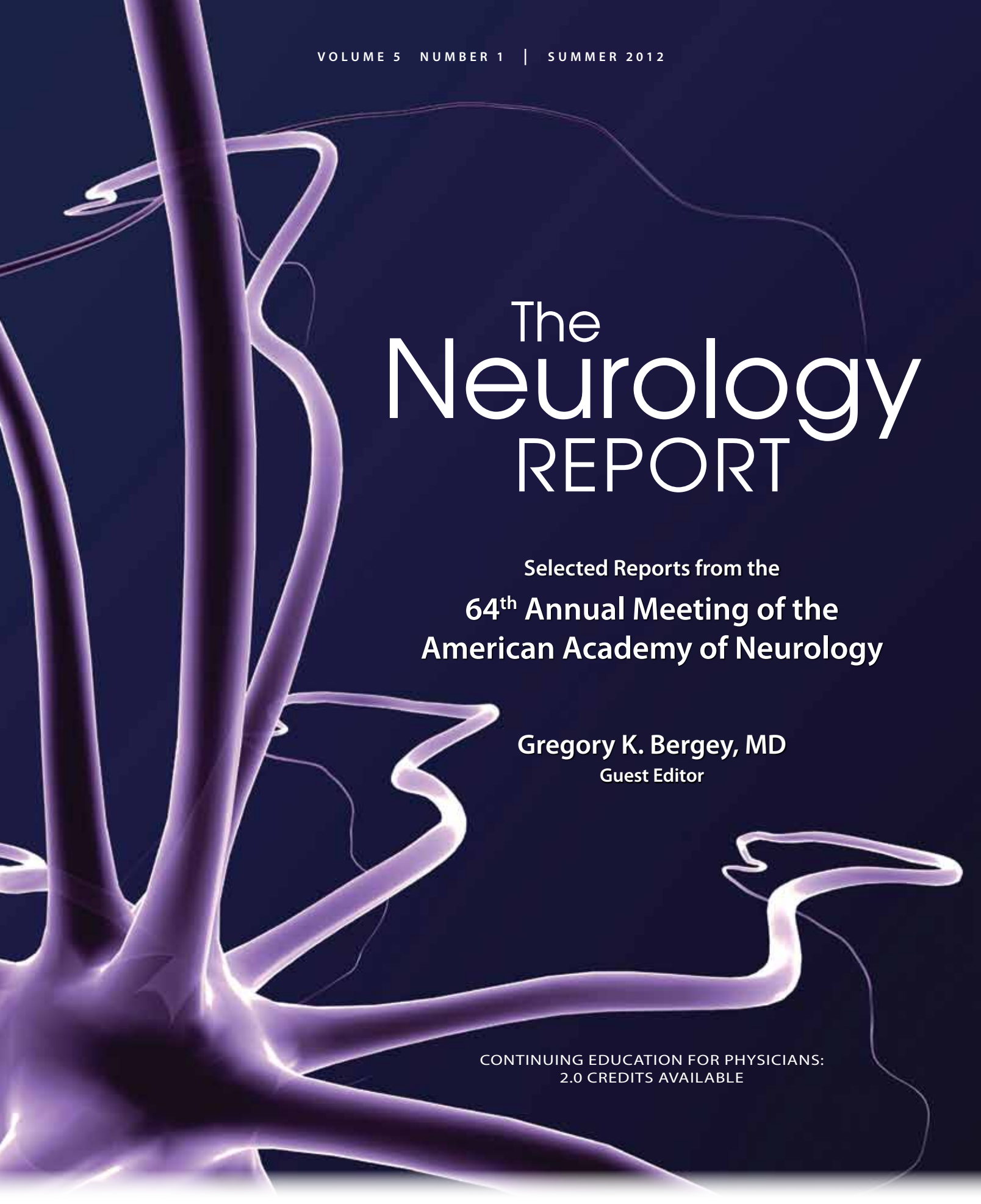
VOLUME 5 NUMBER 1 | SUMMER 2012



The Neurology REPORT

Selected Reports from the 64th Annual Meeting of the American Academy of Neurology

Gregory K. Bergey, MD
Guest Editor

CONTINUING EDUCATION FOR PHYSICIANS:
2.0 CREDITS AVAILABLE

This activity is supported by an educational grant from Eisai Inc.

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Guest Editor: Gregory K. Bergey, MD

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About This CME Activity

RATIONALE AND PURPOSE

Epilepsy is the third most common neurologic disorder, after Alzheimer's disease and stroke. Yet despite advances in its medical and surgical treatment, about one in three patients with epilepsy continues to have seizures, and many more experience various adverse effects from their medication or postsurgically. Clearly, there is much work that still needs to be done to discover better ways of managing this all-too-prevalent neurologic disorder with fewer or less severe adverse effects.

