Neurology at Children’s National Medical Center, Washington, DC, has nothing to disclose. Sarah Hopkins, MD, MSPH, a Child Neurology Fellow at Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio, has nothing to disclose. Bernhard Suter, MD, a Fellow in Neurology at Baylor College of Medicine, Houston, Texas, has nothing to disclose. Thomas Gann, MD, a Neurology Fellow at the University of Alabama at Birmingham Epilepsy Center, Birmingham, Alabama, has nothing to disclose. Vikram Bhise, MD, a Clinical Neurophysiology Fellow at SUNY Downstate Medical Center, Brooklyn, New York, has nothing to disclose.

Continuing Education Credit
CME LLC designates this educational activity for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclaimer
This activity is an independent educational activity under the direction of CME LLC. The activity was planned and implemented in accordance with the Essential Areas and policies of the ACCME, the Ethical Opinions/Guidelines of the American Medical Association, the US Food and Drug Administration, the Office of Inspector General of the US Department of Health and Human Services, and the Pharmaceutical Research and Manufacturers of America Code on Interactions With Healthcare Professionals, thus assuring the highest degree of independence, fair balance, scientific rigor, and objectivity. However, the planning committee, faculty, CME LLC, Eisai Inc., and Direct One Communications, Inc. shall in no way be liable for the currency of information or for any errors, omissions, or inaccuracies in this activity. Discussions concerning drugs, dosages, and procedures may reflect the clinical experience of the planning committee, or they may be derived from the professional literature or other sources and may suggest uses that are investigational in nature and not approved labeling or indications. Participants in this activity are encouraged to refer to primary references or full prescribing information resources.

The opinions and recommendations presented herein are those of the faculty and do not necessarily reflect the views of the provider, producer, or grantor.

Copyright
Copyright owned by Direct One Communications, Inc. © Copyright 2009, Direct One Communications, Inc.

Contact Information
We would like to hear your comments regarding this publication or other educational activities provided by CME LLC. In addition, suggestions for future activities are welcome. Contact us at:

Director, Continuing Medical Education
CME LLC
Harborside Financial Center
Plaza 3, Suite 806
Jersey City, NJ 07311
Phone: 888-618-5781
Fax: 201-946-0700

Activity release date: March 16, 2009
Expiration date: March 16, 2010
Introduction

Joan A. Conry, MD, guest editor
George Washington University and the Children’s National Medical Center, Washington, DC

The phenomenon of unprovoked recurrent seizures—commonly referred to as epilepsy or seizure disorders—remains a baffling and disabling problem for too many patients and their physicians. These events may involve a spectrum of signs and symptoms that range from slight, almost undetectable changes to profound convulsions and their sequelae. They may be manifestations of a neurologic syndrome, or they may stand as neurologic events that simply begin one day and continue to occur over a period of time. Some seizures may respond promptly to drug therapy. Unfortunately, they may continue and become intractable despite heroic medical and surgical interventions.

In late 2008, neurologists and other medical professionals involved in the diagnosis, treatment, and research of epilepsy convened at two major meetings to discuss the varied presentations and best management of this unpredictable and often difficult-to-treat disorder. Our authors for this edition of The Neurology Report attended the 8th European Congress on Epileptology, which met in Berlin, Germany, from September 21 to 25, 2008, and the 62nd Annual Meeting of the American Epilepsy Society, held December 5–9, 2008, in Seattle, Washington. Their reports reflect ongoing discussions on the etiology, presentation, identification, and management of epilepsy that continue to provoke new and exciting research on many different levels around the world.

Speakers at these sessions characterized childhood absence epilepsy (CAE) and its optimal treatment, discussed the many factors that must be considered when managing partial onset seizures, and explained current understanding of immunemediated encephalopathies that may lead to pediatric epilepsy. Further, these fellows related the utility of different kinds of research and quality-of-life (QOL) surveys in studying epilepsy and determining the efficacy of therapy, the common need to prescribe more than one antiepileptic drug to control seizures, and the availability of the recently approved drug rufinamide to manage pediatric patients diagnosed with Lennox-Gastaut syndrome.

NEW INSIGHTS INTO CAE

An epilepsy syndrome that has been recognized since the late 1700s, CAE recently was linked to a greater risk of learning and neuropsychological problems in affected patients. Descriptions of the various phenotypes of CAE ultimately may help investigators to determine the underlying mechanisms of these syndromes and to discover new ways to prevent seizures.

Mackenzie C. Cervenka, MD, a Fellow in Neurology in the Division of Epilepsy, Johns Hopkins Hospital, Baltimore, Maryland, covers the varied explanations of CAE offered by experts over the years and the genetic patterns related to the development of this seizure disorder. After providing an update of a clinical trial sponsored by the National Institutes of Health that compared the effectiveness and tolerability of ethosuximide, valproic acid, and lamotrigine for initial therapy of CAE, Dr. Cervenka discusses a portion of the study that investigated the effect of these drugs on the attention spans of CAE patients. These results provide new insight into this mysterious disease and clues to its best treatment.

IMMUNE-MEDIATED EPILEPTIC ENCEPHALOPATHIES IN CHILDREN

Autoimmunity may contribute to epilepsy syndromes, particularly those collections of medical conditions experienced by children having new-onset focal, multifocal, or generalized seizures. Rasmussen’s and limbic encephalitis have been recognized for years; more recently, clinicians have identified devastating epileptic encephalopathies in school-aged children; acute encephalitis with repetitive, refractory partial seizures; and severe partial epilepsy and encephalopathy due to an immune-mediated disorder among children and adolescents. Encephalopathy and seizures linked to diagnostic antibodies also have been noted among individuals diagnosed with systemic lupus erythematosus, Hashimoto’s or Behçet’s disease, Parry-Romberg scleroderma, and other systemic autoimmune diseases.

Clearly, immunopathologies are involved in some seizure disorders suffered by pediatric patients. Rani K. Singh, MD, a Fellow in Child Neurology at the Children’s National Medical Center, Washington, DC, reviews primary epileptic encephalopathies, their possible autoimmune origins, and the therapeutic modalities that can suppress seizure activity in affected patients. Likewise, Dr. Singh discusses systemic autoimmune diseases that may result in seizures and other neuropathies and treatments currently used to control related epilepsy.

Antibodies to the voltage-gated potassium channel, the glutamate receptor, and glutamic acid decarboxylase have been linked to epilepsy and seizure-related disorders. Dr. Singh reviews the relationship between these antibodies and epileptic activity in particular patient populations.

Dr. Conry is Professor of Neurology, George Washington University and the Children’s National Medical Center, Washington, DC.
Further investigation of these links may yield important clues about the prognosis of affected patients and novel directions for pharmaceutical control of these neurologic events.

**RAISING EXPECTATIONS IN THE MANAGEMENT OF PARTIAL ONSET SEIZURES**

The selection of antiepileptic drugs depends upon many factors, including the type of seizure disorder involved, the pharmacokinetic and pharmacodynamic profiles of the drugs being considered, and the benefits and risks related to their use. Newer antiepileptic agents have different mechanisms of action and metabolic pathways; these drugs allow neurologists to try novel drug combinations that may prevent seizures, minimize adverse reactions, and improve QOL.

Sarah Hopkins, MD, MSPH, a Fellow in Child Neurology at the Cincinnati Children’s Hospital Medical Center, Ohio, reports on presentations delivered by experts during a satellite symposium. The speakers reviewed the possibility of pharmacokinetic and pharmacodynamic drug interactions during antiepileptic polytherapy, stressed the importance of synergism when using more than one drug in patients with seizure disorders, and proposed factors to consider when prescribing a drug regimen for an individual patient with epilepsy. These experts also discussed important issues in regard to prescribing adjunctive therapy to control epilepsy and discussed measures of functional outcomes that may help in assessing therapeutic benefit.

**WHAT TYPE OF DATA MAKES YOU PICK YOUR DRUG?**

Obviously, each type of clinical trial yields certain data and has particular advantages and disadvantages. Regrettably, in many cases, such studies yield contradictory results; this information may be important on one level, but it ultimately may not help the physician seeking a treatment that will best serve a patient’s needs.

Bernhard Suter, MD, a Fellow in Neurology at Baylor College of Medicine, Houston, Texas, recounts a panel discussion describing the benefits and limitations of randomized controlled trials, open-label extension trials, and naturalistic studies as they relate to the investigation of epilepsy and related syndromes and the manipulation of treatment schedules used to manage these medical conditions.

In addition, Dr. Suter delves into the important matter of measuring QOL, a term that covers a variety of issues related to a patient’s satisfaction with well-being and physical function. Epilepsy may cause profound physical and cognitive disabilities; particular tools that measure QOL may supply information about the benefits or disadvantages of therapy, changes in seizure activity over time, or ways that neurologic events affect patients and their daily function during treatment periods. These tools supply powerful data beyond those found by laboratory testing—they give us a glimpse into how therapeutic modalities affect physical and cognitive function and the mental states of patients suffering from seizure disorders.

**RUFINAMIDE: A CLINICAL UPDATE**

Lennox-Gastaut syndrome (LGS) is a devastating epilepsy syndrome marked by frequent, recurrent seizures beginning, usually, between 2 and 5 years of age. Seizures due to LGS are not easily treated, and affected children tend to manifest behavioral problems and developmental delays and premature death.

Rufinamide, a triazole derivative unrelated to any other epilepsy treatment currently marketed in the United States, recently was approved by the US Food and Drug Administration for the adjunctive treatment of seizures associated with LGS in children at least 4 years of age and adults. After discussing conventional measures used to treat LGS and the results of surveys asking physicians about their preferred treatment of this syndrome, Thomas Gann, MD, a Neurology Fellow at the University of Alabama at the Birmingham Epilepsy Center, Alabama, describes the pharmacokinetics of this important drug, recounts the results of pivotal trials investigating its safety and efficacy, and provides an overview of analyses that looked into the drug’s cost-effectiveness compared with that of other, less effective antiepileptic drugs. In addition, he discusses methods of measuring neuropsychologic changes among affected children and the toll that inadequate control of seizures takes on this patient population.

**WHEN MONOTHERAPY FAILS**

Finally, Vikram Bhise, MD, a Neurology Fellow at the State University of New York Downstate Medical Center, Brooklyn, confronts a serious and unfortunate circumstance faced by many patients with epilepsy and their physicians—the failure of a first drug prescribed to prevent seizures. He discusses the definition of mono-therapy failure and methods of selecting pharmaceuticals and surgical procedures to provide greater control of seizures. Importantly, judicious review of a drug’s pharmacodynamics and pharmacokinetics may predict whether a particular patient may tolerate and benefit from certain drugs or combinations of antiepileptic agents.

Dr. Bhise also explains differences noted when an antiepileptic drug is used in animals and humans, describes the types of research that minimize obstacles in gathering informative data, and discusses controversies surrounding the need for new drugs to treat seizures. Finally, he details the Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) study, which investigated the use of deep-brain stimulation in patients suffering from intractable partial or secondarily generalized seizures.

We thank these young practitioners for sharing information from these important medical meetings with us. Complete freedom from seizures remains the goal for every patient with epilepsy. However, we recognize that our current therapies may provide limited control of seizure activity for unpredictable periods. Certainly, future meetings of the neurology community will provide important information on surgical and pharmaceutical treatments, many of which are still in the investigational stage, that can improve the health, function, and QOL of patients with epilepsy.
New Insights into Childhood Absence Epilepsy

Mackenzie C. Cervenka, MD
Johns Hopkins Hospital, Baltimore, Maryland

Abstract Although childhood absence epilepsy (CAE) long has been considered to cause few serious sequelae, this neurologic condition recently was linked to learning difficulties and other neurologic and psychological problems among our young patients. An understanding of the clinical presentation of CAE, the genetic profiles of affected patients, and other medical conditions that may be linked to it can offer important information critical to its optimal treatment. Recently reported results from a comparison of three commonly used anticonvulsants in CAE patients may provide further clues about the most effective treatments for this disorder that would impose the fewest deleterious effects on children affected by it.

Childhood absence epilepsy (CAE), which encompasses up to 15% of all childhood epilepsy syndromes, traditionally has been considered to carry a benign prognosis. However, recent epidemiologic and phenotypic studies have shown that such comorbidities as cognitive and neuropsychological deficits vary considerably from one patient to the next. These individuals have complex genotype ranges, variable treatment responses, and disparate remission rates.

Overall, CAE represents a combination of heterogeneous syndromes rather than a single disease entity. At a symposium entitled “Childhood Absence Epilepsy Symposium: New Insights Into an Old Syndrome,” which was offered during the 62nd Annual Meeting of the American Epilepsy Society, experts provided a comprehensive overview of the variable clinical presentation, genetic heterogeneity, and comorbidities associated with CAE according to current knowledge. This symposium also marked the first release of results from a multicenter, randomized comparison of three commonly used anticonvulsants (ie, ethosuximide, valproate, and lamotrigine) used to treat CAE that was sponsored by the National Institutes of Health (NIH).

Testing Criteria and Using Evidence-Based Definitions

Based on concerns that the new criteria set forth by the ILAE (Table 1) were too stringent, Sadleir et al evaluated 47 cases and epilepsies. Absence seizures were defined as primary generalized seizures that were associated with simple, complex, typical, or atypical subtypes. The criteria were refined in 1985, with typical CAE being defined as primary (idiopathic) generalized epilepsy that occurs in school-aged children (mean age, 6–7 years) and in girls more frequently than boys; further, these events were associated with no comorbid developmental delay, with absences occurring several to many times each day.

Characteristics of atypical or secondary CAE included more heterogeneous findings on EEG, abnormal background EEG activity, and less abrupt clinical and EEG onset and offset. The criteria for CAE were refined further in 1989, as the heterogeneity of absence seizures and three syndromes of idiopathic epilepsy (ie, CAE, juvenile absence epilepsy [JAE], juvenile myoclonic epilepsy [JME]) were identified. The ILAE also defined a syndrome of cryptogenic generalized epilepsy, which featured myoclonic absences.

Definitons

In 1971, the International League Against Epilepsy (ILAE) proposed the first classification system for seizures and epilepsies. 

Dr. Cervenka is an Epilepsy and Clinical Neurophysiology Fellow in the Department of Neurology, Johns Hopkins Hospital, Baltimore, Maryland.
children with newly diagnosed, untreated CAE using ILAE common criteria. They analyzed 339 seizures on pretreatment EEG and applied the previously proposed exclusion criteria to diagnose CAE. Of 47 children evaluated, only 26 had seizures lasting longer than 4 seconds. A total of 43 children were 4–10 years of age; 31 had severe impairment during their seizures, 35 had no features of myoclonia (except mild activity of the eyes, eyebrows, and eyelids), 39 had no photic induction of seizures, 34 had fewer than three spikes per wave, and 22 had no disorganized discharges. Ultimately, 42 of the 47 children were excluded from a diagnosis of CAE based on these criteria. These findings indicated that the common criteria for CAE potentially were too restrictive; they excluded patients who otherwise would benefit from appropriate CAE treatment.

Until 1989, the clinical definition of a syndrome was driven pragmatically and determined by expert opinion, which might not have captured residual within-group variations adequately. Since then, evidence-based research findings largely have replaced expert opinion. Evidence-based definitions allow for further research that may produce useful prognostic information, mechanistic investigations, reliable diagnoses, correct treatment and management, and genetic determinants of the disease process. Evidence-based syndrome definitions have helped to describe phenotypes within CAE that ultimately may help in determining underlying mechanisms of disease processes and ways that various treatment modalities affect outcomes in patient subgroups. In all, such definitions allow for more rigorous testing of hypotheses, objective analysis of statistics, and creation of a system that includes new knowledge as it becomes available.

**UPDATES ON GENETICS OF CAE**

Adapted from a presentation by Ingrid E. Scheffer, MBBS, PhD, FRACP, Professor and Chair, Pediatric Neurology Research, Departments of Medicine and Pediatrics, University of Melbourne; Director, Pediatrics, and Co-Director, Children’s Epilepsy Program, Austin Health; and Pediatric Neurologist, Royal Children’s Hospital, Melbourne, Australia.

Ongoing research is investigating the clinical and molecular genetics of CAE. Established monogenic models have revealed γ-aminobutyric acid (GABA) subunit mutations in mice and humans. Further, susceptibility genes responsible for calcium-channel subunit mutations have been discovered. Clinicians caring for patients with CAE are particularly interested in ways that molecular testing fits into their clinical practices.

Lennox and others published a case-wise concordance study that showed an 80% concordance rate for monozygotic twins and 0% for dizygotic twins. Vadlamudi et al. published a case-wise concordance study that showed an 80% concordance rate for monozygotic twins and 0% for dizygotic twins with this condition. Studies analyzing epilepsy syndromes in affected relatives of probands with CAE have shown a heterogeneous collection of epilepsy phenotypes, including not only CAE but also JAE, JME, IGE with tonic-clonic seizures, febrile seizures, and adult-onset absence epilepsy. Winawer et al. performed a genetic familial aggregation study mapping families with CAE, JAE, and JME, finding concordance between CAE and JAE but not CAE and JME.