The articles in this edition of *The Neurology Report,* based on selected studies and reports presented at the 64th Annual Meeting of the American Academy of Neurology, held April 21–28, 2012, in New Orleans, Louisiana, focus upon the use of both conventional and novel antiepileptic drugs (AEDs) and recent surgical approaches to treating seizure disorders and peer into the future of epilepsy therapy. Included among the subjects discussed are promising new therapeutic agents and potential new indications for older agents that appear to be well tolerated and reduce the frequency of seizures when used to treat refractory partial-onset epilepsy. The authors also explore the usefulness of biomarkers for predicting adverse drug reactions, novel electrophysiologic techniques that may reveal new epileptogenic areas of the brain and record microseizure activity, and the application of functional magnetic resonance imaging in assessing language and memory dysfunction.

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 to meet a perceived educational need to provide neurologists, neurosurgeons, 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:

- Review the outcomes of clinical trials testing novel and established AEDs, alone and in combination, in the treatment of epilepsy.
- Outline the advantages and disadvantages of surgical options for controlling seizures.
- Summarize the relationships of cognitive dysfunction, memory loss, and autism with respect to both the etiology of epilepsy and its treatment.
- Discuss the pharmacogenetics and pharmacogenomics of AEDs as they relate to the clinical management of epilepsy.
- Examine the usefulness of technologic advances in helping predict the risk of memory loss or language dysfunction before surgery in patients with epilepsy and in the assessment of seizure activity and treatment response.

TARGET AUDIENCE

Neurologists, neurosurgeons, and other physicians significantly involved in the management of patients with epilepsy should find participation in this educational activity valuable.

ACCREDITATION AND CREDIT DESIGNATION

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 the University of Cincinnati and Direct One Communications, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

The University of Cincinnati designates this Enduring Material Activity for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CREDIT AVAILABILITY

Activity release date: July 19, 2012
Expiration date: July 20, 2013

METHOD OF PARTICIPATION

This Enduring Material Activity is available in print and online at **www.NeurologyReport.com** and consists of an introduction, five articles, a postactivity assessment, and an evaluation. Estimated time to complete the activity is 2.0 hours.

To receive credit, participants must read the CME information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form online at **www.NeurologyReport.com**. Upon successful completion of the post test (80% correct) and evaluation form, a CME certificate of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

There are no fees for participating in or receiving credit for this activity.

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Gregory K. Bergey, MD, is Professor of Neurology, Director of the Johns Hopkins Epilepsy Center, and Vice-Chair for Research, Department of Neurology, Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland. He has received grant/research support from the National Institutes of Health and is on the advisory board of UCB.

Beth M. Silverstein, DO, a Clinical Neurophysiology/Epilepsy Fellow at North Shore University Hospital, North Shore–Long Island Jewish Health System, Manhasset, New York, has nothing to disclose.

Pearce J. Korb, MD, an Epilepsy Fellow in the Department of Neurology, Emory University School of Medicine, Atlanta, Georgia, has nothing to disclose.

David Wolf, MD, PhD, a Clinical Fellow in Neuro-Oncology at Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland, has nothing to disclose.

Heidi Munger Clary, MD, MPH, a Clinical Neurophysiology/Epilepsy Fellow in the Columbia Comprehensive Epilepsy Center, Neurological Institute of New York, New York, New York, has nothing to disclose.

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Rick Ricer, MD, has nothing to disclose.

Susan P. Tyler, MEd, CMP, CCMEP, has nothing to disclose.

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Discussions concerning drugs, dosages, devices, and procedures may reflect the clinical experience of the planning committee or faculty, may be derived from the professional literature or other sources, or may suggest uses that are investigational and not approved labeling or indications.

In this issue of *The Neurology Report,* Dr. Silverstein discusses eslicarbazepine acetate and an extended-release formulation of topiramate, neither of which is currently approved by the FDA. Dr. Wolf describes a phase III clinical trial comparing zonisamide monotherapy with single-agent carbamazepine in patients with partial-onset seizures; zonisamide is currently indicated only as adjunctive (add-on) therapy in this population. Dr. Wolf also reviews a temporal analysis of data from three studies of an investigational antiepileptic agent, perampanel. Dr. Munger Clary briefly describes the off-label use of midazolam in status epilepticus and laboratory studies of perampanel. Dr. Kennedy describes the off-label use of zonisamide to control partial-onset seizures in pediatric patients and three clinical studies of perampanel as adjunctive antiepileptic therapy in patients with refractory partial-onset seizures.

CONTACT INFORMATION

We would like to hear your comments regarding this or other educational activities produced by Direct One Communications, Inc. In addition, suggestions for future activities are welcome. Contact us at:

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Introduction

Selected Reports from the 64th Annual Meeting of the American Academy of Neurology

Gregory K. Bergey, MD, *Guest Editor*

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Epilepsy is the third most common neurologic disorder, after Alzheimer's disease and stroke. Its prevalence in the United States exceeds that of Parkinson's disease, multiple sclerosis, and cerebral palsy combined. Despite this prevalence and the many recent advances in its diagnosis and treatment, there are many aspects of epilepsy that are not fully understood.

During the 64th Annual Meeting of the American Academy of Neurology (AAN), held April 21–28, 2012, in New Orleans, Louisiana, neurologists and neurosurgeons from around the globe attended sessions involving over 2,000 posters, scientific presentations, workshops, and symposiums on the etiology, identification, treatment, and outcomes of various seizure disorders and other neurologic conditions. This issue of *The Neurology Report* contains articles contributed by a talented group of physicians who are just starting their careers in neurology and have brought back from the AAN meeting their impressions of the exciting developments in epilepsy research presented there. Their reports focus mainly on the management of partial seizures—the most common form of epilepsy—and novel antiepileptic treatments used to prevent and manage these and other types of seizures.

RECENT CLINICAL TRIALS OF THIRD-GENERATION ANTIEPILEPTIC DRUGS

Approximately one third of patients with epilepsy continue to have seizures despite surgery and drug treatment and despite therapeutic trials of multiple antiepileptic drugs (AEDs) with different mechanisms of action and adverse-effect profiles. Beth M. Silverstein, DO, from North Shore University Hospital in Manhasset, New York, offers information on several third-generation AEDs that are showing promise when used as adjunctive therapy with other seizure medications. She summarizes studies presented at the meeting on the safety, efficacy, and tolerability of ezogabine (known as retigabine outside the United States), a novel potassium channel activator, used with and without sodium-channel blockers in patients with partial-onset seizures; the efficacy and safety of clobazam used alone and with other AEDs in pediatric and adult patients with Lennox-Gastaut syndrome; the pharmacokinetics and tolerability of a new once-daily, extended-release formulation of topiramate; the short- and long-term (up to 8 years) safety and efficacy of adjunctive therapy with lacosamide in patients with refractory focal seizures or partial-onset seizures; and the efficacy of eslicarbazepine acetate, a novel voltage-gated sodium-channel blocker, in patients with refractory partial-onset seizures taking other AEDs.

CURRENT CONTROVERSIES IN EPILEPSY: BRAIN INJURY AND COGNITIVE CONSEQUENCES

Seizure disorders may result from a head injury or may coexist with a number of other medical disorders. Pearce J. Korb, MD, from Emory University School of Medicine in Atlanta, reviews the risk of seizures following head trauma and the links between epilepsy and autism. He addresses novel surgical and radiosurgical techniques to treat mesial temporal lobe epilepsy and the questions regarding cognitive consequences that may follow. In addition, Dr. Korb describes studies focusing on the course of epilepsy and associated cognitive outcomes, emphasizing the key role of comorbidities in predetermining function.

POTENTIAL NEW MEASURES TO MANAGE PARTIAL-ONSET SEIZURES

Zonisamide, a benzisoxazole derivative with multiple mechanisms of action and a long half-life, is currently indicated for adjunctive therapy of partial-onset seizures in conjunction with other AEDs. David Wolf, MD, PhD, from the Johns Hopkins School of Medicine and Hospital in Baltimore, summarizes the results of a head-to-head comparison of single-agent zonisamide and carbamazepine in previously untreated adults with newly diagnosed partial-onset epilepsy. In addition, he covers recent research on perampanel, a novel compound with an acceptable side-effect profile that selectively and effectively inhibits a glutamatergic ion channel implicated in epilepsy.

Dr. Bergey is Professor of Neurology, Director of the Johns Hopkins Epilepsy Center, and Vice-Chair for Research, Department of Neurology, Johns Hopkins University School of Medicine and Hospital, Baltimore, Maryland.

PROMISING NEW DIRECTIONS IN EPILEPSY MANAGEMENT

Heidi Munger Clary, MD, MPH, from the Columbia Comprehensive Epilepsy Center of the Neurological Institute of New York, recounts the results of recent clinical trials of ezogabine, clobazam, and perampanel in patients with epilepsy and the use of intramuscular midazolam to treat convulsive status epilepticus. In addition, Dr. Munger Clary reports on emerging techniques for managing epilepsy, including advances in monitoring patients for drug toxicity using pharmacogenomic and pharmacogenetic biomarkers, novel electrophysiologic techniques and microelectrode arrays for evaluating patients with epilepsy, and the use of magnetic resonance imaging to assess memory and language functions.

EMERGING DEVELOPMENTS IN ANTIEPILEPTIC DRUG THERAPY

Finally, Jeffrey D. Kennedy, MD, from the Northwestern University Feinberg School of Medicine in Chicago, Illinois, summarizes other recent clinical studies of novel AEDs, including a phase III, double-blinded, placebo-controlled trial evaluating the safety and efficacy of zonisamide in pediatric patients with partial-onset seizures who were responding inadequately to other AEDs (zonisamide is currently indicated only for use in adults). In addition, Dr. Kennedy describes three phase III trials evaluating the adjunctive use of perampanel with other agents, pharmacokinetic information for physicians prescribing such therapeutic combinations, and the span of time patients stayed free of seizures when using the drug.

The authors of these reports chronicle current developments in the medical and surgical treatment of epilepsy in a pointed, descriptive, and analytic manner. As described, these developments offer real hope for the improvement of epilepsy management.