**Patterns of Heredity**

Most cases of CAE have a complex inheritance pattern; rarely, the disease is related to simple or monogenic inheritance patterns. Monogenic causes for IGE pathology have been linked to channelopathies, including mutations in voltage-gated ion channel subunits and ligand-gated channels.

GABA receptors are ligand-gated chloride channels that contain a pentameric subunit composition incorporating two α, two β, and one γ subunit. A mutation of the GABA subunit has been implicated to be a cause of familial CAE. GABA receptors with R43Q mutations expressed in HEK-293 cells of frog oocytes demonstrated an altered response to benzodiazepines. GABA receptor mutations in a mouse model resulted in behavioral arrest associated with 6- to 7-Hz spike-and-wave discharges that was blocked by ethosuximide. Recordings of cortical pyramidal neurons revealed fewer GABA-mediated synaptic currents, suggesting an underlying reduction in cortical inhibition for the mechanism of CAE in patients with R43Q mutations. Fedi et al. then demonstrated in vivo evidence for increased intracortical excitability among 14 human subjects with GABA R43Q mutations. The pathology of most IGEs appears to be polygenic and related to several susceptibility alleles (Table 2). However, these susceptibility alleles alone cannot account for the full phenotype of CAE, although their detection may provide a model for identifying components of complex inheritance.

At this time, no specific molecular tests for identifying genes of clinical importance are available. However, reported studies have provided the foundation for further investigation.
from failure. Drug-related systemic toxicity was defined by the presence of rash, an increase in body mass index (BMI) of 3 kg/m² or more, a decline in absolute neutrophil or platelet count, an increase in aspartate transaminase or alanine aminotransferase level, or an increase in bilirubin level above normal limits within the first year of initiating therapy. Failure also included patients who stopped taking the study drug or discontinued its use because of recommendations by their family or physician for any reason.

Secondary outcome measures included cognitive, behavioral, and quality-of-life (QOL) measures that were collected at the time of enrollment and after 4 months of treatment. Cognition was measured using the Connor Continuous Performance Test (CPT), a computer-based test of sustained attention requiring a rapid response or response inhibition. Behavior was measured using the Childhood Behavior Checklist; QOL was measured using the Sabaz QOL in CAE test. Serum was obtained from all patients to assess pharmacogenetic and nonheritable factors (eg, pharmacokinetics, EEG changes) that may have impacted treatment efficacy.

Randomization and repeated randomization. Patients who met the entrance criteria (Table 4) underwent double-blinded randomization at the time of study entry. They returned for monthly titration visits; at each evaluation, the family was interviewed regarding any seizures they may have witnessed since the patient entered into the study. If patients experienced no seizures, they underwent hyperventilation; if they did not have a clinical seizure following this provocation, they underwent a 1-hour video EEG with hyperventilation. If patients remained seizure-free, their anticonvulsant dose was not titrated. If they had a clinical or EEG-detectable seizure during any of these evaluations, their medication was titrated.

Patients were randomized again to receive one of the two remaining anticonvulsants if they failed treatment with the first agent. Patients having generalized tonic-clonic seizures during the study were not secondarily randomized to receive ethosuximide; likewise, patients

### Table 2: Studies Revealing Susceptibility Alleles in Childhood Absence Epilepsy

<table>
<thead>
<tr>
<th>Epilepsy syndrome</th>
<th>Gene products</th>
<th>Susceptibility allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic generalized epilepsy</td>
<td>T-type calcium channel</td>
<td>CACNB4&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>T-type calcium channel</td>
<td>CACNA1H&lt;sup&gt;25–27&lt;/sup&gt;</td>
</tr>
<tr>
<td>Childhood absence epilepsy</td>
<td>T-type calcium channel</td>
<td>CACNA1H&lt;sup&gt;25–28&lt;/sup&gt;</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy</td>
<td>R-type high voltage-dependent calcium channel</td>
<td>EFHC1&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Table 3: Previous Studies of Treatment for Childhood Absence Epilepsy

<table>
<thead>
<tr>
<th>Class of evidence</th>
<th>Number of studies</th>
<th>Level of evidence</th>
<th>Drugs evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>None</td>
<td>Level A</td>
<td>None</td>
</tr>
<tr>
<td>Class II</td>
<td>None</td>
<td>Level B</td>
<td>None</td>
</tr>
<tr>
<td>Class III</td>
<td>6</td>
<td>Level C</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lamotrigine</td>
</tr>
</tbody>
</table>

### Table 4: Entry Criteria into the NIH Childhood Absence Epilepsy Trial

#### Inclusion criteria
- Baseline 1-hour EEG showing a burst of 2.7- to 5-Hz spikes and slow-wave activity on a normal background lasting ≥ 3 seconds
- Age, 2.5–13 years
- Weight, > 10 kg
- BMI < 99<sup>th</sup> percentile for gender and age

#### Exclusion criteria
- Anticonvulsant treatment more than 7 days before randomization
- Diagnosis of juvenile myoclonic epilepsy or juvenile absence epilepsy
- History of major depression, autism, or pervasive developmental delay
- Generalized tonic-clonic seizures

NIH = National Institutes of Health; EEG = electroencephalogram; BMI = body mass index
who developed a rash or who began taking systemic contraceptives were not secondarily randomized to receive lamotrigine, and patients who developed hepatitis or pancreatitis were not secondarily randomized to receive valproate. Instead, these patients were assigned to the appropriate remaining study drug.

**Drug delivery.** Two methods of drug delivery—a double-dummy method for patients who could not take pills and an over-encapsulation method for those who could—were used. In the double-dummy method, all patients received either liquid ethosuximide and a placebo tablet, a chewable lamotrigine tablet, or a valproate capsule and liquid placebo. In the over-encapsulation group, patients received an ethosuximide capsule, a lamotrigine tablet, or a valproate coated tablet in a larger capsule that looked identical to each drug. Ethosuximide and valproate were titrated to a maximum daily dose of 60 mg/kg over 13 weeks, and lamotrigine was titrated to a daily dose of 12 mg/kg over 15 weeks.

**Results**

In all, the study was conducted at 32 sites, and 453 patients were enrolled between June 2004 and December 2007. The three treatment groups showed no significant differences in gender and ethnicity. The percentage of female patients was between 52% and 62% (average, 57%). The patients’ ages ranged between 2.5 and 13 years, per the inclusion criteria; overall, the age distribution was shifted toward the younger population. Patients had 1–35 seizures within a 1-hour routine EEG at the time of enrollment; a shift in distribution toward fewer seizures during the 1-hour period was noted.

**Freedom-from-failure rates.** At 4 months, freedom-from-failure rates were 53% in the ethosuximide group, 58% in the valproate group, and 29% in the lamotrigine group. The reason for treatment failure in most patients who failed lamotrigine therapy was lack of seizure control, and the majority of these seizures were clinical rather than only electroencephalographic in nature. Increased BMI was a greater cause for treatment failure in the valproate group than in the ethosuximide or lamotrigine groups. The rate of failure due to rash or patient withdrawal was similar among the groups.

**Adverse effects.** Of the other adverse side effects identified besides an increase in BMI and rash, nausea and vomiting were significantly more common with use of ethosuximide, and fatigue and hostility were most common among patients taking valproate. In comparing pharmacokinetics of the anticonvulsants, no significant differences in trough blood levels between responders and nonresponders were noted.

Based on the primary outcome measure (freedom from failure), ethosuximide was equivalent to valproate, and both of these drugs were superior to lamotrigine.

---

**For initial treatment of childhood absence epilepsy, ethosuximide was superior to valproate—and both were better than lamotrigine.**

The NIH investigators also examined a secondary outcome—cognitive deficits. That research is described in the following section.

### COGNITIVE DEFICITS IN CAE

Adapted from a presentation by David Masur, PhD, ABPP, Clinical Professor of Neurology and Director of Neuropsychology, Department of Neurology, The Children’s Hospital at Montefiore, Bronx, New York.

CAE patients have shown worse performance on visual attention and memory tasks than have age-matched peers and have exhibited frontal lobe dysfunction. However, no consistent pattern of cognitive deficits has emerged, and sample sizes of CAE patients have been relatively small.

As a component of the NIH CAE trial, participants performed neuropsychological batteries and intelligence quotient (IQ) testing administered by local psychometrists who were blinded to their treatment arm; results were double-scored.

The hypothesis—that specific aspects of attention are affected in patients with CAE—also was used as the secondary outcome for this study, in case no one particular anticonvulsant emerged as superior during analysis for freedom from failure. (As noted previously, in fact, no one anticonvulsant was found to be superior.)

### Methods

Patients who were at least 6 years of age performed the Connor’s Continuous Performance Test (CPT) II, and those who were 4–5 years of age performed the Kiddie CPT. Participants sitting at a computer terminal were shown letters on a screen at different rates and were instructed to respond by pressing the space bar unless they saw the letter “X.”

Tests were scored based on a confidence index (CI) that considered all variables and measures, including response time, errors of omission, and errors of commission. Errors of omission occurred when the participant did not respond to the presented stimulus before the next stimulus was presented (ie, when participants were losing focus); errors of commission occurred when the participant responded when they were supposed to inhibit a response (ie, when the “X” was shown on the computer screen). The CI indicated the percent chance of having an attention profile similar to that of attention deficit hyperactivity disorder (ADHD). For instance, a CI of 0.5 indicated that the participant had a 50% chance of having an attention profile similar to that of ADHD. For the purpose of this study, a CI of 0.6 heralded a significant deficit in attention.

### Results

At baseline, 34% of CAE patients had significant difficulty with attention. This prevalence was four times greater than that seen among the general population, which is estimated to be 3%–8%. Patients performed significantly more errors of
omission than commission, suggesting their failure to maintain focus. Baseline neuropsychiatric IQ, learning, and memory were not different from those of the general population. At 4 months after anticonvulsant treatment, patients treated with valproate had a significant increase in attention difficulties when compared with their baseline performance. Meanwhile, no adverse changes or significant improvement in performance were noted with the use of ethosuximide or lamotrigine.

Thus, children with CAE who participated in this study had average IQs, memory, and language function, but they experienced a significant increase in attention deficits when compared with the prevalence reported among the general population. These deficits persisted despite control of seizures with anticonvulsant therapy. Further, use of valproate worsened attention spans of CAE patients; such a finding ultimately may impact learning and achievement negatively.

When combining results of the primary outcome data and the secondary outcome measure (ie, CI on CPT as a measure of attention), investigators determined that ethosuximide was superior to valproate. Attention declined in patients taking valproate over 4 months, indicating a potential deleterious effect of valproate therapy on attention in CAE patients. Ultimately, ethosuximide therapy was superior to that of valproate—and both were superior to lamotrigine—for the initial treatment of CAE.

## CONCLUSION

CAE likely encompasses a wide range of phenotypes and genotypes. Better definition of phenotype groupings will facilitate accurate determination of genotypes. The ultimate goal is to identify disease mechanisms and to tailor individualized therapy based upon these mechanisms.

New evidence from a multicenter, NIH-sponsored trial suggested that ethosuximide is the most effective therapy for the initial treatment of CAE. Although valproate is equally effective initially, its cognitive side effects may outweigh some anticonvulsant benefits. CAE patients are at an increased risk for attention deficits; however, when compared with their peers, these patients have otherwise intact cognitive functioning.

Several caveats to the preliminary findings of the NIH investigators are apparent. First, the characteristics of patients most likely to benefit from each medication are not yet known. Second, the results of the long-term (ie, 1-year) outcomes of this research have not yet been analyzed. Third, and finally, outcomes for patients who failed the first medication and who received a new treatment have yet to be determined. Thus, these results should be applied to other patients on an individual basis, considering the benefits of treatment versus the risk of cognitive and other side effects.

## REFERENCES

Mackenzie C. Cervenka, MD  New Insights into Childhood Absence Epilepsy

2008;70:2137–2144.
Immune-Mediated Epileptic Encephalopathies in Children

Rani K. Singh, MD
Children’s National Medical Center, Washington, DC

**Abstract** The causes of most epilepsy syndromes are unknown, but autoimmunity may contribute to the disease, especially in children with new-onset focal, multifocal, or generalized seizures. Aside from Rasmussen's and limbic encephalitides, newly described syndromes that cause encephalopathy or seizures with or without fever and that lack any evidence of infection have been characterized. They include devastating epileptic encephalopathy in school-aged children; acute encephalitis with repetitive, refractory partial seizures; and severe partial epilepsy and encephalopathy due to an immune-mediated disorder. Additionally, patients having any of a number of systemic autoimmune diseases (eg, systemic lupus erythematosus, Hashimoto’s or Behçet’s disease, and Parry-Romberg scleroderma) may present with encephalopathy and seizures associated with the presence of characteristic diagnostic autoantibodies. In some patients with seizure disorders, antibodies to the voltage-gated potassium channel, the glutamate receptor, and glutamic acid decarboxylase may serve as prognostic markers. In a child having a recent onset of refractory seizures associated with progressive decline in cognitive function, an immune-mediated encephalopathy should be considered. Immunotherapy may be beneficial in such cases, although the choice of immunotherapy and the extent of possibly effective treatment remain unclear.

In a majority of epilepsy syndromes, a specific cause remains unknown. Genetic mutations in central nervous system (CNS) ion channel genes have been identified in several different epilepsy syndromes. Further, autoimmunity may contribute to epilepsy, because some syndromes, particularly those affecting children, may respond to immunomodulation.

During a session entitled “How Many Immunomediated Epileptic Encephalopathies Exist in Children?” held during the 8th European Congress on Epileptology (ECE) in Berlin, Germany, speakers investigated the possibility that immunopathologies have a role in some types of epileptic disease experienced by our youngest patients. This article reviews the major immune-mediated epileptic encephalopathies, discusses newly described childhood diseases of this type that may have an autoimmune origin, considers systemic autoimmune diseases that are associated with epileptic encephalopathies, and identifies key immunologic markers that have been linked to epilepsy.

The session was chaired by Federico Vigevano, MD, Head of the Department of Neurology, Bambino Gesù Children's Hospital, Rome, Italy.

**OVERVIEW OF CLINICAL ENTITIES**

Adapted from presentations by Lucia Fusco, MD, Department of Neurology, Bambino Gesù Children’s Hospital, Rome, Italy; Olivier Dulac, MD, Professor of Pediatrics, Université René Descartes, and Hôpital Saint-Vincent-de-Paul, Service de Neuropédiatrie, Paris, France; and Christian F. Bien, MD, Department of Epileptology, University of Bonn, Germany.

The word “encephalopathy” generally refers to a CNS disorder with impaired cognition of any cause. “Epilepsy” refers to a heterogeneous condition characterized by recurrent seizures that may have many underlying, and often unrelated, causes. A close investigation of medical conditions that may contribute to the advent and recurrence of seizures provides insight into the interrelationships of CNS disorders that ultimately result in epilepsy.

Table 1 lists the diagnostic features of the epileptic encephalopathies discussed in this section.

**Rasmussen’s Encephalitis**

As one of the most well-described epileptic encephalopathies of childhood, Rasmussen’s encephalitis is characterized by the triad of intractable focal seizures, progressive hemiparesis, and increasing intellectual impairment. Approximately 85% of patients suffering from this condition are less than 10 years of age.

In most patients, seizures are the initial neurologic manifestation of this condition. During the early stages, focal motor and generalized tonic-clonic seizures are most common; over time, various seizure types evolve, with the presence of early subclinical seizures and the development of epilepsia partialis continua (EPC). Progressive hemiparesis, often accompanied or shortly followed by slowly progressive intellectual deterioration, may develop. Initial cognitive deficits are in speech (primarily dysphasia and dysarthria), cortical sensory loss, and visual deficits.

As the disease progresses, the seizures
Ultimately may abate, and progression of the neurologic deficit and intellectual impairment may cease. By this stage, patients may experience moderate-to-severe hemiparesis, a visual-field defect, and mild-to-severe cognitive impairment.3

The pathology initially described by Rasmussen and Andermann2 consisted of chronic inflammatory changes with perivascular cuffing by round cells in the cortex and white matter, nodular and diffuse microglial infiltration, leptomeningeal round cell accumulation, loss of nerve cells, astrocytosis, spongiosis, and vascular changes. Magnetic resonance imaging (MRI) results are characterized by hemiatrophy; abnormal, high-signal intensity on proton density; and T2-weighted imaging that suggests gliosis.3

**Antibodies.** This condition has been described for half a century, yet its etiology remains unclear and speculative. Viral etiologies causing a chronic or acute viral infection leading to an abnormal immune response have shown mixed results, but there has been a resurgence of interest in the possibility of an autoimmune cause for the disease.