Recent Clinical Trials of Third-Generation Antiepileptic Drugs

Beth M. Silverstein, DO

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Abstract Effective treatment of epilepsy remains a medical juggling act. Neurologists must weigh effective control of seizure activity with patients' medical histories and comorbidities to create a treatment plan that often includes two or more antiepileptic drugs (AEDs) with different mechanisms of action, increasing the potential for significant adverse effects and also drug interactions. At the 2012 Annual Meeting of the American Academy of Neurology, the results of a variety of recent clinical trials were presented on novel, third-generation AEDs, including ezogabine; clobazam; lacosamide; eslicarbazepine acetate; and a once-daily, extended-release formulation of topiramate.

Although epilepsy therapy has improved greatly over recent years, 30%–40% of patients continue to experience uncontrolled seizures when using just one antiepileptic drug (AED).[1] In such patients, more than one AED is used in attempts to control seizure activity.[2]

Since 1993, more than 10 AEDs have joined the core armamentarium of valproic acid, carbamazepine, phenytoin, phenobarbital, and the benzodiazepines.[3] Novel drugs offer hope to patients who continue to experience seizures after receiving multiple drugs or are unable to tolerate their side effects. However, the effectiveness of combination therapy using AEDs with separate mechanisms of action remains largely unknown.[4]

During the 64th Annual Meeting of the American Academy of Neurology (AAN) in New Orleans, a number of posters were presented describing recent clinical studies of novel AEDs, including ezogabine; clobazam; lacosamide; eslicarbazepine acetate; and a once-daily, extended-release formulation of topiramate.

EZOGABINE

Treatment with ezogabine (known as retigabine outside the United States) stabilizes the resting membrane potential, controls subthreshold excitability, and suppresses seizures by opening neuronal voltage-gated potassium channels.[5]

The clinical effectiveness of adjunctive ezogabine therapy in patients with inadequately controlled partial-onset seizures was demonstrated in the phase II Retigabine Efficacy and Safety Trials for Partial Onset Epilepsy, RESTORE-1[6] and RESTORE-2.[7] When compared with a placebo group, patients taking 600, 900, and 1,200 mg/d of this third-generation AED were significantly more likely to experience a 50% or greater reduction in 28-day total partial-onset seizure frequency during a 12-week maintenance period and throughout an entire 16- to 18-week double-blinded treatment phase. The ezogabine group had significantly greater median reductions in 28-day total partial-onset seizure frequency from baseline than did the placebo group, regardless of patient age, race, gender, or seizure activity at baseline. Most adverse events were mild to moderate, and use of the drug generally was well tolerated.[5]

Which AED to use with ezogabine is an ongoing controversy. Ezogabine therapy enhances the activity of KCNQ (Kv7) potassium channels and reduces neuronal excitability.[8] The drug is not likely to cause any pharmacokinetic interaction with other AEDs.[9] However, concomitant use of phenytoin or carbamazepine with ezogabine may lower plasma ezogabine levels.[10]

Efficacy, Safety, and Tolerability With and Without Sodium-Channel Blockade

A number of AEDs share a common mechanism of action by blocking sodium channels; these drugs include carbamazepine, lamotrigine, phenytoin, and oxcarbazepine. Understandably, sodium-channel blockers would therefore be the most common type of AED used in clinical trials of adjunctive epilepsy therapy. Non–sodium-channel blockers include valproic acid, levetiracetam, pregabalin, and topiramate.

Two recent studies[11,12] investigated the effectiveness and safety of ezogabine therapy in patients with partial-onset seizures who were taking sodium-channel blockers or non–sodium-channel blockers. Participants in these studies were taking at least one traditional sodium-channel blocker but no other types of AEDs or at least one AED with a mechanism of action other than sodium-channel blockade, such as γ-aminobutyric acid (GABA) enhancement, SV2A modulation, or α2δ calcium-channel interaction, and no sodium-channel blockers.

Dr. Silverstein is a Clinical Neurophysiology/Epilepsy Fellow at North Shore University Hospital, North Shore–Long Island Jewish Health System, Manhasset, New York.

An integrated analysis on pooled data from three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, 205,[13] 301 (RESTORE-1),[6] and 302 (RESTORE-2),[7] was performed. These trials included an 8-week baseline phase, randomization to thrice-daily treatment with ezogabine or placebo, and then a titration phase of 2–6 weeks to achieve a target daily ezogabine dose of 600, 900, or 1,200 mg. Thereafter, a double-blind maintenance phase lasting 8 weeks (study 205) or 12 weeks (studies 301 and 302) led to an open-label extension study or a 3-week dosage-tapering phase.

Patients in study 205 were 16–70 years of age; those in studies 301 and 302 were 18–75 years of age. Patients in study 205 were receiving up to two AEDs, and those in studies 301 and 302 were taking up to three AEDs, with or without vagal stimulation. All participants in these trials had experienced at least four partial-onset seizures over the past 28 days; they could not have been free of seizures for over 30 days (study 205) or more than 21 consecutive days (studies 301 and 302) during the baseline phase. Data on all patients given at least one dose of ezogabine or placebo and using only traditional sodium-channel or non–sodium-channel blockers were included.

Using data from these three trials, Brodie et al[11] evaluated the effectiveness of ezogabine as adjunctive therapy when given with either traditional sodium-channel blockers or non–sodium-channel blockers to patients with partial-onset seizures. In a separate study, French et al[12] investigated the safety and tolerability of ezogabine therapy in these same patients. Among 1,240 patients included in the intention-to-treat (ITT) double-blind population, 344 (28%) were using at least one sodium-channel blocker with no non–sodium-channel blockers, and 196 (16%) were using at least one non–sodium-channel blocker without any sodium-channel blockers.

The baseline characteristics and demographics of the two groups were similar, although slightly more patients in the sodium-channel blocker group (59%) than in the non–sodium-channel blocker group (45%) were taking only one background AED.

TABLE 1
Frequency of Adverse Events in Patients Taking Ezogabine vs Placebo

	Patients taking traditional sodium-channel blockers		Patients taking non–sodium-channel blockers	
Adverse event	**Ezogabine (n = 238)**	**Placebo (n = 106)**	**Ezogabine (n = 119)**	**Placebo (n = 77)**
All adverse events	81%	72%	85%	81%
Serious adverse events	9%	7%	9%	3%
Adverse events leading to study withdrawal	24%	9%	30%	13%
Dizziness	26%	9%	26%	7%
Somnolence	20%	18%	23%	18%
Headache	20%	18%	8%	21%
Fatigue	16%	7%	17%	3%
Confusional state	12%	4%	9%	3%
Tremor	9%	2%	5%	5%
Abnormal coordination	5%	1%	8%	5%
Blurred vision	7%	2%	4%	1%

Source: French et al[12]

Efficacy. As reported by Brodie et al,[11] the median percent reduction in seizures over the double-blind treatment period in all patients taking sodium-channel blockers was 36% in the ezogabine group versus 14% in the placebo group. Among patients taking non–sodium-channel blockers, the median percent reduction in seizures was 45% in all patients using ezogabine versus 21% in the placebo group. During the maintenance therapy phase, the median percent reduction in seizures for all patients in the sodium-channel blocker group was 46% in patients given ezogabine versus 29% in those given placebo. Among all patients using non–sodium-channel blockers, the reduction was 48% in all patients using ezogabine versus 27% in those using placebo.

Safety and tolerability. French and colleagues[12] analyzed these same three datasets for treatment-emergent adverse events, serious adverse events, and adverse effects leading to withdrawal from the study during ezogabine therapy.

Tolerability between the subgroups generally was similar (Table 1).[13] Ezogabine is metabolized via glucuronidation; consequently, its exposure may be lessened in some patients using sodium-channel blockers that also induce glucuronyl transferases, such as carbamazepine and phenytoin. Overall, no differences in adverse events or serious adverse events were evident among patients with partial-onset seizures who were treated with ezogabine in conjunction with sodium-channel blockers or AEDs having other mechanisms of action.

Thus, ezogabine therapy offered similar efficacy with no apparent safety issues in adults with drug-resistant partial-onset seizures who also were taking either traditional sodium-channel blockers or non–sodium-channel blocker AEDs.

CLOBAZAM

Lennox-Gastaut syndrome (LGS) is a severe form of childhood-onset epilepsy characterized by frequent tonic, atonic, and atypical absence seizures; behavioral disturbances; cognitive dysfunction; and resistance to treatment. Treatment often focuses on attempts to improve injurious drop seizures (sudden tonic or atonic falls); these seizures are some of the most challenging to control.[14] Currently, clobazam, clonazepam, felbamate, lamotrigine, topiramate, and rufinamide have been approved by the US Food and Drug Administration (FDA) for the treatment of LGS. However, many patients continue to experience seizures despite AED therapy.

Clobazam, a novel benzodiazepine, recently was approved by the FDA for adjunctive treatment of seizures associated with LGS in patients at least 2 years of age.[15] Its exact mechanism of action is

unclear, but it probably involves potentiation of neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

Efficacy

The double-blind, phase III Clobazam in Patients with Lennox-Gastaut Syndrome (CONTAIN) study[16] compared three different daily doses of clobazam with placebo in patients ranging from 2 to 60 years of age; LGS was documented by both clinical and electroencephalographic criteria. A total of 305 patients were screened; 238 were randomized. There were 217 patients in the modified ITT (mITT) population, and 177 individuals (mean age, 12.4 years; 60.5% male) completed the study. Patients in the mITT population had baseline data, had received at least one clobazam dose, and had at least one seizure measurement during the maintenance phase. Demographics and clinical characteristics were similar between the groups.

The study featured a 4-week baseline period, a 3-week titration period, and a 12-week maintenance period. On day –1, patients were stratified by weight and randomly assigned to receive a target of 0.25 mg/kg/d (maximum, 10 mg/d), 0.5 mg/kg/d (maximum, 20 mg/d), or 1.0 mg/kg/d (maximum, 40 mg/d) of clobazam or placebo. Use of clobazam resulted in significantly lower frequencies of drop and total seizures linked to LGS that were dose-related. Improved drop seizure rates experienced by LGS patients during the first 4 weeks of the CONTAIN 12-week maintenance period were sustained during the last 4 weeks among patients using 0.5 and 1.0 mg/kg/d of clobazam.