Some 15 years ago, circulating antibodies to the glutamate receptor (GluR) type 3 (GluR3), a member of the ligand-gated ion channel family, were identified in rabbits and, later, in affected children.4 The antibodies may trigger seizures directly by overstimulating these GluRs of the CNS. However, autoantibodies to GluR3 may not be specific for Rasmussen’s encephalitis—they also may be associated with other forms of epilepsy, particularly the catastrophic types.5

In 2000, autoantibodies against the presynaptic protein Munc18-1, a member of the Sec1 family of proteins that are required for every step of intracellular membrane fusion, were identified in one patient with Rasmussen’s encephalitis who previously exhibited anti-GluR3 antibodies; this finding suggested that a new subgroup of patients may have been discovered.4 Thereafter, autoantibodies against Munc18-1 were found in 20% of patients with biopsy-proven Rasmussen’s encephalitis.7

Recent data challenged the role of humoral immunity, acknowledging a possible role for cytotoxic T cells in this disease. A high density of T cells, microglial nodules, and reactive astrocytes have been identified in affected tissue, especially in samples from patients having early stages of the disease. Inflammatory infiltrates have consisted mainly of CD3+CD8+ T lymphocytes that were stained with granzyme B, a serine protease released by activated cytotoxic T cells that induces apoptosis.8

**Treatment.** The suggestion that an autoimmune process may underlie Rasmussen’s encephalitis led to the use of intravenous immunoglobulin (IVIg) and steroids to modify its progression. Patients with this disease may benefit from IV methylprednisolone.9 Andrews et al10 found that plasma exchange provided dramatic improvement; they suggested that a protocol of five or six single volumes of plasma exchange be given over 10–12 days to start, with an infusion of 1 g/kg of IVIg administered on the next day.

Most recently, tacrolimus, which suppresses T-cell activation, has proven beneficial against Rasmussen’s encephalitis. In an open trial, Bien and others11 noted that patients treated with tacrolimus had a superior outcome when compared with historical controls when neurologic function and progression of cerebral atrophy were considered. Presently, this group is conducting a prospective, randomized, controlled trial of IVIg and tacrolimus in patients with Rasmussen’s encephalitis.

Functional hemispherectomy has been accepted widely as helpful in producing seizure control and in preventing further physical and cognitive decline in patients with Rasmussen’s encephalitis. Currently, physicians tend to consider surgery during the earlier course of the illness to attempt to limit dysfunction in the opposite hemisphere. Immunomodulatory treatments usually are considered before a definitive surgical approach is attempted.12

**Limbic Encephalitis**

In 1968, limbic encephalitis was described, with symptoms including a subacute onset of episodic memory impairment, disorientation, and agitation. In addition, the condition commonly is associated with seizures, hallucinations, sleep disturbance, and histologic evidence of mesial temporal lobe inflammation.13

This form of encephalitis usually presents during adulthood as a paraneoplastic disorder associated with such onconeural antibodies as Hu in patients with lung cancer, Ma2 in patients with testicular tumors, or CRMP5/CV2 in patients with thymomas.14 More recently, it also was identified as a nonparaneoplastic disorder that is associated partially with serum antibodies against voltage-gated potassium channels (VGKC-Abs).15,16

Initially, the MRI of affected patients may show temporomedial hypertensive signal changes in T2 and a fluid-attenuated inversion recovery sequence; in adults, these changes may evolve into hippocampal sclerosis.17 Onconeural antibodies of paraneoplastic syndromes are intracellular; they may persist over the disease course and lead to a poor memory prognosis.

Both nonparaneoplastic and paraneoplastic types of this condition have responded to immunotherapies (eg, IV steroids, Igs, plasma exchange). Antibody titers in nonparaneoplastic and paraneoplastic types may reflect clinical response

---

**TABLE 1**

Characterization of Immune-Mediated Epileptic Encephalopathies

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Fever</th>
<th>Infection</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen’s encephalitis</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>–/+</td>
<td>–/+</td>
<td>–/+</td>
</tr>
<tr>
<td>Devastating epileptic encephalopathy in school-aged children (DESC)</td>
<td>–</td>
<td>–</td>
<td>+/–</td>
</tr>
<tr>
<td>Acute encephalitis with repetitive, refractory partial seizures (AERRPS)</td>
<td>–</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Severe partial epilepsy and encephalopathy due to an immune-mediated disorder (SPEEDI)</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
</tr>
</tbody>
</table>

a Herpes encephalitis often is considered an infectious subset in this group.
to treatment. Less information on the course of this disease in children is known, although a European-wide effort to collect data on pediatric limbic encephalitis is ongoing.

**Devastating Epileptic Encephalopathy in School-Aged Children (DESC)**

Over the past decade, a syndrome of childhood-onset, intractable, convulsive status epilepticus following an unidentified febrile illness has been recognized. The entity has been given many names—epilepsy of acute encephalitis, idiopathic catastrophic epileptic encephalopathy, severe refractory status epilepticus owing to presumed encephalitis, fever-induced epileptic encephalopathy in school-aged children, and, most recently, DESC.

In this condition, status epilepticus persists for weeks regardless of treatment, even general anesthesia. Its main features include (1) onset in previously healthy, school-aged children; (2) an initial febrile context but no evidence of infection; (3) onset with prolonged, intractable status epilepticus followed by intractable epilepsy without any latent period in between; (4) clinical and electroencephalographic (EEG) features of focal-seizure onset during both status epilepticus and follow-up, primarily in the perisylvian areas; (5) bilateral mesial temporal dysfunction on neuropsychological tests with atrophy and/or in hypersignal on MRI; and (6) frontal lobe involvement in half of the cases. Morbidity of this group consists of severe memory, language, and behavioral troubles, with permanent cognitive sequelae.

Patients usually are considered to suffer from an encephalitis; however, no evidence of inflammation or infection has been reported. The death rate is high, and survivors remain with epilepsy and severe cognitive dysfunction.

**Acute Encephalitis with Repetitive, Refractory Partial Seizures (AERRPS)**

Another entity presents with refractory partial seizures during a prolonged acute phase followed by intractable epilepsy; it is referred to as AERRPS. Its diagnostic criteria include a prolonged acute phase of more than 2 weeks; partial seizures that persist from the acute phase to convalescence with the same symptoms; seizures that frequently evolve into convulsive status epilepticus, especially during the acute phase; marked intractability of seizures; and exclusion of related disorders (eg, known viral encephalitis, metabolic disorders). Additional characteristics may include refractory seizures despite treatment with antiepileptic drugs or the presence of serum anti-GluR antibodies. Analysis of cerebrospinal fluid (CSF) often shows pleiocytosis; the diagnosis of encephalitis is made with no identified infectious or metabolic cause.

One patient with AERRPS tested positive for autoantibody to N-methyl-D-aspartate (NMDA-type) GluRε2; a combination of mild hypothermia therapy, steroid pulse therapy, and massive IgG therapy was effective.

**Severe Partial Epilepsy and Encephalopathy due to an Immune-Mediated Disorder (SPEEDI)**

Very recently, an entity known as SPEEDI has been characterized. The syndrome occurs in previously healthy children who suffer from severe epilepsy after an acute febrile encephalopathy; they experience frequent seizures or even status epilepticus with cognitive dysfunction.

Among a cohort of eight patients, the average age of onset was 5 years (L. Fusco, unpublished observations). Fever always was found upon presentation; seven patients presented in status epilepticus. Blood and CSF studies showed no evidence of infection; however, some analyses showed markers of immune dysfunction. Results of EEG showed slow-wave components in the δ and θ ranges. In three patients, results from MRI were normal; isolated hyperintensities noted in another three patients were treated with either pulse steroids or IV Ig. Cognitive regression occurred in the majority of the cohort; the severity was mild to moderate in two patients and severe in three others.

**Systemic Lupus Erythematosus (SLE)**

Usually, SLE presents during adulthood; onset before age 5 years is rare. Up to 25% of children and adolescents with SLE may present signs of the disease within the first year of life. Neuropsychiatric involvement is common; the most frequent manifestation are seizures, both at disease onset (15%) and during its evolution (36%).

Autoantibody profiles between juvenile and adult forms of the disease also differ, with children more frequently testing positive for antibodies against cardiolipin (IgG), DNA, Smith antigen, and ribonucleoprotein. Previous studies in adults and children with SLE suggested that the presence of antiphospholipid antibody is an important determinant of morbidity and, possibly, mortality in patients with neuropsychiatric disease. Recently, the prevalence of antibodies against β2-glycoprotein I was found to be higher in a group of SLE patients with neuropsychiatric disease than it was in those without that pathology.

**Hashimoto Encephalopathy**

Occurring predominantly in females, Hashimoto thyroiditis is the most common cause of thyroid enlargement and hypothyroidism in children over 6 years of age in North America and is the most common type of thyroiditis in both children and adults.

The effects of Hashimoto encephalopathy are broad and include cognitive dysfunction.
impairment, psychiatric symptoms, movement disorders, seizures, myelopathy, and varying degrees of impaired consciousness. The most frequent clinical symptoms in one recent review by Alink and de Vries were seizures (80%), confusion (52%), headache (40%), hallucinations (32%), and ataxia (36%). The onset of symptoms usually is acute or subacute, followed by a progressive or relapsing-remitting course.

The diagnosis of Hashimoto encephalopathy is based on the triad of (1) neuropsychiatric symptoms, often affecting more than one area of the CNS; (2) the detection of antimicrosomal or antithyroglobulin antibodies in serum; and (3) the elimination of other potential etiologies. Mild-to-moderate elevations in CSF protein may occur, but serum levels of antithyroid antibodies often are normal. The presence of antimicrosomal antibodies may be more specific for Hashimoto encephalopathy. No prospective, controlled studies have been done in children.

Either methylprednisolone pulse therapy or daily oral prednisone/prednisolone is recommended to treat this condition. Corticosteroid therapy may be necessary for a few months or for as long as 1–2 years; dosage tapering may be attempted intermittently as tolerated by the patient.

Behçet’s Disease

A chronic systemic inflammatory disorder of unclear etiology that primarily affects adults, Behçet’s disease is characterized by the clinical triad of recurrent oral aphthous ulcers, genital ulcers, and inflammatory eye disease. Common neurologic features may include seizures, headache, cranial nerve signs, ataxia, and sensory disturbances.

CSF studies may show an increased opening pressure, mild elevations of protein levels, or pleocytosis, but the overall pattern often is not consistent. In many different ethnic groups, Behçet’s disease is associated with the gene for human leukocyte antigen (HLA) B51, which may be the major susceptibility gene for the disease.

Behçet’s disease may be treated with a wide range of immunosuppressants, including prednisolone, azathioprine, colchicine, cyclosporine, cyclophosphamide, and methotrexate.

Scleroderma

Parry-Romberg syndrome (PRS), also known as localized linear scleroderma (LSCS), is a rare and puzzling disorder characterized by progressive and self-limited atrophy of skin, subcutaneous tissue, muscles, and underlying bone. Pathologic findings from the skin and brain of affected patients have suggested that the disease may have an autoimmune basis.

Zulian et al performed a multinational study of juvenile scleroderma patients, finding that neurologic manifestations were present in 17%. These effects consisted of epilepsy, CNS vasculitis, peripheral neuropathy, vascular malformations, headache, and neuroimaging abnormalities; they occurred more often in patients with fascioscleroderma and PRS. Serum autoantibodies isolated in samples from PRS patients include antinuclear, antithistone, and anticentromere antibodies; however, neither rheumatoid factor nor anti-DNA antibodies were noted.

The combination of progressive unilateral brain atrophy, epilepsy, and chronic inflammatory brain changes in some PRS patients closely resembles that of individuals with Rasmussen’s encephalitis. Thus, immunosuppressive therapy should be considered in patients with PRS who have disabling neurologic symptoms.

IMMUNOLOGIC MARKERS IN EPILEPSY

Adapted from a presentation by Angela C. Vincent, PhD, FRCPath, FMedSci, Head, Department of Clinical Neurology, and Fellow, Somerville College and Professor of Neuroimmunology, University of Oxford, United Kingdom.

Our understanding of epileptic encephalopathies is improving, leading us to measure antibodies to neuronal proteins regularly in adults and children. As a result, three additional antibodies have been correlated with epilepsy and seizure-related disorders. Table 2 lists serum antibodies associated with epileptic encephalopathies and other autoimmune disorders with seizures.

VGKC-Abs

As mentioned previously, VGKC-Abs have been reported in cases of reversible limbic encephalitis. Vincent and others published a review of adults who presented with subacute symptoms of memory loss, confusion, and seizures. Serum levels of VGKC-Abs ranged from 450 pM to 5,128 pM; levels in neurologic and healthy controls, in comparison, were less than 100 pM. In five patients, CSF VGKC-Ab levels varied between less than 1% and 10% of serum values, and the majority of patients had low sodium plasma concentrations upon presentation. Patients treated with various regimens that included some form of steroids, plasma exchange, and administration of IVlg experienced variable falls in serum VGKC-Ab levels to 2%–88% of the initial values. The researchers noted marked improvement of neuropsychological functioning in six patients, slight improvement in three patients, and no improvement in one individual. The improvement in neuropsychological functioning in seven patients correlated broadly with the fall in antibody levels.

In an all-ages study of patients with seizure disorders, the highest titers of VGKC-Abs were found primarily in older-onset patients having acute or subacute encephalopathic disorders. However, VGKC-Abs have been present in 6% of patients with typical long-standing epilepsy not associated with limbic encephalopathy. In the few reported cases of children with this condition, younger patients almost always have low antibody levels. Thus, there is less of a correlation between VGKC-Abs in this age group.

NMDA GluR Antibodies

The inotropic NMDA GluR plays a role in synaptic plasticity, learning, and memory and in the pathologic processes of ischemic brain injury, neurodegenerative diseases, and epilepsy.

Takahashi et al studied autoantibodies against the NMDA GluRε2 and its epitopes in serum and CSF samples from...
enry M D  Immune-Mediated Epileptic Encephalopathies in Children

TABLE 2
Serum Antibodies Linked to Medical Conditions Associated with Seizures

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen’s encephalitis*</td>
<td>Anti-GluR3, Anti-GluRε2, Anti-Munc18-1</td>
</tr>
<tr>
<td>Limbic encephalitis</td>
<td>Onconeural Anti-Hu, Anti-Ma2, Anti-CRPMP/CV2, Non-paraneoplastic VGKC-Abs</td>
</tr>
<tr>
<td>AERRPS</td>
<td>Anti-GluRε2β</td>
</tr>
<tr>
<td>SLE encephalopathy</td>
<td>Anti-cardiolipin Anti-smooth muscle Anti-RNP Anti-phospholipid Anti-β2GPI</td>
</tr>
<tr>
<td>Hashimoto encephalopathy</td>
<td>Anti-microsomal Anti-thyroid</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>HLA-B51*</td>
</tr>
<tr>
<td>Parry-Romberg syndrome</td>
<td>Anti-nuclear Anti-histone Anti-centromere</td>
</tr>
<tr>
<td>Refractory localization-related epilepsies</td>
<td>Anti-GAD</td>
</tr>
</tbody>
</table>

Glutamate receptor; anti-GluR3 = circulating antibodies to the GluR type 3; anti-GluRε2 = antibody to GluR ε2; anti-VGKC-Abs = serum antibodies against voltage-gated potassium channels; anti-RNP = antibodies to ribonucleoprotein; anti-β2GPI = β2-glycoprotein I; HLA = human leukocyte antigen; AERRPS = acute encephalitis with repetitive, refractory partial seizures; SLE = systemic lupus erythematosus
* Also has associated cytotoxic/cell-mediated immunity
β Also isolated in cerebrospinal fluid
* Not an antibody but a major susceptibility gene for the disorder

20 patients. Five patients had definitive Rasmussen’s encephalopathy with EPC, 4 had definitive Rasmussen’s encephalopathy without EPC, and 11 had clinical Rasmussen’s encephalopathy with EPC. All 9 patients with biopsy-proven Rasmussen’s encephalopathy, and 10 of the 11 patients with clinical Rasmussen’s encephalopathy had GluRε2 antibodies in serum or CSF. Thus, GluRε2 antibodies may represent another diagnostic marker for Rasmussen’s encephalopathy with or without EPC.

In a prospective review of nonviral limbic encephalitis, Dalmau and Bataller14 found that paraneoplastic antibodies to the NR1/NR2B heteromers of NMDA were present in young women with benign–appearing cystic tumors of the ovary (mature or immature teratomas) who developed a severe and characteristic encephalitis. The overall prognosis for epilepsy associated with the anti-NMDA receptor is fairly positive, but the underlying tumor also must be addressed.

Glutamic Acid Decarboxylase (GAD) Antibodies

The enzyme GAD catalyzes the conversion of L-glutamic acid to gamma-aminobutyric acid (GABA). GAD primarily is expressed in GABA-secreting neurons and in pancreatic β cells, which also may secrete GABA as a paracrine signal molecule.

Anti-GAD antibodies (GAD-As) were first implicated in the pathogenesis of type 1 diabetes and stiff-man syndrome.43 Peltola et al44 reported that in patients with refractory localization-related epilepsy, GAD-As were found in eight patients and were absent in patients with generalized epilepsy, other neurologic disorders, and controls. High levels of GAD-A (> 1,000 U) were linked to a younger onset of a chronic, drug-resistant epilepsy associated with focal EEG abnormalities but normal brain MRI results.40

CONCLUSION

Of the primary CNS encephalopathies discussed, Rasmussen’s encephalopathy has the most evidence favoring an autoimmune mechanism for pathogenesis. Administration of IVIg, high-dose steroids, and plasma exchange have provided benefit; however, the more recent suggestion of a cell-mediated process may prove true, and tacrolimus may emerge as the most beneficial current treatment for this condition. Immune-mediated treatments may modify the clinical course of the disease; however, it is not yet clear whether they also can modify the endpoint.12

Limbic encephalitis may be subdivided into paraneoplastic and non-paraneoplastic forms. The presence of certain antibodies in samples from affected patients may have prognostic significance.

In an otherwise healthy child who develops status epilepticus a few days after a febrile illness along with a progressive decline in cognitive function, both DESC and SPEEDI (in the case of concomitant fever) should be considered. In the case of partial status epilepticus with encephalopathy, AERRPS should be in the differential. The goal of therapy should focus on stopping seizures before the start of status epilepticus. Anti-inflammatory medications or antiepileptic drugs targeting the glutamatergic pathway may be the most promising.

The diagnosis of VGKC-Ab–associated limbic encephalitis should be suspected in patients of either sex presenting with a subacute onset of disorientation, confusion, and memory loss, particularly when signs and symptoms are associated with medial temporal lobe signal change on MRI. The presence of autoantibodies to VGKC, NMDA receptors, and GAD suggests that the immune system may contribute to certain forms of epilepsy or seizure-associated disorders.

It remains unclear which immunotherapeutic treatment confers the best outcome and to what extent such a treatment may be effective. The presence or absence of autoantibodies may help us to realize a patient’s prognosis and may guide treatment. Further studies are needed to determine whether antibodies are primarily pathogenic or are a secondary target, especially in children.

REFERENCES

8. Bien CG, Urbach J, Deckert M, et al. Diagno-
Until the early 1980s, most patients with epilepsy were treated with multiple antiepileptic drugs (AEDs) to maximize seizure control and to minimize doses of medications causing significant neurotoxicity—which included most of the medications available at that time.\(^1,2\) Polytherapy was so common that some drugs were provided in combination formulations. However, clinical evidence eventually indicated that polytherapy resulted both in little improvement of seizure burden and in adverse effects related to neurotoxicity.\(^2,4\)

Currently, physicians select an AED based upon the type of seizure that the patient has and the side-effect profile and interactions associated with the medication. Some 60%–70% of patients have a good response with the initial AED and become seizure-free.\(^5\) The remaining 30%–40% of patients, however, may need to switch to another agent or to receive add-on therapy.\(^6\) However, if a patient is not seizure-free after attempting monotherapy with different drugs, that patient is not likely to become seizure-free with polytherapy.\(^5\)

The availability of new AEDs with varying mechanisms of action and modes of metabolism may offer new opportunities to combine drugs with different mechanisms of action to yield synergistic effects; this practice may help more patients to become seizure-free, as it minimizes negative interactions. The pharmacokinetic profile of drugs is important in limiting interactions and negative side effects and in maximizing efficacy. Many of the newer AEDs have more favorable pharmacokinetics (eg, linear kinetics) than do older drugs, and they also offer excellent oral bioavailability and minimal interactions with other agents.

Lastly, the physician must consider the impact that a medication has on the patient’s quality of life (QOL). Neurologists commonly say that they strive for the best seizure control with the fewest side effects. The use of newer AEDs, including lacosamide (which has been approved by the US Food and Drug Administration but is not yet commercially available for use in the US), may help us to achieve that goal more often.

At a satellite symposium offered during the 8th European Congress on Epileptology in Berlin, Germany, experts in epilepsy and its treatment reviewed current knowledge of the adjunctive treatment of refractory partial seizures. The session was chaired by Günter Krämer, MD, Medical Director of the Swiss Epilepsy Centre, Zurich, Switzerland.

**Abstract** Until about 25 years ago, most patients diagnosed with epilepsy used more than one drug, commonly combined in one formulation, both to control seizures and to allow use of lower drug doses to minimize the chances of adverse reactions. More recently, the development of new antiepileptic drugs (AEDs) allows a greater selection of drugs to prescribe depending upon the type of epilepsy diagnosed and considerations related to other agents used. During a satellite symposium offered at the 8th European Congress on Epileptology, experts in epilepsy and its treatment reviewed pharmacokinetic and pharmacodynamic factors that physicians must consider when prescribing these pharmaceuticals. In addition, they discussed the use of adjuvant therapy in patients having partial or refractory seizures and methods to optimize therapy to improve outcomes.

**Raising Expectations in the Management of Partial Onset Seizures**

Sarah Hopkins, MD, MSPH

Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio

---

**Does Mode of Action Generate Synergistic Effects?**

Adapted from a presentation by Philippe Ryvlin, MD, PhD, Senior Neurologist, Department of Functional Neurology and Epileptology, Hospices Civils de Lyon, Lyon, France.

The treatment goal for patients with epilepsy is to become seizure-free while taking only one medication, but this goal is not always attainable. In fact, the chance that adding a second medication will improve a patient’s seizure frequency is approximately 6%–30%.\(^5,6\) In studying 470 patients with newly diagnosed epilepsy, Brodie and Kwan\(^5\) found that the chance of remission was 47% on first monotherapy, 13% on second monotherapy, and 1% on third monotherapy;
an additional 3% of patients became seizure-free on two drugs.

Pharmacodynamic interactions that occur during combined use of AEDs with different mechanisms of action may be more effective against seizures than is use of either agent alone. Taking advantage of these interactions could lead to a greater percentage of patients becoming seizure-free.

**Pharmacokinetic vs Pharmacodynamic Interactions**

Pharmacokinetic interactions comprise the effects that a drug has on the metabolism of another medication. On the other hand, pharmacodynamic interactions refer to the way that a drug may modify another drug's effects without affecting serum concentration. Pharmacodynamic interactions may be additive (ie, the response is the same as expected if the effects of the drugs taken alone were summed) or synergistic (ie, the response is greater than the sum of those for each agent taken independently). Pharmacodynamic interactions also may be infraadditive (ie, the combined effects of two drugs are less than those predicted based on dose additivity), which may cause one or both of the involved medications to be less effective when the combination is used. Pharmacodynamic interactions may result from different effects of drugs at the molecular target of the medication (eg, ion channels, neurotransmitter systems) or other physiologic changes.

Basic mechanisms of action for older and newer AEDs appear in Table 1. Some AEDs have similar sites of action, but they may exert very different effects. For example, 10 medications listed in Table 1 exert their effects at sodium channels, but their exact mechanisms of action and biologic effects are different and often are not understood fully. Lacosamide, the newest AED on the list, is novel because it selectively enhances slow sodium-channel inactivation to normalize activation thresholds.

**Seeking Synergism**

Multiple studies have investigated synergistic drug interactions in animal models. However, not all of the studies controlled for pharmacokinetic interactions, and the performance of these medications in animal models does not always apply directly to epilepsy patients.

Jonker et al assessed the quality of evidence for AED synergism in animal models. In all, they included 536 interaction experiments using four different animal models of epilepsy in their review, reporting synergistic interactions in 293 (54%) and additive interactions in another 232 (43%). However, investigators must control for pharmacokinetic interactions before they can conclude that pharmacodynamic interactions occur. In 54% of the studies included in the review, pharmacokinetic interactions were not evaluated; most studies that included an analysis of pharmacokinetic interactions examined levels of one medication.

Most of the studies included in the Jonkers study assessed pharmacodynamic interactions by evaluating the dose of one drug required to produce a change in the ED50 of another drug. The ED50 is the drug dose required for effectiveness in 50% of the population. Studies using this semiquantitative method were more likely to find a significant interaction than were those using such fully quantitative methods as isobolographic analysis. Additionally, most studies did not examine drug levels in central nervous system tissue and did not test multiple doses of each AED. The report concluded that further, quantitative studies, including assessment of both pharmacokinetic and pharmacodynamic interactions of selectively acting medications, are needed to develop synergistic drug combinations.

**Lamotrigine/valproate.** The results of animal studies done to date suggest that synergistic effects of AEDs occur, but they do little to suggest what combinations may be most advantageous. There are even fewer data available from human studies. The combination of lamotrigine and valproate is studied frequently because of its presumed synergistic effects in humans. Brodie and Yuen studied this combination in 347 patients with epilepsy who were poorly controlled on either valproate, carbamazepine, or phenytoin.
The researchers added lamotrigine to the medication regimens of these patients. If this addition was helpful, they weaned the patients off the initial AED used; eventually, the patient was using only lamotrigine. Approximately 60% of the patients in the valproate sodium group responded well to the addition of lamotrigine, as compared with only about 40% of the carbamazepine and phenytoin groups (Figure 1). In the group using valproate/lamotrigine, the number of generalized and partial seizures increased when sodium valproate was removed.

A crossover study of these medications by Pisani et al found that patients tended to have fewer seizures when lamotrigine and valproate sodium were combined, and the optimal dosage and serum concentration were lower for both medicines when they were combined.

**Other AED combinations.** Synergistic effects have been found with combined use of valproate sodium and ethosuximide for absence seizures and of valproate and carbamazepine for partial seizures. In the latter combination, however, valproate sodium inhibits the metabolism of carbamazepine and increases the levels of toxic carbamazepine-10,11-epoxide.

No randomized, controlled studies have been done to clarify synergistic effects of AEDs in humans. Therefore, human studies, along with animal studies using quantitative methods, must be performed to clarify the potential for AED synergism in patients with epilepsy.

### IDEAL PHARMACOKINETICS OF ADJUNCTIVE AEDs USED FOR PARTIAL ONSET SEIZURES

Adapted from a presentation by Philip N. Patsalos, FRCPath, PhD, Professor of Clinical and Experimental Epilepsy, Institute of Neurology, Queen Square, London, and Pharmacology and Therapeutics Unit, Chalfont Centre for Epilepsy, Chalfont St. Peter, Buckinghamshire, United Kingdom.

Pharmacokinetic interactions may occur during drug absorption, or the distribution of medications may be affected by protein binding, and metabolism may be altered via the cytochrome P450 system in the liver or by body processes. Additionally, saturation of transport during drug excretion may cause interactions.

The first choices for monotherapy in a patient with epilepsy are based on seizure semiology and the efficacy of a medication against a seizure type. The addition of a second drug is not quite as straightforward, because polytherapy carries the risk of drug interactions and side effects.

**Pharmacokinetics and Drug Selection**

Consideration of a drug’s pharmacokinetics is important to enhance patient compliance and limit toxicity. The most important characteristics include optimal bioavailability; a 12- to 24-hour half-life, to allow for convenient dosing; linear pharmacokinetics, so that the dose increase causes a relatively predictable change in AED levels; and the absence of drug interactions. Additionally, a drug that is metabolized by the kidneys is often preferred to one metabolized by the liver, because renal metabolism produces fewer active metabolites. These factors also are important to consider when weaning a patient from a medication to avoid toxicity or undertreatment.

Bioavailability of a medication is a concern, because an adequate serum level must be obtained via oral dosing. Bioavailability is particularly important when prescribing gabapentin; absorption of this drug is saturable, which leads to decreasing availability as the dose is increased.

Phenytoin, valproate, and carbamazepine have nonlinear pharmacokinetics that may lead to undertreatment or toxicity. Many of the newer AEDs, including levetiracetam, tiagabine, and lacosamide, have linear pharmacokinetics.

**Metabolic Considerations**

When drugs are metabolized by the same cytochrome P450 enzymes, drug interactions are more likely. Medicines that induce enzymes in the cytochrome P450 system include phenobarbital, primidone, phenytoin, and carbamazepine. Valproic acid, on the other hand, inhibits the cytochrome P450 system. Problems resulting from use of isoenzyme inducers may take longer to become apparent than do those involving inhibition, because induction requires the synthesis of more proteins over the course of days to weeks. Over time, the induction of drug metabolism may lead to decreased levels of an AED and breakthrough seizures.

Inhibition of a drug’s metabolism by another agent may be advantageous or deleterious. For example, the serum level

![Figure 1](image-url)
of the affected drug may increase to the extent that there is toxicity, but then the dose or frequency of administration of the drug may be reduced as seizure control is maintained. Combined use of medications that induce cytochromes may result in “chasing levels” of the drugs to maintain efficacy. Altered hepatic metabolism also is a concern in patients who are taking other drugs, such as warfarin and oral contraceptives.

AEDs that are metabolized minimally or not at all are desirable, because their use reduces the rate of medication interactions. Currently used drugs that are minimally metabolized are gabapentin, levetiracetam, and vigabatrin. Pharmacokinetics have become an important consideration during drug development; thus, newer AEDs tend to have fewer medication interactions and to fulfill more criteria for optimal pharmacokinetics. Medications that may be used adjunctively for partial epilepsy and that have favorable pharmacokinetic profiles include gabapentin, levetiracetam, lacosamide, tiagabine, and pregabalin.

Unfortunately, although we have more options for treatment than ever, we still may find difficulty in selecting a drug that fulfills all of the ideal requirements. The newer AEDs initially were approved as adjunctive therapy for refractory epilepsy; however, these drugs continue to be tested against various types and stages of epilepsy.

**Lacosamide.** The most recently approved European AED, lacosamide, increases sodium-channel slow inactivation, which helps to normalize activation thresholds. In addition, this drug modulates collapsing response-mediator protein 2, which may offer neuroprotective effects.

In a multicenter, double-blind, placebo-controlled trial, Ben-Menachem et al randomized 418 patients who already were using one or two AEDs to also receive either lacosamide in various doses or placebo. The proportion of patients experiencing at least a 50% reduction in seizure frequency was significant for those using lacosamide doses of 400 mg/d (50%) and 600 mg/d (38%).

Lacosamide has an oral bioavailability of almost 100%. It is minimally bound to plasma proteins, and it has a half-life of 13 hours. Dizziness and nausea are its main adverse effects.

**Rating Pharmacokinetics**

Patsalos published a pharmacokinetic rating scale of 0–100. This scale considers such factors as oral absorption, linear versus nonlinear pharmacokinetics, protein binding, metabolism, and drug interactions.

Figure 2 lists AED scores from the lowest to the highest according to this scale. Drugs having the highest scores (eg, levetiracetam, vigabatrin, and lacosamide) are the most pharmacokinetically favorable when considered as add-on therapy. Phenytoin and carbamazepine have the lowest scores (ie, 50).

Newer medications have improved pharmacokinetic characteristics when compared with older AEDs. However, we have less clinical experience with these medications—and such novel drugs may cause long-term side effects that have not yet been discovered.

**CLINICAL CONSIDERATIONS WHEN ADDING A SECOND AED**

Adapted from a presentation by Gregory Krauss, MD, Associate Professor of Neurology, Johns Hopkins University, Baltimore, Maryland.

The selection of an initial AED for a newly diagnosed or previously untreated patient should take into consideration the type of seizure, the safety of the medication, and the ability of the patient to tolerate the drug chosen. Patients who do not achieve seizure freedom with the initial AEDs selected are less likely to achieve seizure freedom through the addition of new AEDs.

If the first drug prescribed is completely unsuccessful, another agent alone may be substituted. If, however, the initial AED is effective but does not fully control the seizures, adjunctive therapy may be added. Combinations of two or three AEDs sometimes may be effective when monotherapy has failed. Even individuals who do not achieve seizure freedom may have improved QOL if a combination improves their functional outcomes.

The many considerations involved when adding an adjunctive medication to an existing medication regimen include the pharmacokinetic parameters mentioned above. Further, the effects of AEDs may be assessed in many ways beyond the primary outcome of a significant decrease...
in seizure frequency. It is important to balance the efficacy of the medication with safety and tolerability. Adjunctive therapy may have a significant effect on functional outcome whether or not the patient becomes seizure-free.

Because newer AEDs are approved initially as adjunctive treatment for refractory seizures, these medications are tested first in patients who have failed many other AEDs; in some cases, patients may have tried as many as 8 or 10 of these drugs. In this sense, these drugs are held to a higher standard than are older AEDs. The newer medications have been shown to be effective in reducing seizure frequency by more than 50% in refractory patients. This efficacy in very-difficult-to-treat seizures suggests that these drugs may be even more beneficial for patients who are at an earlier stage in the course of their epilepsy.

**Refractory Epilepsy and QOL**

Patients with symptomatic or cryptogenic epilepsy are more likely than other epilepsy patients to have refractory seizures. Refractory epilepsy is associated with depression, cognitive dysfunction, polypharmacy with increased probability of drug side effects, dependent behavior, and decreased QOL. In addition, the duration of disease correlates with poorer verbal memory scores.

Gilliam et al investigated factors that influence perceived QOL. They found that concerns about driving (64%), independence (54%), employment (51%), and social embarrassment (36%) were the four biggest contributors to perceived decreases in QOL.

In some cases, seizure freedom is not the most important factor involved in improved QOL. For instance, improving seizure severity so that a patient has fewer seizures that generalize secondarily may have a huge impact on independence and employment. In addition, a drug’s side effects may outweigh its ability to lower seizure frequency. In a project conducted by the US Department of Veterans Affairs Cooperative Study Program, geriatric patients with new-onset epilepsy were randomized to receive lamotrigine, gabapentin, or carbamazepine. At 12 months, 64.3% of patients taking carbamazepine, 51.4% of those using lamotrigine, and 47.4% of individuals taking gabapentin were free of seizures, yet the carbamazepine group had the highest drop-out rate because of side effects.