Independence of efficacy on age, gender, or race/ethnicity. Mitchell et al[17] studied the efficacy of clobazam in preventing drop attacks in LGS patients of different ages, gender, and race (white, Asian, other) or ethnicity (Hispanic/Latino vs non-Hispanic/Latino). The primary endpoint was the percentage reduction in the average frequency of drop seizures per week during maintenance therapy versus the frequency at baseline. In addition, average weekly responder rates (ie, 25%, 50%, 75%, and 100%) were evaluated.

When compared with the age-matched controls receiving placebo, patients receiving all three doses of clobazam exhibited a greater average and median percentage reduction in the frequency of drop seizures during the maintenance phase. The one exception was a statistically insignificant median reduction in seizure frequency among patients ≥ 12 to < 17 years old who took 0.25 mg/kg/d of clobazam, possibly due to the small sample size (n = 8). The seizure reduction was dose-dependent, which was consistent with the overall CONTAIN results. Further, seizure reduction in patients ≥ 17 years of age was consistent with that observed in younger LGS patients. No differences in the percentage reduction in seizure frequency were observed between men and women or among racial or ethnic subgroups of patients receiving clobazam.

Sustained efficacy. Ng et al[18] compared the number of drop seizures experienced by LGS patients given clobazam or placebo between the first 4 weeks (weeks 4–7) and the last 4 weeks (weeks 12–15) of maintenance therapy. Patients experienced LGS before 11 years of age; their diagnoses were based on evidence of more than one type of generalized seizure (including drop seizures for at least 6 months) and slow spike-and-wave electroencephalograms (< 2.5 Hz) and multifocal spikes. Patients had to have at least two weekly drop seizures over 4 weeks and use up to three AEDs at stable dosages for at least 30 days before screening. Finally, participants could not use benzodiazepines chronically for ≥ 30 days before screening.

Dropout rates for treatment groups potentially confounded these analyses. However, relative to placebo, the mean percentage reductions observed during the first 4 weeks of maintenance therapy persisted through the last 4 weeks for all treated patients. The mean percentage reductions in seizure frequency were higher during the first 4 weeks of maintenance therapy in all groups. Still, differences between treatment and placebo groups were statistically significant for all pairwise comparisons except for the group receiving 0.25 mg/kg/d of clobazam from week 12 to week 15.

Use with other AEDs. Renfroe and colleagues[19] studied the safety and efficacy of clobazam used in conjunction with lamotrigine or valproate and the potential for drug-drug interactions among these three AEDs. Participants were screened according to the same standards used by Ng et al.[18] The mean and median percentage weekly reductions in average drop and total seizure rates from baseline to the 12-week maintenance phase were calculated for 72 patients receiving clobazam plus lamotrigine and 113 patients receiving clobazam plus valproate.

When compared with the placebo group, patients receiving all doses of clobazam plus concomitant lamotrigine had a greater mean percentage decrease in the average weekly rate of drop seizures, as did all groups receiving concomitant valproate. The percentage decrease in total seizures was similar for clobazam plus lamotrigine and clobazam plus valproate. The percentages of patients experiencing a ≥ 50%, ≥ 75%, and 100% decrease in the average weekly frequency of drop seizures generally increased with increasing clobazam dose. No dosage adjustment of lamotrigine or valproate appeared to be needed during combination therapy.

Patients given clobazam plus lamotrigine or valproate showed a general pattern of adverse events similar to that of the overall population. Two patients treated concomitantly with 0.25 mg/kg/d of clobazam and lamotrigine experienced an unspecified adverse drug reaction or pneumonia, and one patient each receiving placebo with lamotrigine had a jaw fracture or lobar pneumonia. Among those treated concomitantly with 0.25 mg/kg/d of clobazam and valproate, pneumonia occurred in one patient, and cyanosis, thrombocytopenia, vomiting, and pneumonia were reported in two patients. A drug administration error was reported in five patients using 0.5 mg/kg/d of clobazam with valproate; bronchopneumonia, influenza, and lobar pneumonia occurred in two patients taking 1.0 mg/kg/d of clobazam with valproate; and

lobar pneumonia occurred in one patient given placebo with valproate.

EXTENDED-RELEASE TOPIRAMATE

Topiramate is an oral, twice-daily, broad-spectrum AED indicated for the treatment of primary generalized tonic-clonic seizures,[20] partial-onset seizures,[21–23] and seizures associated with LGS.[24,25] The drug also is indicated for prophylaxis of migraine headaches.[26] An extended-release formulation of topiramate that could be taken once daily presumably might increase patient adherence to topiramate therapy and might lead to more consistent plasma concentrations of the drug.[27–29] Two phase III trials currently under way are evaluating the clinical efficacy and safety of extended-release topiramate in patients with refractory partial-onset seizures (ClinicalTrials.gov NCT01191086 and NCT01142193).