Considering measures of functional outcome may provide a more appropriate assessment of the potential benefits of AED therapy. Thus, clinicians should contemplate factors such as patient retention in trials (a marker of medication tolerability), reduction in seizure severity and frequency, and patient satisfaction when deciding which medications to add to an existing regimen.

### CONCLUSION

No studies have investigated how many individual drug regimens an epilepsy patient should try before polytherapy is prescribed. Every attempt should be made to appropriately classify the particular type of epilepsy that a patient has when a diagnosis is made and treatment is started, since failed monotherapy may be followed by the development of refractory epilepsy. However, as more new AEDs are developed, more synergism among medication combinations may be found, thereby increasing efficacy beyond the additive effects of the drugs used.

Clinicians must consider mechanisms of action when adding AEDs to an existing regimen, because medications with complementary modes of action may be more likely to have a synergistic effect. A knowledge of pharmacokinetics also is integral to the selection of an adjunctive AED, especially when adding medications to the regimens of patients already using more than one drug. Finally, it is important to consider functional outcome measures (eg, level of independence, QOL) when selecting an AED to be used alone or to be added to an existing regimen to treat epilepsy.

### REFERENCES

What Type of Data Makes You Pick Your Drug?

Bernhard Suter, MD
Baylor College of Medicine, Houston, Texas

Abstract
Epilepsy strikes different individuals in different ways, and response to therapy for this disease is even more variable. To study the effects of antiepileptic drugs, clinical investigators conduct different types of clinical trials. However, each type of these research projects has its own unique advantages and disadvantages. In a panel discussion held during the 8th European Congress on Epileptology, speakers characterized randomized controlled trials, open-label extension trials, and naturalistic studies, covering their limitations and the information that may be culled from analysis of their results. In addition, they discussed various tools that may be used to assess quality of life in patients with epilepsy.

During the 8th European Congress on Epileptology (ECE) in Berlin, Germany, speakers at a panel discussion described different types of clinical studies and their advantages and disadvantages. In addition, they addressed methods of assessing quality of life (QOL) as it pertains to patients with epilepsy.

Types of Studies—And Influences on Decisions

Adapted from presentations by Josemir (Ley) Sander, MD, PhD, MRCP, Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, United Kingdom; Michel Baulac, MD, Chair, Department of Neurology—Epilepsy, and Professor of Neuroanatomy and Neurology, Université Paris VI, Paris, France; Stephen Wroe, MD, FRCP, National Hospital for Neurology and Neurosurgery, London, United Kingdom; and Eugen Trinka, MD, Epilepsy Service and Electroencephalography Laboratory, Universitätsklinik für Neurologie, Innsbruck, Austria.

The results of randomized controlled trials, open-label extension trials, and naturalistic studies continue to supply a wealth of data about antiepileptic agents and their possible usefulness in the clinical setting.

Randomized Controlled Trials

Generally considered to be the “gold standard” in research, randomized controlled trials provide the highest level of evidence for a given drug’s effectiveness. To minimize bias, these studies have several features, such as control groups, randomization, and blinding. Further, well-defined inclusion/exclusion criteria and predefined primary and secondary endpoints of this type of research contribute to scientific rigor.

The randomized controlled trial may be the most scientific way to compare the effectiveness of a drug with that of a placebo. However, even a placebo may cause a response rate as high as 20%1 or as low as 6.8%.2 Therefore, interpretation of the placebo effect and of methods to compare a drug’s efficacy with this effect presents a problem, particularly in the study of children, in whom the placebo effect traditionally is quite strong.

Is it possible to carry out randomized controlled trials to reflect dosage adjustments needed in clinical practice? Brodie et al3 used flexible, but well-defined, dosage adjustments in a study showing carbamazepine and levetiracetam to be about equal in effecting freedom from seizures. In addition, Glauser and others4 used the randomized controlled trial approach to focus on the use of rufinamide in a specific patient population (namely, patients with Lennox-Gastaut syndrome). This study featured two co-primary endpoints (ie, reduction in seizure frequency among patients with all seizure types and those having tonic-atonic seizures). This group reported that rufinamide was much more effective than placebo when both endpoints were considered.

Limitations. Among the limitations inherent to randomized controlled trials are their strict inclusion and exclusion criteria. Such exclusions necessitate the extrapolation of findings to persons who would not have been included in the study, such as women of childbearing age; patients with comorbidities; children with learning disabilities; and the elderly, who often are not included in clinical trials because of their use of multiple drugs, their greater risk of experiencing side effects, and their decreased excretion of therapeutic agents.

In addition, randomized controlled trials use fixed-dose regimens and forced-titration schedules; these qualifications prevent individual therapeutic adjustments for each patient as would be done in a clinic. Further, the time frames of blinded studies do not allow for the long-term evaluation of adverse events.

Overall, however, randomized controlled trials provide rigorous and mean-
Open-Label Extension Trials

Randomized controlled trials supply a vast amount of important information, yet they report on only a limited number of patients, use very restrictive criteria for entry, and last for a relatively short duration. The study of epilepsy, a chronologic disease, is not always amenable to these restrictions. Open-label extension trials, on the other hand, can address these points and allow for the titration of therapy to a patient's individual needs.

Open-label extension trials may provide more information about a drug's efficacy, safety, and tolerability than can randomized controlled trials for a number of reasons. First, this type of research allows for flexible dosing and, therefore, individual treatment regimens that closely reflect true clinical situations. Second, it allows for slow titration to an individual target dose, which especially is essential when treating epilepsy.

Third, the longer time span of open-label extension trials allows the gathering of better evidence about the safety of a drug and its uncommon adverse effects, patient-reported outcomes, and QOL issues. Various adverse effects have been detected only after drugs have been studied for an extended time (eg, visual-field defects during vigabatrin use, renal stones during zonisamide therapy, aplastic anemia during felbamate treatment). Essentially, this type of information would not be detected during a randomized controlled trial.

Fourth, open-label extension trials allow determination of long-term efficacy. Fifth, these studies consider patient preferences and balance efficacy and side effects. Sixth, and importantly, open-label extension trials account for adjustment of other antiepileptic drugs that also may be used.

Many times, it is difficult to assess long-term efficacy from information extrapolated from a randomized controlled trial. The last observation carried forward (LOCF) method, in which missing values are replaced ("carried forward") by the last observed value for that variable, represents one approach for dealing with this problem. Wroe et al used the LOCF method recently in an open-label extension study that examined the efficacy of adjunctive zonisamide given according to a flexible, adjusted dosing regimen over a prolonged period. They found that the drug's therapeutic effect as noted during the original randomized controlled trial was maintained over the 3 years of the study.

In addition, open-label extension trials may include individuals who normally are excluded from drug trials by restrictive entry criteria.

**Limitations.** A drawback of open-label extension trials is that their various features may cause confusion when efficacy is being interpreted. The nonrandomized, nonblinded nature of these trials, however, may affect accuracy adversely.

Further, the lack of controls and difficulty in interpreting dropouts from studies may cause problems related to bias. The long-term study of drugs allows accurate analyses of retention rates, which usually are related to the "tolerability" of a drug. However, the reasons for patient dropout from studies would supply invaluable information—was it because of side effects, insufficient therapeutic benefit at the prescribed doses, or other factors?

In all, open-label extension trials give information on flexible, individualized treatment regimens such as those used in the epilepsy clinic. These studies contribute a great deal of data on safety and tolerability; however, physicians must analyze these data cautiously when trying to determine drug efficacy.

Naturalistic Studies

As previously discussed, subjects are selected specifically for randomized controlled trials. In fact, only 10% of patients who present to an outpatient clinic actually would be eligible for inclusion in such research. Further, these trials usually include only patients who respond to a drug, so only a small sample of the general population of epilepsy patients participates in them. To more closely reflect clinical practice, naturalistic studies are performed to include a more diverse patient population, such as those having disease that is more or less refractory to therapy. In addition, this type of research allows for flexible, individualized dosing.

The KEEPER trial, a study of levetiracetam, included patients with various comorbid conditions who used a number of other antiepileptic drugs. This study, which had no upper limit of age, sought to gather data on the use of levetiracetam in community-based practices. Over a 16-week study period, 20% of patients became completely seizure-free, 40% experienced at least a 75% reduction in seizure frequency, and 58% experienced at least a 50% reduction in the frequency of these events. The most common adverse reactions recorded were mild-to-moderate somnolence, dizziness, headache, and asthenia.

**Limitations.** Naturalistic studies do not include control groups—and this difference could be a confounder during data analysis. Nonrandomized studies tend to overestimate effectiveness; however, they also demonstrate and allow proper reporting of adverse events. In fact, they tend to be more advantageous in detecting adverse events because of the heterogeneity of their patient populations.

Naturalistic studies also allow for dosage titration, which some might argue is not a truly naturalistic approach. A truly naturalistic study would simply study a population of people with epilepsy and not allow interventions or adjustment of drug dosages; however, this unethical strategy is not followed. The closest we can come to a "true" naturalistic study is to give a drug to patients and to report on its effects at different time points—in other words, perform a pure cross-sectional observational study with defined endpoints.

In summary, data from naturalistic studies are gathered under conditions that mirror routine clinical practice more closely. They incorporate a more diverse patient population that reflects the average clinical practice, with patients who are more or less refractory to treatment, who use a number of concomitant anti-
epileptic drugs, and who have comorbid conditions. In addition, they use flexible and clinically relevant dosing schedules that feature doses lower than those used in randomized clinical trials.

**QOL ASSESSMENTS AND PATIENT-REPORTED OUTCOMES**

Adapted from a presentation by Joyce Cramer, Associate Research Scientist, Yale University School of Medicine, New Haven, Connecticut.

In spite of the development of various effective antiepileptic drugs, about one third of patients do not become seizure-free. Therefore, a patient’s expectation of treatment, along with a method for assessing therapeutic effect, must be determined.

**Defining QOL**

Although QOL is a commonly used term in medicine, it has different definitions. To the general population, the definition of QOL may include happiness, family and friends, work, self-esteem, and independence. However, more specific issues may be cited by patients with epilepsy. For example, patients may report that their seizures impede their work, give them tremors, make them afraid to leave the house, or even cause depression for 18 hours a day. The definition of QOL in epilepsy, therefore, includes such domains as health-related issues, cognitive and memory capacity, physical activity, transport needs, mood, and daily function. Logically, these domains would be endpoints of clinical trials.

However, clinical investigators must do more than simply ask about the number of seizures or adverse events that a patient suffers. Patient-reported outcomes help us to understand patients’ needs and expectations from clinic visits and, crucially, to appreciate the impact of their experiences between seizures.7

**Assessing QOL**

When assessing the QOL of epilepsy patients, clinical investigators may use a variety of validated test instruments specifically designed for this patient population.

**Quality of Life in Epilepsy-31 (QOLIE-31)**

This 31-item subset of the original 89-question QOLIE survey has been validated and reliability-tested. It includes several subscales (eg, seizure worry, emotional well-being, cognitive effects, overall health, overall QOL, energy and fatigue, social function, and living independently). Numerous cross-cultural translations of these subscales are available. The total and subscale scores available from this questionnaire are useful for statistical analysis and allow assessment of patient change over time and improvement with treatment.

A newer version of this test instrument, the QOLIE-31P, includes seven extra patient-distress items related to energy and fatigue. Now widely used in clinical trials, these questionnaires are being considered for use as secondary endpoint measures.

The QOLIE-31 and QOLIE-31P attempt to assess a “clinically important change” rather than just statistical significance. For example, a 10-point overall improvement in the total QOLIE-31 score is needed to prove real change in a patient’s life; on different subscales, however, required changes vary. For example, on the seizure worry scale, a clinically important change is heralded by 15 points, whereas only 8–9 points are needed on the mood scale to signify an important change.

**Seizure Severity Questionnaire (SSQ).** The assessment of seizure severity is important in understanding the impact of individual seizures on patients. The SSQ can help with this task. Cramer et al,8 for example, used an SSQ to relate patients’ perception of seizures to depression.

SSQ results have demonstrated that QOL is related to the number of seizures experienced and to the different effect that each type of seizure has on the individual. A patient may have “bad” and “easy” events; we really must assess how the patient perceives seizure severity and how the postictal state affects the perception of the seizures.

SSQs help us to understand the life changes that patients experience over treatment periods. During the study of children, clinical investigators use instruments for family members to answer together; for example, the Epilepsy and Learning Disabilities QOL (ELDQOL) scale currently is being used in a study of rufinamide in patients with Lennox-Gastaut syndrome.

**Patient-Reported Outcomes**

Patient-reported outcomes represent the insights of the patient and not of the doctor. Even when patients have 50% fewer seizures, clinicians really want them to achieve 100% fewer seizures. Given that this goal is not achievable, patient-reported outcomes allow appreciation of the impact of therapy on QOL.

Obviously, we cannot simply assess seizure frequency alone to determine whether a patient is being treated optimally. Also assessing severity and other factors of QOL characterizes the impact of treatment and the change achieved during a particular therapeutic trial. Assessment of patient-reported outcomes represents one method of quantitatively following the effect of treatment on patient response and QOL.

**REFERENCES**


Rufinamide: A Clinical Update

Thomas Gann, MD
University of Alabama at Birmingham Epilepsy Center, Birmingham, Alabama

Abstract

Some 1%–4% of all children with epilepsy are diagnosed with Lennox-Gastaut syndrome (LGS), one of the most severe forms of childhood epilepsy encountered by pediatric neurologists. Rufinamide, an antiepileptic drug not structurally related to any other agent, now is available to physicians in the United States for adjunctive treatment of seizures associated with LGS in children 4 years of age and older and adults. During poster sessions offered at the 62nd Annual Meeting of the American Epilepsy Society, speakers discussed this new drug in detail, describing its pharmacokinetics, the results of pivotal trials testing its safety and efficacy, and analyses determining its cost-effectiveness when used in LGS patients. In addition, investigators discussed factors important to patients affected by epilepsy and the neurocognitive effects of seizure control in pediatric patients.

In 2004, the US Food and Drug Administration (FDA) originally designated rufinamide as an orphan drug for the treatment of Lennox-Gastaut syndrome (LGS). In November 2008, the FDA approved the use of rufinamide for the adjunctive treatment of seizures associated with LGS in children 4 years and older and adults.

During the 62nd Annual Meeting of the American Epilepsy Society in Seattle, Washington, experts in the treatment of LGS discussed the pharmacokinetics of rufinamide, its safety in adult and pediatric populations, and its efficacy in managing LGS. In addition, they offered new information on the cost-effectiveness of treating LGS with rufinamide in children and adolescents, a factor that may be important to patients affected by epilepsy, and the possible neurocognitive impact of seizure control on pediatric patients.

Rufinamide: Pharmacokinetics, Metabolism, and Use

Rufinamide, a triazole derivative, is structurally unrelated to any other antiepileptic drug currently on the market. Its precise mechanism of action is not understood fully; however, this drug apparently modulates the activity of sodium channels and prolongs the inactive state of these tubular passages.

Pharmacokinetics

Rufinamide is absorbed relatively slowly; the extent of absorption decreases with the administration of increasing doses. Following oral administration of one 600-mg dose under fed conditions, the extent of absorption was at least 85%. In healthy volunteers given one 400-mg dose, food increased rufinamide absorption by 34% and increased peak exposure by 56%; however, the peak plasma concentration did not increase.

After oral administration, peak plasma concentrations are achieved within 4–6 hours in both fed and fasting patients. The apparent volume of distribution and oral clearance of this drug are related to body size and best predicted by body surface area. Plasma concentrations rise in a less-than-linear fashion with dose escalation, apparently as a function of the drug’s solubility.

Rufinamide does not seem to bind to protein in serum avidly; only 34% binds to human serum proteins, and 27% binds to albumin. It is metabolized extensively by the liver, although not via the cytochrome P450 pathway, and its metabolites largely are excreted in the urine. The drug has no known active metabolites. Twelve-hour dosing intervals and a half-life of 6–10 hours yield an expected steady-state peak concentration of approximately two to three times the peak concentration after ingestion of a single dose.

Apparently, clearance of rufinamide is 6%–14% lower in women than in men, although this effect is not important clinically. No difference in clearance or volume of distribution has been observed between black and Caucasian subjects after controlling for body size. Based on a population analysis performed in 117 children (age 4–11 years) and 99 adolescents (age 12–17 years), the pharmacokinetics of rufinamide in pediatric patients are similar to those in adults. However, potential pharmacokinetic differences between children and adults have not been investigated systematically in formal studies.

Special-risk populations. In nine patients with severe renal impairment (creatinine clearance < 3 mL/min), the pharmacokinetics of the drug were similar to those of healthy subjects. A dosage adjustment should be considered for dialysis patients; a reduction in area under the curve and maximum plasma concentration has been reported in patients undergoing dialysis 3 hours after receiving rufinamide.

No studies have investigated the effect of hepatic dysfunction on the pharmacoki-
TABLE 1

Summary of Drug-Drug Interactions of Rufinamide with Other Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Coadministered antiepileptic drug</th>
<th>Influence of rufinamide on concentration of the antiepileptic drug</th>
<th>Influence of the antiepileptic drug on rufinamide concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Decrease of 7%–13%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Decrease of 19%–26% (dependent upon carbamazepine dose)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Decrease of 7%–13%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No effect</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Increase of 8%–13%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decrease of 25%–46% (independent of phenobarbital dose or concentration)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increase of 7%–21%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Decrease of 25%–46% (independent of phenytoin dose or concentration)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Valproate</td>
<td>No effect</td>
<td>Increase of &lt; 16%–70% (dependent upon valproate concentration)</td>
</tr>
<tr>
<td>Primidone</td>
<td>Not investigated</td>
<td>Decrease of 25%–46% (independent of primidone dose or concentration)</td>
</tr>
<tr>
<td>Benzodiazepines&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not investigated</td>
<td>No effect</td>
</tr>
</tbody>
</table>

<sup>a</sup> Predictions are based on rufinamide concentrations at the maximum recommended dose.
<sup>b</sup> Maximum changes predicted for children and patients who achieve significantly higher rufinamide levels, as the effect of rufinamide on these antiepileptic drugs is concentration-dependent.
<sup>c</sup> Larger effects in children at high doses/concentrations of antiepileptic drugs.
<sup>d</sup> Phenobarbital, primidone, and phenytoin were treated as a single covariate (phenobarbital-type inducers) to examine the effect of these agents on rufinamide clearance.
<sup>e</sup> All compounds of the benzodiazepine class were pooled to examine for "class effect" on rufinamide clearance.

Source: Banzel package insert<sup>11</sup>

Drug-Drug Interactions

Results of in vitro studies showed that rufinamide causes little or no inhibition of most cytochrome P450 enzymes at clinically relevant concentrations, although it inhibits cytochrome P2E1 weakly. Increased plasma levels of drugs that are substrates of cytochrome P2E1 (e.g., chlorzoxazone) may occur; however, this reaction has not been studied. Rufinamide is a weak inducer of CYP3A4 and, consequently, can decrease serum levels of drugs that are substrates of this cytochrome enzyme, such as triazolam.<sup>3,4</sup>

This drug is metabolized by carboxyl esterases; drugs that may induce the activity of carboxyl esterases may increase the clearance of rufinamide, and drugs that may inhibit carboxyl esterases may decrease its metabolism.<sup>3,4</sup>

Table 1 summarizes drug-drug interactions between rufinamide and other antiepileptic drugs.<sup>3,4</sup> Concomitant administration of rufinamide did not impact the plasma concentrations of phenytoin, carbamazepine, vigabatrin, primidone, phenobarbital, valproic acid, or lamotrigine to the point of probable clinical significance. Similarly, the influence of rufinamide on the clearance of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate in children, adults, and adolescents is modest and believed to be of unlikely clinical significance.<sup>3,8</sup>

Lamotrigine, topiramate, and benzodiazepines do not affect the pharmacokinetics of rufinamide; concurrent administration of valproate, however, may elevate plasma rufinamide levels by up to 70% in children.<sup>3,4</sup> Concomitant use of carbamazepine, vigabatrin, phenytoin, phenobarbital, and primidone has been associated with a slight-to-moderate decrease in plasma rufinamide concentrations (range, –13.7% in female children given vigabatrin to –46.3% in female adults given phenytoin, phenobarbital, or primidone).<sup>3,5</sup> Any effects noted likely were more marked among pediatric patients.<sup>3,4</sup>

Rufinamide therapy may render hormonal contraceptives less effective; thus, patients should be advised to use non-hormonal types of contraception during treatment with this drug.<sup>3</sup>

Adverse Events

The long- and short-term use of rufinamide generally has been well tolerated. The most frequent (≥ 10%) adverse events observed among adult and pediatric epilepsy patients given rufinamide (200–3,200 mg/d) as adjunctive therapy in double-blinded studies—and that occurred with a higher frequency than among patients given placebo—were headache, dizziness, fatigue, somnolence, and nausea.<sup>3,4</sup> Serious adverse events, including convulsion, status epilepticus, and pneumonia, also have been reported, but they generally were not attributed to use of the drug. No deaths occurring during these studies were linked to rufinamide.<sup>4</sup>

Similar investigations were undertaken in pediatric populations; a summary of treatment-emergent events recorded in children is provided in Table 2.<sup>3</sup> Ultimately, children tolerated both short-term (median, 3 months) and long-term (> 12 months) use of rufinamide well.<sup>4</sup> Again, the most common adverse events were mild to moderate and included somnolence, vomiting, and headache.<sup>3,4,9-11</sup>

AN OVERVIEW OF LGS

As one of the most severe encephalopathies causing epilepsy of childhood, LGS may be symptomatic or cryptogenic. It commonly is characterized by three signs—multiple seizure types, slow spike-wave complexes on electroencephalographic (EEG) recordings, and impairment of cognitive function.<sup>12</sup> In addition, personality disorders have been noted among affected patients.<sup>13</sup>

Presentation and Course

LGS represents a heterogeneous class of conditions entailing refractory seizures with a variety of semiologies, mental retardation, and a set of distinctive EEG changes. LGS may occur in the setting of various neurologic insults, including perinatal asphyxia, infections of the central nervous system, significant head trauma, neurodegenerative conditions, and metabolic syndromes.<sup>14</sup>
The precise limits, causes, and diagnosis of the syndrome remain unresolved. LGS occurs more frequently in males; it usually presents before 8 years of age (peak, 3–5 years). Rarely, late-onset cases that occur during adolescence and early adulthood have been reported. Patients frequently experience slow language in terms of ideation and expression and difficulties of motor dysfunction. Affected patients almost always exhibit severe behavioral disorders (eg, hyperactivity, aggressiveness, autistic tendencies) and personality disorders along with a tendency toward eventual psychosis.

The long-term prognosis of stricken patients is poor. Often, although their epilepsy improves, LGS patients rarely achieve complete freedom from seizures. In addition, over time, mental and psychiatric disorders tend to worsen.

Prevalence

In a population-based study that was part of the Metropolitan Atlanta Developmental Disabilities Study (MADDS), Trevathan et al\textsuperscript{15} investigated the prevalence and descriptive epidemiology of LGS among children living in metropolitan Atlanta, Georgia. Children were considered to have LGS if they suffered multiple seizure types before 11 years of age (with at least one seizure type resulting in falls) and an EEG that demonstrated slow spike-wave complexes; the criteria for inclusion did not include mental retardation.

The lifetime prevalence of LGS at 10 years of age was 0.26/1,000. Further, 91% of patients with LGS had mental retardation, and 39% had a history of infantile spasms. When compared with children having multiple seizure types without slow spike-wave complexes, children with LGS were more likely to have a history of infantile spasms, mental retardation, and multiple disabilities (ie, mental retardation, cerebral palsy, blindness, impaired hearing). In all, 17% of children in Atlanta having profound mental retardation suffered from the syndrome.

Thus, only 4% of all childhood epilepsy is associated with LGS, yet the syndrome contributes significantly to childhood morbidity.

Treatment Strategies

The variable etiology, multiple types of intractable seizures, and cognitive impairment associated with LGS, along with its frequent resistance to treatment with standard antiepileptic drugs, make it one of the most difficult epilepsy syndromes to treat.\textsuperscript{16}

Historically, a variety of antiepileptic drugs (eg, valproic acid, topiramate, lamotrigine, felbamate) have been employed to manage this condition. A survey on management of epilepsy and seizures completed by 42 European specialists in pediatric epilepsy and seizures revealed that lamotrigine is chosen by 39 US specialists responding to a similar questionnaire, although these physicians also considered topiramate and lamotrigine to be first-line therapies for the syndrome.\textsuperscript{18} In addition, add-on therapy with lamotrigine, topiramate, and felbamate may be useful.\textsuperscript{13}

Some investigators have explored the use of surgical techniques to relieve the symptoms of LGS. In comparing the usefulness of these two techniques in 14 patients who underwent corpus callosotomy and 10 patients who underwent vagus-nerve stimulation, You et al\textsuperscript{19} found that the two procedures were comparable in terms of efficacy and safety in this patient population.

\section*{RUFINAMIDE IN PATIENTS WITH INADEQUATE SEIZURE CONTROL}

Despite vigorous efforts, however, complete seizure control in LGS patients is rare. Consequently, new therapeutic options are being sought. In particular, rufinamide is providing new hope for managing this epilepsy syndrome.

Evidence of the efficacy and safety of rufinamide for treating LGS was provided by study CRUF331-0022\textsuperscript{20} and its open-label extension (CRUF331-0022E).\textsuperscript{21,22}

Efficacy

The multicenter, randomized, double-blind, placebo-controlled study CRUF331-0022 included 138 LGS patients who had inadequate seizure control when using stable doses of one to three concomitant antiepileptic drugs. The patients suffered \geq 90 seizures, including some tonic-atonic events, during the month preceding enrollment; they also had EEG results showing a slow spike-and-wave pattern within 6 months of inclusion and imaging that was negative for any progressive lesions. Additional information about these patients is given in Table 3.\textsuperscript{22}

In all, 74 patients were titrated to a dose of 45 mg/kg/d of rufinamide over 1–2 weeks; 64 patients received placebo. All participants were followed for 70 days. For the initial study, the primary endpoints were percent change in both total seizures and tonic-atonic seizures and the change in seizure severity on a seven-point scale.

During study CRUF331-0022, statistically significant reductions in the numbers of total seizures, atomic seizures, and combined absence and atypical absence seizures were found for patients using

\begin{table}
\centering
\caption{Treatment-Emergent Adverse Events in Pediatric Patients\textsuperscript{a}}
\begin{tabular}{|l|c|c|}
\hline
\textbf{Adverse event} & \textbf{Rufinamide} & \textbf{Placebo} \\
\hline
Somnia/ence & 17\% & 9\% \\
Vomiting & 17\% & 7\% \\
Headache & 16\% & 8\% \\
Fatigue & 9\% & 8\% \\
Dizziness & 8\% & 6\% \\
Nausea & 7\% & 3\% \\
Influenza & 5\% & 4\% \\
Nasopharyngitis & 5\% & 3\% \\
Decreased appetite & 5\% & 2\% \\
Rash & 4\% & 2\% \\
Ataxia & 4\% & 1\% \\
Diplopia & 4\% & 1\% \\
Bronchitis & 3\% & 2\% \\
Sinusitis & 3\% & 2\% \\
Psychomotor hyperactivity & 3\% & 1\% \\
Upper abdominal pain & 3\% & 2\% \\
Aggression & 3\% & 2\% \\
Ear infection & 3\% & 1\% \\
Disturbance in attention & 3\% & 1\% \\
Pruritus & 3\% & 0\% \\
\hline
\end{tabular}
\textsuperscript{a}Recorded in all pediatric double-blind adjunctive trials by preferred term at the recommended dose of 45 mg/kg/d; adverse reactions occurred in at least 3\% of rufinamide-treated patients and occurred more frequently than in placebo patients.
\textsuperscript{b}Source: Banzel package insert
\end{table}
adjunctive rufinamide therapy when compared with those using placebo. No significant difference in the frequency of tonic, myoclonic, tonic-clonic, or partial seizures was detected, although there was a trend toward benefit for the treatment group (Table 3). Additionally, the authors determined that the rufinamide group experienced an improvement in seizure severity when compared with the placebo group.

Cognitive/psychiatric adverse events (eg, psychomotor hyperactivity and lethargy) occurred less frequently in the rufinamide group (17.6%) than in the placebo group (23.4%).

During the open-label extension study, rufinamide was introduced to the placebo group. All patients then were followed for 3 years. In all, 124 of the 138 participants in study CRUF331-0022 remained in the extension trial for an average of 432 days; 83 (66.9%) of the 124 patients received rufinamide for more than 1 year, 74 (59.7%) for more than 18 months, 51 (41.1%) for 2 years or more, and 15 (13%) for 3 years or more. Only 42 of 124 patients (33.9%) completed the 36-month extension study.

The seizure frequency of groups treated for 6, 12, 18, 24, 30, or 36 months were compared with that recorded at baseline. Each cohort exhibited at least a 42.6% sustained reduction in total seizures per 28 days and a mean decrease of at least 48.1% in tonic-atonic seizures per 28 days. Additionally, 36.1% of patients were considered to be rufinamide responders (ie, experiencing at least a 50% reduction in total seizure frequency over the course of the extension trial). Further, when compared with baseline findings, 44.4% of the participants experienced an overall decrease in the frequency of tonic-atonic seizures of at least 50%.

### Safety

In study CRUF331-0022E, 87 patients (70.2%) reported experiencing any adverse event. The majority of these events, including vomiting, pyrexia, upper respiratory tract infection, and somnolence, were mild to moderate in severity.

Overall, 12 patients (9.7%) using rufinamide withdrew from the studies due to adverse events. The most common adverse events leading to treatment discontinuation were vomiting and rash. Serious antiepileptic drug hypersensitivity syndrome has occurred with rufinamide use; patients developing rash during therapy should be monitored closely.

A total of 34 patients experienced severe adverse events resulting in treatment discontinuation in 12 patients. Serious adverse events that occurred during the open-label extension study included rash and two deaths, neither of which was considered to be related to rufinamide therapy.

Overall, the safety profiles observed in the original trial and in its extension were similar. The investigators concluded that rufinamide generally was well tolerated.

#### PREFERENCES FOR HEALTH STATES IN LGS

In the setting of limited resources for healthcare, establishing the utility of a treatment relative to its cost is an important consideration. Individuals suffering from LGS typically are unable to respond to standard questionnaires. Utilities represent preferences for health states; they are needed to estimate quality adjusted life-years (QALYs), and they may help healthcare providers and decision-makers to evaluate the true benefits of a particular intervention.

Preferences may be measured directly from patients, or they may be gathered from caregivers, members of the general public, or clinical experts. Assessments of the cost-effectiveness of interventions used within a public healthcare system should reflect societal values.

### Determining Preferences and QOL

Verdian et al. sought to determine the cost-effectiveness of rufinamide by comparing QALYs related to its use with the financial burden of the treatment. Toward this end, they calculated utility values for health states among LGS patients.

The investigators derived QALY values by describing four health states as defined by reductions in drop-attack frequency (Table 4).

In all, 44.4% of LGS patients treated with rufinamide experienced a decrease of at least 50% from baseline in the frequency of tonic-atonic seizures.

---

### Table 3

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rufinamide (n = 74)</th>
<th>Placebo (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>14.5</td>
<td>13.6</td>
</tr>
<tr>
<td>Median number of tonic-atonic seizures per 28 days</td>
<td>92.0</td>
<td>92.5</td>
</tr>
<tr>
<td>Duration of double-blind phase, weeks</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Concomitant antiepileptic drugs: One</td>
<td>10.8%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Two</td>
<td>51.4%</td>
<td>54.8%</td>
</tr>
<tr>
<td>Three</td>
<td>37.8%</td>
<td>32.8%</td>
</tr>
<tr>
<td>Outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50% reduction in tonic-atonic seizures</td>
<td>42.5%</td>
<td>16.7%</td>
</tr>
<tr>
<td>≥ 75% reduction in tonic-atonic seizures</td>
<td>21.9%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Source: All Wales Medicines Strategy Group

---

Thomas Gann, MD  Rufinamide: A Clinical Update
and that a 50% reduction in the frequency of drop attacks was useful.

THE COST-EFFECTIVENESS OF RUFINAMIDE IN LGS

Yeates et al25 applied the results reported by Verdian et al24 in a subsequent analysis comparing the cost-effectiveness of rufinamide therapy with that of topiramate or lamotrigine as adjunctive treatment for children with LGS, according to standards imposed by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.

The researchers constructed a Markov state-transition model incorporating the four health states used by Verdian et al24 plus “death” to generate QALYs for treatment of representative LGS patients and associated costs. Specifically, the model assigned patients to adjuvant treatment with rufinamide, brand-name topiramate, or lamotrigine and then reassessed patients at 3-month intervals, allowing for changes in the antiepileptic drug regimen, according to the patient’s evolving health state or the presence of serious adverse events linked to the existing therapeutic regimen.

Treatment benefits (ie, percent of patients achieving a given decrease in drop-attack seizure frequency over 3 years) were translated into QALYs. Existing literature on the efficacy and safety of these medications was used to determine anticonvulsant effectiveness and adverse effects. Expenditures associated with medications were ascertained from the British National Formulary. Use of resources was based upon a survey of pediatric epileptologists; these costs then were calculated using norms for the UK National Health Service.

The researchers calculated QALY values of 1.44 for rufinamide, 1.36 for brand-name topiramate, and 1.42 for lamotrigine. The cumulative costs were estimated to be £24,992 for rufinamide, £23,360 for brand-name topiramate, and £21,783 for lamotrigine. Consequently, the incremental cost per QALY was £20,538 for rufinamide when compared with brand-name topiramate and £154,831 when compared with generic lamotrigine.