Steady-State Profiles and Tolerability

Two open-label studies reported at the 2012 Annual Meeting of the AAN focused on the steady-state pharmacokinetics and tolerability of immediate- versus extended-release topiramate. Braun et al[30] and Lambrecht et al[31] used a two-way crossover design to evaluate 38 healthy volunteers randomized 1:1 to one of two treatment groups. In the *extended-release to immediate-release group,* subjects were started on 50 mg of extended-release topiramate once daily, followed by 50-mg increases in dosage every 4 days and then 200 mg once daily for 14 days. On day 15, they were switched without a washout period to 100 mg of immediate-release topiramate every 12 hours for 14 days. The dosage was then downtitrated to 50 mg of immediate-release topiramate every 12 hours for 4 days and subsequently to 25 mg every 12 hours for 4 days.

In the *immediate-release to extended-release group,* subjects were given 25 mg of immediate-release topiramate every 12 hours to start, followed by 50-mg/d increases every 4 days and then 100 mg every 12 hours for 14 days. They were then immediately switched to 200 mg of extended-release topiramate once daily and maintained on that dosage for 14 days before being downtitrated to 100 mg of extended-release topiramate once daily for 4 days, followed by 50 mg once daily for 4 days.

Steady-state pharmacokinetics. Administration of extended-release topiramate once daily for 14 days provided an area under the curve (AUC) equivalent to the steady-state AUC observed with immediate-release topiramate in both groups.[30] When compared with immediate-release topiramate, once-daily treatment with the extended-release formulation of topiramate resulted in a lower peak plasma concentration (C_{max}), a higher trough plasma concentration (C_{min}), and less fluctuation in steady-state values.

> A once-daily formulation of topiramate might increase patient adherence to therapy and lead to more consistent plasma drug concentrations.

Tolerability and maintenance of steady-state plasma concentrations. Lambrecht et al[31] evaluated tolerability and maintenance of steady-state plasma concentrations when subjects were switched between immediate- and extended-release forms of topiramate. Steady-state plasma levels were maintained if the slope estimates for C_{min} were not significantly different from zero. The tolerability of both dosage forms were evaluated via monitoring of adverse events, vital signs, and clinical laboratory findings.

No significant differences in steady-state plasma concentrations of topiramate were seen when subjects taking 200 mg/d in two divided doses switched from the immediate-release formulation to 200 mg once daily of the extended-release formulation. Further, there was no apparent difference in the frequency or type of treatment-related adverse effects during the 24 hours after subjects switched treatment, suggesting a minimal risk of developing an adverse event when patients change from one formulation to another. All adverse events occurring during treatment with either immediate-release or extended-release topiramate were mild.

Dose-Proportionality, Linearity, and Tolerability of Extended-Release Topiramate

Halvorsen et al[32] assessed the dose proportionality and tolerability of a single dose of extended-release topiramate. Thirty healthy fasting subjects were given 25, 50, 100, 200, or 400 mg of topiramate in random order. Blood sampling and tolerability assessments continued for 14 days after each dose during a 21-day washout period. The subjects were confined to the clinic for at least 10 hours before and 36 hours after treatment.

Exposure to extended-release topiramate was linear and proportional to the dose administered from 25 mg to 400 mg. The AUC and C_{max} of topiramate rose with higher doses of the extended-release formulation. The median time to C_{max} ranged from 16 to 23 hours. The mean elimination half-life ranged from 71 to 95 hours and decreased with ascending doses. Total topiramate exposure was proportional and linear over the entire dosing range. C_{max} was dose-proportional when double-dose increases at higher levels (100 mg vs 200 mg, 200 mg vs 400 mg) were compared, and it was linear over the entire dosing range. Treatment-related adverse events generally increased with incremental doses; these events all were mild to moderate.

LACOSAMIDE

Lacosamide has a novel mechanism of action: selective enhancement of slow inactivation of voltage-gated sodium channels.[33] The oral forms of this third-generation AED are indicated for adjunctive therapy in treating partial-onset seizures in patients at least 17 years of age; the parenteral form is indicated

as a short-term replacement when oral administration is not feasible.[34]

Safety and Efficacy

Parra-Gómez and colleagues[35] evaluated the safety and efficacy of adjunctive lacosamide in patients with refractory focal epilepsy in a multicenter, prospective, open-label, observational study. They recruited 105 patients with epilepsy who were not controlled on monotherapy. The patients were assessed at months 3, 6, and 12; endpoints were seizure freedom for 6 months, mean seizure reduction rate > 50%, and study withdrawal due to lack of efficacy or side effects.

Thus far, 50 patients have been assessed at 6 months. In all, 80% had formerly tried 2–10 other AEDs before adding lacosamide to their antiepileptic regimen. The investigators observed a significant reduction in accumulated seizure frequency each month, with the monthly median rate decreasing from 4.0 to 1.2 seizures ($P < 0.0001$). Altogether, 42% of patients responded to lacosamide, and 13 of these patients achieved remission for the last 3 months. Eight patients entered remission since starting lacosamide; patients using a sodium-channel blocker were as likely as those using non–sodium-channel blockers to achieve a good outcome.

Adverse effects occurred more frequently in patients taking lacosamide with sodium-channel blockers than among those using other AEDs with lacosamide. In all, 13 patients reported a transitory neurotoxic effect (most commonly dizziness and somnolence) that occurred mainly during lacosamide titration.