Assuming a willingness to pay thresholds at £20,000 and £30,000 per QALY, the authors concluded that rufinamide may represent a cost-effective alternative to brand-name topiramate as adjunctive therapy of LGS. Conversely, rufinamide was not a cost-effective alternative to lamotrigine in this setting; however, it provided another treatment choice for this rare neurologic condition.

SEIZURE CONTROL AND NEUROPSYCHOLOGICAL CHANGES IN A PEDIATRIC POPULATION

Neuropsychological issues are more common among children and adolescents with epilepsy than their healthy peers. The effect of obtaining seizure control in these patients, however, remains unclear.

Fastenau and others26 prospectively followed 272 children between the ages of 6–14 years who had intelligence quotients of more than 55; they also studied 143 sibling controls. After a first seizure was noted, examinations occurred at 9-month intervals for 3 years. At baseline and at 18 and 36 months, neuropsychological testing examining four parameters (ie, language, processing speed, verbal memory, executive function/attention/concentration) was administered.

On the basis of their degree of seizure control, subjects were categorized into one of three groups: no recurrent seizures, recurrent seizures (ie, at least one subsequent seizure but no interval seizures at some follow-up visits), and persistent seizures (ie, interval seizures at all follow-up visits). Additionally, patients with epilepsy syndromes were identified by pediatric epileptologists for further analysis. The investigators then compared the performance of each of these groups with that of their sibling controls.

The persistent-seizure group demonstrated statistically significant reductions in the development of processing speed (Figure 1), verbal memory (Figure 2), and executive function/attention/concentration when compared with their siblings. No differences with regard to neuro-

### TABLE 4

<table>
<thead>
<tr>
<th>Health state</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (anchor state)</td>
<td>Uncontrolled; 21–28 drop attacks/week</td>
</tr>
<tr>
<td>2</td>
<td>Not well controlled; &lt; 50% reduction in drop attacks (14–28/week)</td>
</tr>
<tr>
<td>3</td>
<td>Well controlled; 50%–75% reduction in drop attacks (7–14/week)</td>
</tr>
<tr>
<td>4</td>
<td>Very well controlled; &gt; 75% reduction in drop attacks (1–7/week)</td>
</tr>
</tbody>
</table>

Source: Verdian et al24

![FIGURE 1 Change in processing speed by seizure control among children having persistent seizures, recurrent seizures, or no recurrent seizures and a sibling group. Adapted from Fastenau et al.26](image1)

![FIGURE 2 Change in verbal memory by seizure control among children having persistent seizures, recurrent seizures, or no recurrent seizures and a sibling group. Adapted from Fastenau et al.26](image2)
psychological changes were noted among groups having an epilepsy syndrome.26

Thus, in this study, inadequate seizure control resulted in suboptimal mental processing, with the largest declines noted among individuals who suffered from persistent seizures. Additionally, epilepsy syndromes apparently did not lead to neuropsychological decline in school-aged children having relatively uncomplicated epilepsy and lacking significant existing neurologic deficits. Although it is reasonable to conclude from this observation that "benign" pediatric epilepsy syndromes are not associated with encephalopathy, regardless of whether the seizures are controlled, the authors of this report did not explicitly make that conclusion or attempt to differentiate, define, or isolate benign epilepsy syndromes aside from excluding individuals who were not otherwise neurologically normal from the study.

REFERENCES


10. Arroyo S, Sachdeo R, Rosenfeld W, Critchley D, Perdomo C. Pharmacokinetics and safety of ascending doses of adjunctive rufinamide in pediatric patients with inadequately controlled seizures. Presented at the 59th Annual Meeting of the American Epilepsy Society; December 2–6, 2005; Washington, DC.


25. Fastenau PS, Johnson CS, Dunn DW, et al. Relationship between seizure control and neuropsychiatric changes during the first three years following seizure onset in children. Presented at the 62nd Annual Meeting of the American Epilepsy Society; December 5–9, 2008; Seattle, Washington. Poster 1.339.
When Monotherapy for Epilepsy Fails

Vikram Bhise, MD
SUNY Downstate Medical Center, Brooklyn, New York

Abstract
The first prescription of an antiepileptic drug is written with hopes of therapeutic effectiveness and safety. Too often, though, physicians must select a second medication or consider other therapies to control the frequency and intensity of a patient’s seizures. At a symposium held during the 62nd Annual Meeting of the American Epilepsy Society, criteria for defining the failure of monotherapy, the selection of add-on or alternative courses of treatment, and the importance of considering pharmacokinetic and pharmacodynamic properties carefully when prescribing more than one drug were discussed, as well as some of the reasons why the results of drug-combination trials in animals do not necessarily translate well to the treatment of patients. Further, preliminary data from a recently completed trial of neurostimulation in patients with partial onset seizures and studies of new antiepileptic treatments in the late stages of clinical development were presented.

Antiepileptic therapy is chosen according to the type of seizure disorder presented by the patient, the drug’s side-effect profile, and its potential to interact with other medications the patient may be taking. In many cases, patients respond to the first drug prescribed to control seizures; however, a significant number of patients must try add-on therapy and even surgery to keep their seizures under control.

During the 62nd Annual Meeting of the American Epilepsy Society in Seattle, Washington, experts in the pharmacologic management of epilepsy reviewed the criteria for defining monotherapy failure, the rationale for prescribing additional or alternative agents after monotherapy does not impart the desired actions, the importance of a drug’s pharmacokinetic and pharmacodynamic properties when choosing combination therapy, the difficulties in extending laboratory results to the clinical setting, and the promise of new antiepileptic drugs now being developed. In addition, researchers released preliminary data from the double-blinded, placebo-controlled Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) study, which examined the usefulness of deep-brain stimulation (DBS) in patients with refractory epilepsy.

WHAT DEFINES MONOTHERAPY FAILURE?
Adapted from a presentation by Katherine D. Holland, MD, PhD, Assistant Professor of Neurology, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio.

Thus, the reason that antiepileptic monotherapy fails may help physicians to predict whether or not a patient will respond to a second agent.

Possible predictors of an increased likelihood of monotherapy failure include a history of 10 or more seizures at presentation, a family history of epilepsy, a history of febrile seizures or traumatic brain injury, intermittent recreational drug use, previous or current psychiatric comorbidity, and atypical presentations of IGE. Among pediatric patients, associated fac-

had a much lower seizure-freedom rate (11%) when compared with the rate in patients who had intolerable side effects (Figure 2).

In a study of a pediatric population (2–18 years of age) with partial seizures, a similar failure rate of 57% was observed; this rate decreased to 22% after continued medical treatment (Figure 3). These patients exhibited a lower likelihood of seizure freedom (33%) if their reason for treatment failure was lack of efficacy, although patients with localization-related epilepsy had a better response (Figure 4). A similar pattern was observed in a study of adults with idiopathic generalized epilepsy (IGE).3

Predicting the Likelihood of Therapeutic Failure

Thus, the reason that antiepileptic monotherapy fails may help physicians to predict whether or not a patient will respond to a second agent.

Possible predictors of an increased likelihood of monotherapy failure include a history of 10 or more seizures at presentation, a family history of epilepsy, a history of febrile seizures or traumatic brain injury, intermittent recreational drug use, previous or current psychiatric comorbidity, and atypical presentations of IGE. Among pediatric patients, associated fac-
tors include a cryptogenic or symptomatic etiology; high initial seizure frequency; and focal slowing on electroencephalography, which may suggest an underlying symptomatic etiology (Table 1).

### Determining Relationships Between Doses and Responses

Dose-response relationships for antiepileptic drugs must be examined. Common practice has been to titrate to toxicity before switching to a new agent. However, at some point, an increase in dose may no longer lead to an increase in seizure freedom, although it may increase the incidence of side effects.

These relationships have been examined for carbamazepine, lamotrigine, and valproic acid in adults with new-onset epilepsy. A total daily dose of 600 mg/d of carbamazepine, for example, leads to seizure freedom in approximately 80% of patients, but higher doses provide little additional benefit. In general, modest doses of antiepileptic drugs tend to be effective. Long-term follow-up of patients who failed initial monotherapy shows a similar low subsequent freedom from seizures among those who failed initial therapy because of a lack of efficacy and those who experienced intolerable adverse effects at high doses. Therefore, an alternative and recommended approach would be to switch to a second agent if the patient receives no benefit from a modest dose, even when side effects are absent. The best response generally is seen after an initial agent is started (40%–60%); this response drops substantially when the second agent is prescribed and even more when the third is tried. Treatment with three or more agents likely will be ineffective.

In summary, the first antiepileptic drug prescribed usually is the most effective. Patients who fail initial therapy because of adverse effects at low doses or an idiosyncratic reaction appear to have a better chance of responding to a second agent than do individuals who fail because of a lack of efficacy or because of adverse effects at high doses. In the setting of monotherapy failure, the clinician should first consider switching the patient to a second agent before raising the dose of the initial drug so much that toxicity occurs.

---

**TABLE 1**

Factors Associated with Monotherapy Failure

<table>
<thead>
<tr>
<th>Adult epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More than 10 seizures at presentation</td>
</tr>
<tr>
<td>• Family history of epilepsy</td>
</tr>
<tr>
<td>• History of febrile seizures</td>
</tr>
<tr>
<td>• Traumatic brain injury</td>
</tr>
<tr>
<td>• Intermittent recreational drug use</td>
</tr>
<tr>
<td>• Prior or current psychiatric comorbidity</td>
</tr>
<tr>
<td>• Atypical presentations of IGE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High initial seizure frequency</td>
</tr>
<tr>
<td>• Cryptogenic or symptomatic etiology</td>
</tr>
<tr>
<td>• Focal slowing on EEG</td>
</tr>
</tbody>
</table>

EEG = electroencephalogram; IGE = idiopathic generalized epilepsy

Adapted from a presentation by Katherine Holland, MD, PhD, at the 62nd Annual Meeting of the American Epilepsy Society, Seattle, Washington.

---

**Figure 1** Therapy outcome in patients (primarily adults) with epilepsy. Adapted from a presentation by Katherine Holland, MD, PhD, at the 62nd Annual Meeting of the American Epilepsy Society, Seattle, Washington.

**Figure 2** Seizure-freedom rate due to monotherapy and reasons for failure during continued treatment. AED = antiepileptic drug. Adapted from a presentation by Katherine Holland, MD, PhD, at the 62nd Annual Meeting of the American Epilepsy Society, Seattle, Washington.
When Monotherapy for Epilepsy Fails

n is there such a thinG as rational polypharMacy?

Adapted from a presentation by Tracy A. Glauser, MD, Associate Professor of Pediatrics and Neurology and Director, Children’s Comprehensive Epilepsy Program at Cincinnati Children’s Hospital, Cincinnati, Ohio.

A clinician’s common dilemma involves a decision to switch to or add a second agent if initial monotherapy fails. Current practice suggests that selection of these agents often is haphazard; however, polypharmacy may be approached rati-

In 2006, the International League Against Epilepsy published evidence-based guidelines on the use of monotherapy and polypharmacy in patients with newly diagnosed or untreated epilepsy. The guidelines’ authors clearly stated that the absence of rigorous, comprehensive data on the adverse effects of antiepileptic drugs makes it impossible to identify or recommend the overall optimal drug for use as initial monotherapy. In particular, the authors pointed out that there is an “especially alarming” lack of well-designed, properly performed, randomized, controlled clinical trials for patients with generalized seizures/epilepsies and for children in general. Therefore, they concluded, “When selecting a patient’s [anti-epileptic drug], physicians and patients should consider all relevant variables and not just efficacy and effectiveness.”

The Science of Polypharmacy

Pharmacology comprises both pharmacodynamics and pharmacokinetics. Pharmacodynamics examines the effects of a drug on the body (ie, efficacy and adverse events), whereas pharmacokinetics deals with the effects that the body has on the drug (ie, absorption, distribution, metabolism, and elimination).

Drugs may be categorized by mechanism of action, such as sodium-channel antagonists, calcium-channel antagonists, γ-aminobutyric acid (GABA) agonists, or agents that act upon novel targets. Drug-interaction information is combined from animal studies to create an “isobolographic” model. The data then may be summarized to describe the actions as additive (ie, each drug contributes equally to a response or side effect), synergistic (ie, the drugs interact in ways that enhance or magnify one or more of their effects), antagonistic (ie, the drugs interact in ways that interfere with or diminish one or more of their effects), or complex. For example, if freedom from seizures is better than expected when two drugs are combined, the efficacy of this combination would be considered synergistic.

Ideally, physicians desire synergism in efficacy and antagonism in toxicity. The doses required to create an effect of two
drugs in 50% of individuals (ED₉₀) may be plotted against each other and examined at different ratios (eg, 1:3, 1:1, or 3:1) to create a graph that may demonstrate synergism, addition, or antagonism. A generated summary table then shows the effects of combined efficacy and toxicity among many drugs. Our current chart lacks much information, because too few studies have been done to fill in gaps; however, a few summary statements may be made. For example, the combination of two sodium-channel blockers adds little to efficacy and worsens toxicity; this suggests that mixing agents with different mechanisms of actions may offer greater benefit.

**Taking Theory to the Clinic**

Human studies of epilepsy have been limited by the lack of controlled trials. In a large-scale study by Brodie and Yuen, 347 patients initially were started on valproate, carbamazepine, or phenytoin; at 12 weeks, they also were given lamotrigine. The groups showed a tendency toward experiencing the same efficacy at the study’s end, yet the valproate group showed improvement midway into the study, suggesting that combined use of valproate and lamotrigine may have a synergistic effect.

A second, smaller study examined patients with refractory, complex, partial seizures who were started on valproate alone for 3 months, given lamotrigine alone for 3 months, and then given both drugs together for an additional 3 months. The study began with 20 patients; successful treatment was accomplished in 3 patients given valproate, 4 given lamotrigine, and 8 given both drugs, leaving 5 patients uncontrolled.

Tolerability data are difficult to establish. The average daily dose (ADD) may be estimated by dividing the prescribed dose by the assumed average daily dose (a preset standard). For example, the ADD of 600 mg/d of carbamazepine would be 600 mg/1,000 mg (the usual recommended daily dose), or 0.6. The sum of the ADD of each drug prescribed correlates better with medication tolerance than the actual number of medications a patient takes, particularly when the total ADD is < 1.0.

Appreciation of these issues should aid the clinician with drug management. Each year, over 100,000 patients die from drug reactions unrelated to hospital accidents, and two million patients experience serious but nonfatal drug reactions. Phillips and others discussed the 27 most dangerous drugs, which included both carbamazepine and phenytoin (probably due to drug–drug interactions).

Ultimately, a computational system that incorporates such important information as efficacy, tolerability, safety, pharmacokinetics, and pharmacodynamics will be devised to assist physicians with clinical decision-making about polypharmacy. Until then, clinicians should consider pharmacokinetics and pharmacodynamics carefully when prescribing more than one drug. More animal models are needed, and the aid of pharmaceutical companies will be vital in obtaining pharmacologic data on human trials.

Firm prescribing recommendations cannot be made at this point, but combining drugs that have different mechanisms of action may provide greater benefit than combining those that have the same mechanisms. Ultimately, new types of clinical trials must be designed to answer these questions.

### CAN ANIMAL MODELS PREDICT EFFECTIVE COMBINATION THERAPIES?

Adapted from a presentation by H. Steve White, PhD, Professor, Pharmacology and Toxicology, University of Utah, Salt Lake City.

Further insight into monotherapy and polypharmacy requires a closer look at animal studies. However, animal models, including those used currently, are not optimal for the shapping of informed decisions. The majority of studies have been performed in normal animals with acutely induced seizures, but these models may not reflect the chronic nature of epilepsy. Instead, studies involving animals with induced status epilepticus are preferable.

A sample crossover design for an ideal study using seizure frequency as the outcome measure would include the following sequential elements for group 1: baseline > drug 1 > off treatment > drug 2 > off treatment versus the opposite for group 2: baseline > drug 2 > off treatment > drug 1 > off treatment. Even the chronic model is problematic, however, because it may present a predicted increase in seizure frequency after 4–6 months (after inducing status epilepticus), variable frequency of seizures, clustering of seizures, and increased cost for conducting the study. Thus, a repeated-measures crossover design is preferred to minimize these confounding factors. A sample design would have the pattern: baseline > drug 1 > off treatment > drug 2 > off treatment > drug 1 > off treatment > drug 1 > off treatment > drug 2 > off treatment. Each group thus would receive each drug three times in an alternating pattern.

Another problem has involved administration of medication, which can be difficult in rats with behavioral problems and may be secondary to the phenomenon of frequent seizures. Previous studies used either intraperitoneal injection, oral gavage, or a surgically placed infusion pump. The use of a chocolate-coated pellet containing the medication has been quite effective though.

Once the data are gathered, they are converted to a logarithmic scale and measured using analysis of variance (ANOVA).

### Topiramate vs Carisbamate/Carbamazepine

Several studies in rats have compared topiramate with carisbamate and carbamazepine. Grabenstatter et al demonstrated that topiramate afforded a seizure-freedom rate of 12.5%, at best, compared with a seizure-freedom rate of nearly 90% with carisbamate (Figure 5). The study used a 5-day, single-crossover design that compared each drug with vehicle alone. The same researchers then examined carbamazepine at the highest doses (30 and 100 mg/kg). The drug eliminated all convulsive seizures but not necessarily nonconvulsive seizures. The linear response indicated that a dose of 6–8 mg/kg was the ideal dosing range for...
minimum total efficacy, which correlates well with the human dose range. Video
electroencephalographic monitoring identified nonconvulsive seizures, such
that the highest proportion of remaining seizures switched dramatically from convulsive to nonconvulsive as the dose was increased (Figure 6). Thus, carbamazepine
has a dose-dependent response for control of convulsive, but not nonconvulsive,
seizures.

■ NEW THERAPIES
ON THE HORIZON

Adapted from a presentation by Meir Bialer, PhD, MBA, David
H. Eisenberg Professor, Pharmacy, The Hebrew University of
Jerusalem, Israel.

Currently, at least 19 drugs are available to treat epilepsy. Within a short pe-
riod, a variety of new drugs will become available. The most notable of these new
agents are brivaracetam, carisbamate, 2-deoxyglucose, eslicarbazepine acetate,
ganaxolone, huperzine, retigabine, JZP-
4, lacosamide, and the valproic acid
analogues. The question is, do we need
new drugs?

Regulation, Industry, and Research

Epilepsy is a common and ancient
disorder. Despite the availability of 19 dif-
ferent approved agents to control seizures,
approximately 30% of treated patients still
are not seizure-free. And, unfortunately,
all of the agents we do have cause side
effects.

The pharmaceutical industry has its
own share of concerns about this new
 glut of potential remedies. For example,
are there too many drugs out there al-
ready? The chances of a newly designed
or discovered drug being both effective
and safe are limited. Only 10% of agents
designated as investigational new drugs
ultimately are approved by the US Food
and Drug Administration (FDA). When
drugs finally are approved, however, can
they generate sufficient revenue to con-
tinue further drug development?

The answers to these and other ques-
tions may rely on the development of pharmacokinetic-based designs for
research. Newer drugs to treat epilepsy
should be developed against other patho-
lógic targets, such as migraine and bipolar
disorder; to extend their utility. A partner-
ship between industry and academia may
help in attaining this goal. Animal models
have been used to screen antiepileptic
drugs since 1938; however, the goals of
current research should be to establish ef-
ficacy; an unbiased mechanism of action,
clear pharmacokinetics, and information
on any drug–drug interactions. Still, these
newer models are limited; for example,
they are unable to predict toxicity.
TABLE 2
Pending New Antiepileptic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rufinamide</td>
<td>Treatment of Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Linear pharmacokinetics</td>
</tr>
<tr>
<td></td>
<td>Bioavailability of 61%</td>
</tr>
<tr>
<td>Carisbamate</td>
<td>Inducible</td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>More potent than levetiracetam</td>
</tr>
<tr>
<td>Retigabine</td>
<td>Opens potassium channel</td>
</tr>
<tr>
<td></td>
<td>Partial-onset epilepsy</td>
</tr>
<tr>
<td></td>
<td>Does not interfere with the pharmacokinetics or metabolism of oral contraceptive agents</td>
</tr>
<tr>
<td></td>
<td>No clinically relevant pharmacokinetic interactions with a wide range of other AEDs (eg, phenobarbital, valproate, topiramate, phenytoin, lamotrigine, or carbamazepine)</td>
</tr>
<tr>
<td>Valrocemide</td>
<td>Response rate of 45%</td>
</tr>
<tr>
<td>Valpromide</td>
<td>Nonteratogenic</td>
</tr>
<tr>
<td>Valnoctamide</td>
<td>Three to six times more potent than valproate</td>
</tr>
</tbody>
</table>

AEDs = antiepileptic drugs
Adapted from a presentation by Meir Bialer, PhD, MBA, at the 62nd Annual Meeting of the American Epilepsy Society, Seattle, Washington

When Monotherapy for Epilepsy Fails

Vikram Bhise, MD

During the 9th Eilat Conference on New Antiepileptic Drugs (Eilat IX) held in Sitges, Spain, June 15–19, 2008, researchers discussed a number of these new therapeutics (Table 2). Newer agents are on the horizon; however, we should focus on pharmaceuticals that offer the broadest therapeutic options and the greatest efficacy and safety.

- **NONPHARMACOLOGIC APPROACH: PRELIMINARY RESULTS FROM THE SANTE TRIAL**

Adapted from a presentation by Robert S. Fisher, MD, PhD, Professor of Neurology and Neurological Sciences and Neurosurgery, Stanford Epilepsy Center, Stanford University, Palo Alto, California

The SANTE study investigated the use of DBS in reducing refractory, partial-onset seizures. Clinical investigators enrolled 100 patients (ages 18–65 years) with intractable partial or secondarily generalized seizures from 17 sites nationwide. To be enrolled, patients must have experienced more than six partial-onset seizures per month, must have continued to have seizures despite treatment with three antiepileptic drugs, must have been using one to four antiepileptic drugs upon enrolling, and must have had a minimum intelligence quotient of 70. The authors made a conscientious decision to exclude candidates for temporal lobe resection at the time of study. Patients who underwent implantation of a vagal nerve stimulator (VNS) needed to consent to its replacement with the DBS device.

### Design

The surgery involved implantation of wires in both the left and right anterior nuclei of the thalamus via Burr holes; these wires led to a control device made by Medtronic that was placed in the chest. According to the study protocol, all patients continued to receive epilepsy drugs during the trial. The device was not activated during the initial 1-month period (baseline); thereafter, the device either was activated or left unactivated, depending upon the group to which patients were assigned randomly. After 3 months (ie, 4 months after implantation), the patients then were switched to an open-label study for 9 months; during this period, clinicians were free to adjust the parameters according to certain guidelines (ie, physicians could decide to make one adjustment to a specified voltage or frequency at two specified time points). Finally, patients were evaluated during long-term follow-up; during this phase, they continued to receive neurostimulation, and physicians could change stimulation parameters.

### Demographics

Almost half of the patients already had a VNS implanted, and one quarter of the patients already had undergone epilepsy surgery. Their mean age was 30 years old; patients had lived with epilepsy for an average of 20 years.

### Outcomes

The FDA requested that investigators use a generalized estimating equation, which is an ANOVA equivalent of a repeated-measures study that uses discrete intervals. The primary outcome was the difference in seizure frequency between the stimulus and control groups. Long-term results were available from the last 3 months for each patient; some individuals have remained on the study for over 4 years (range, 13–49 months).

The mean seizure-freedom rate was 38% for the test group and 14% for the control group ($P = 0.038$). However, during month 3 of the 3-month period, the statistical significance was at the level of $P = 0.002$. Furthermore, a 20% improvement was noted in both groups during the baseline period before the device was turned on. This improvement may have resulted from a placebo effect, issues related to the placement of leads, or a regression to the mean (ie, a worse initial frequency because patients entered the study at their sickest stage).

One patient developed complex partial status epilepticus (> 100 seizures daily) after the device was turned on at 5 µV. After the device was turned off and the patient returned to baseline, the patient was restarted...
at 4 µV and eventually was increased to 9 µV over time without a return of status epilepticus. Information from this patient was removed from the reported data; however, the results remained positive, even with inclusion of these data.

The investigators also examined data on patients with a VNS (44.5% of subjects), with prior epilepsy surgery (24.5%), with both (15.5%), and with neither. All groups demonstrated a benefit; significant improvement could not be demonstrated, however, because few patients in each subgroup were available for analysis. Nevertheless, patients who experienced the most severe seizures appeared to benefit the most.

These benefits persisted throughout the open-label period (ie, 4–13 months). The control patients also demonstrated a benefit when the device was activated during the open-label phase. By the end of that period, a 40.3% reduction in seizure frequency was evident across all groups; this effect was found among 63.6% of the subjects at the end of long-term follow-up.

Seizure freedom was seen in only one patient in the control group at 3 months, in two patients at month 9 of the open-label phase, and in 9% of patients at long-term follow-up; at that time, 19% of the patients had a reduction in seizure activity of greater than 90%.

Adverse Effects

The investigators mainly were concerned about the adverse reactions of intracranial surgery such as death, hemorrhage, infection, and status epilepticus. Five patients died, one during the baseline phase and four during the open-label phase; and in 9% of patients at long-term follow-up; at that time, 19% of the patients had a reduction in seizure activity of greater than 90%.

Development of DBS is still in its early stages. It has imparted benefit, yet remains an invasive procedure that must be used selectively. Future issues to be studied include predictors of patients who would benefit, optimal parameters of such a device, and use of other types of stimulation to prevent refractory seizures.

Conclusion

The SANTE study met its primary objective with a positive outcome. The group as a whole showed natural improvement initially over time, but patients treated with the DBS improved significantly when compared with the placebo group during the blinded phase (38% vs 14%; P = 0.038). Patients in the placebo arm also improved during the open-label phase.

The device was well tolerated, and no clinically significant intracranial hemorrhages occurred. Some possible concerns regarding depression, memory impairment, and anxiety were addressed. Finally, the researchers noted that patients offered this procedure should undergo the surgery at centers experienced in its method.

The development of DBS is still in its early stages. It has imparted benefit, yet remains an invasive procedure that must be used selectively. Future issues to be studied include predictors of patients who would benefit, optimal parameters of such a device, and use of other types of stimulation to prevent refractory seizures.

References

CME Post Test

Using these pages as a worksheet, select the best answer to each question based on your reading of the articles in this issue of The Neurology Report, then complete the evaluation on page 40 and see the instructions below it to obtain CME credit.

1. Winawer et al performed a genetic familial aggregation study mapping families with childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME), finding concordance between:
   a. CAE and JME but not CAE and JAE
   b. CAE and JAE but not CAE and JME
   c. CAE, JAE, and JME
   d. None of these subtypes

2. Results of the National Institutes of Health (NIH) Childhood Absence Epilepsy Trial, which compared the efficacy and tolerability of ethosuximide, valproic acid, and lamotrigine in the initial treatment of CAE, showed at 4 months that:
   a. The ethosuximide group had the highest rate of freedom from failure.
   b. Most seizures among patients receiving lamotrigine were clinical rather than electroencephalographic.
   c. Increased body mass index was a greater cause for treatment failure in the valproate group than in the ethosuximide or lamotrigine groups.
   d. All of the above

3. In evaluating cognitive deficits of children participating in the NIH Childhood Absence Epilepsy Trial, investigators found that:
   a. At baseline, patients performed significantly more errors of commission than omission.
   b. At 4 months after anticonvulsant treatment, patients given lamotrigine showed a significant increase in attention difficulties when compared with their baseline performance.
   c. At 4 months after anticonvulsant treatment, no adverse changes or significant improvement in performance were noted among children treated with ethosuximide or lamotrigine.
   d. None of the above

4. Which of the following statements about immunomediated epileptic encephalopathies is true?
   a. Limbic encephalitis is characterized by the triad of intractable focal seizures, progressive hemiparesis, and increasing intellectual impairment.
   b. Autoantibodies to glutamate receptor type 3 may be associated with Rasmussen's encephalitis and other forms of epilepsy, particularly the catastrophic types.
   c. Although paraneoplastic types of limbic encephalopathy have responded to immunotherapies, nonparaneoplastic types have not.
   d. None of the above

5. A chronic systemic inflammatory disorder of unclear etiology that primarily affects adults and that is characterized by the clinical triad of recurrent oral aphthous ulcers, genital ulcers, and inflammatory eye disease, along with seizures and other neurologic features, is:
   a. Scleroderma
   b. Systemic lupus erythematosus
   c. Hashimoto encephalopathy
   d. Behçet's disease

6. In an otherwise healthy child who develops status epilepticus a few days after a febrile illness, along with a progressive decline in cognitive function, which of the following should be considered?
   a. Devastating epileptic encephalopathy in school-aged children
   b. Rasmussen's encephalitis
   c. Acute encephalitis with repetitive, refractory partial seizures
   d. Hashimoto encephalopathy

7. An antiepileptic drug that selectively enhances slow sodium-channel inactivation to normalize activation thresholds is:
   a. Vigabitrin
   b. Lacosamide
   c. Levitiracetam
   d. Pregabalin

8. Medications that may be used adjunctively for partial epilepsy and that have favorable pharmacokinetic profiles include gabapentin, levetiracetam, lacosamide, tiagabine, and pregabalin.
   a. True
   b. False
9. Epilepsy may be best studied in a naturalistic study, which allows for flexible dosing, slow titration to an individual target dose, a prolonged time span, determination of long-term efficacy, consideration of patient preferences, balance of efficacy and side effects, and adjustment of doses of other antiepileptic drugs.
   a. True
   b. False

10. The Seizure Severity Questionnaire (SSQ):
   a. Attempts to assess a “clinically important change” rather than just statistical significance
   b. Helps us to understand the life changes that patients experience over treatment periods
   c. Provides total and subscale scores that are useful for statistical analysis
   d. None of the above

11. Which of the following statements about rufinamide is true?
   a. Its influence on the clearance of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate in children, adults, and adolescents is modest and believed to be of unlikely clinical significance.
   b. Its short- and long-term use has been well tolerated.
   c. No difference in its clearance or volume of distribution has been observed between blacks and Caucasian subjects, and no significant difference in its pharmacokinetics has been noted among patients of different ages.
   d. All of the above

12. Data from the CRUF331-0022 study showed that when compared with placebo, adjunctive use of rufinamide in patients with Lennox-Gastaut syndrome resulted in statistically significant reductions in the numbers of:
   a. Total seizures, atonic seizures, and combined absence and atypical absence seizures
   b. Total seizures and atonic, tonic, and myoclonic seizures
   c. Total seizures and atonic, tonic-clonic, and partial seizures
   d. Total seizures and atonic seizures; combined absence and atypical absence seizures; and myoclonic, tonic-clonic, and partial seizures

13. A possible predictor that monotherapy for epilepsy will fail is:
   a. A family history of Parkinson’s disease
   b. A higher number (> 25) of seizures at presentation
   c. Intermittent recreational drug use
   d. Typical presentations of idiopathic generalized seizures

14. The International League Against Epilepsy clearly stated that the present availability of rigorous, comprehensive data on the adverse effects of initial drugs given alone for newly diagnosed or untreated epilepsy allowed the development of evidence-based guidelines to identify the best monotherapy against seizure disorders.
   a. True
   b. False

15. Results from the SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) trial of deep-brain stimulation (DBS) in patients with refractory epilepsy showed that:
   a. The mean seizure freedom was 38% for patients whose DBS devices were activated and 14% for those whose devices were left inactivated.
   b. A 40% improvement attributed to a placebo effect was noted in all patients during the baseline period, before the device was turned on.
   c. Patients who had undergone previous epilepsy surgery demonstrated no benefit from DBS.
   d. All of the above
## Evaluation

Your candid and thorough completion of this evaluation will help CME LLC improve the quality of its CME/CE activities. Thank you for your participation.

1. As a result of this activity …
   a. I have a greater understanding of the genetic and immunologic bases of some types of epilepsy and the use of antibodies as prognostic markers.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   b. I am more knowledgeable about the role of encephalopathy in prompting seizures and the role of immunotherapy in treating affected patients.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   c. I am more familiar with recent clinical trials of various antiepileptic drugs (AEDs) and the promise of new AEDs in clinical development.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   d. I have a better appreciation of the cognitive and neuropsychological effects of childhood absence seizures.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   e. I am more knowledgeable about the challenges of managing Lennox-Gastaut syndrome and the potential role of rufinamide in its treatment.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  

2. I found the content of this educational activity …
   a. Clearly written and well organized.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   b. Accurate and timely.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   c. Related to its overall objectives.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   d. Free from commercial bias.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   e. Relevant to my own clinical practice.  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  

3. Did the information you received from this CME activity:
   a. Confirm the way you currently manage your patients?  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  
   b. Suggest new options for managing your patients that you might apply in the future?  
   ![Strongly agree](false)  ![Agree](false)  ![Disagree](true)  

4. I used the information in this issue for … (check all that apply)  
   ![Patient management](false)  ![Board review](false)  ![CME credit](true)  

5. Approximately how long (in minutes) did it take you to complete this activity, including this evaluation?  
   _______ minutes

### Instructions for Obtaining CME Credit

To receive CME credit for this free educational activity and a certificate from CME LLC:

- Study the educational material presented in this issue of *The Neurology Report*.
- Using pages 38–39 as a worksheet, answer all of the post-test questions based on the content of the articles.
- Complete the CME LLC enrollment form, enter your post-test answers from the worksheet on pages 38–39, and respond to all of the questions on the evaluation form, then click the “Submit” button. The full text of each article may be accessed at www.NeurologyReport.com, should you need to refer to it again.
- If you answer correctly at least 12 (80%) of the 15 post-test questions, you will immediately receive credit for this educational activity and can access your certificate online by clicking “View/Print Certificate” on the acknowledgment page. Follow the on-screen instructions to print your certificate.