Lacosamide appeared to be an effective and well-tolerated adjunctive AED that may be used with both sodium-channel blockers and other AEDs. The tolerability of this drug is improved with slow dose escalation and eventual reduction of the AEDs used concomitantly.

Long-Term Therapy

Rosenfeld and others[36] studied the open-label use of lacosamide to treat adults with partial-onset seizures for up to 8 years. After completing a corresponding phase II/III double-blind trial of adjunctive lacosamide, the patients entered one of three open-label extension trials (ClinicalTrials.gov NCT00552305, NCT00522275, or NCT00515619).

In all, 1,054 patients initiated adjunctive therapy with lacosamide. At greater than 1, 3, and 5 years, 75%, 53%, and 18% of patients, respectively, were exposed to lacosamide; the decrease with time was due to premature drug discontinuations and study completion because lacosamide became commercially available. Main reasons for drug discontinuation were lack of efficacy (28%), consent withdrawal (12%), and treatment-emergent adverse effects (11%). Common adverse effects related to treatment were dizziness (37%), headache (19%), nasopharyngitis (16%) and diplopia (15%). Adverse effects leading to discontinuation in ≥ 0.5% of patients were dizziness (1.7%) and convulsion (0.9%).

For 1-, 3-, and 5-year completers, the median percent seizure reduction from baseline was 52%, 60%, and 65%, respectively; the ≥ 50% responder rate was 53%, 60%, and 65%; the ≥ 75% responder rate was 26%, 31%, and 41%; and the seizure-free rate was 3.0%, 2.5% and 1.6%. Treatment with lacosamide for up to 8 years generally was well tolerated and associated with reduced seizure frequency and maintained efficacy.

ESLICARBAZEPINE ACETATE

Eslicarbazepine acetate, a prodrug of eslicarbazepine, is a third-generation AED related to carbamazepine and oxcarbazepine.[37] It was granted approval in Europe as adjunctive therapy for partial-onset seizures in patients ≥ 18 years of age; the FDA has not yet approved the marketing of this novel prodrug for a voltage-gated sodium-channel blocker.

Efficacy and Time to Adverse Events

Separate analyses of data from two double-blind, placebo-controlled phase II studies[38,39] evaluated once-daily use of eslicarbazepine acetate given as adjunctive therapy to 790 patients with partial-onset seizures. Patients in the ITT population received at least one 400-, 800-, or 1,200-mg dose of eslicarbazepine acetate or placebo added to a regimen of one to three concomitant AEDs and underwent at least one post-dose seizure assessment.

Efficacy according to concomitant therapy. Versavel and colleagues[38] evaluated the efficacy of adjunctive eslicarbazepine acetate based on the AED used concomitantly. AEDs most commonly used were carbamazepine (58.7%), lamotrigine (23.5%), valproic acid (23.5%), and topiramate (16.7%).

Administration of 800 or 1,200 mg of eslicarbazepine acetate once daily significantly reduced seizure frequency when compared with placebo. No significant interactions between type of AED used and treatment effect were found. However, because patients may have been on more than one concomitant AED, the investigators could not assess the impact of particular drug combinations.

Time to adverse events. Sperling et al[39] performed an analysis to review the timing and incidence of adverse events during eslicarbazepine acetate therapy. The dose of the drug was titrated per protocol; no dose adjustments for any AED in response to treatment-emergent adverse reactions were permitted. The weekly incidence and time to onset of adverse events for patients completing the 14-week titration and maintenance periods were calculated. The studies were similar in overall design but had different titration schedules and starting doses.

During the first 2 weeks of therapy, the most common adverse events reported were dizziness, headache, somnolence, diplopia, and nausea. In each dosing group, some 30% of all adverse effects occurred during week 1, with the incidence declining during later weeks. After 4 weeks of therapy, the incidence of new adverse events appeared to be similar among patients receiving eslicarbazepine acetate and those given placebo.

Based on these results, eslicarbazepine acetate-related adverse events most likely would start when therapy began; over the ensuing weeks, the incidence of new adverse events was similar among the active treatment and placebo groups. However, this analysis was conducted post hoc without formal statistical testing, and adverse events were not evaluated by severity.

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Current Controversies in Epilepsy: Brain Injury and Cognitive Consequences

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Abstract The onset of seizures may follow head injury or may be a symptom related to any number of medical conditions. At a session held during the 2012 Annual Meeting of the American Academy of Neurology, experts discussed surgical interventions that may benefit patients who experience seizures, cognitive problems related to seizure activity, links between autism and epilepsy, and current knowledge concerning the occurrence of epilepsy following brain injury.

Epilepsy, one of the most common neurologic conditions, is associated with significant morbidity and mortality. It affects more than 70 million people around the world.[1] At a symposium held during the 2012 Annual Meeting of the American Academy of Neurology (AAN), experts reviewed current controversies regarding epilepsy, its comorbidities, and its treatment. Among topics covered were optimal therapeutic strategies for refractory epilepsy, the natural history of cognitive dysfunction in epilepsy, and associations between epilepsy and other disorders (eg, autism) or trauma (eg, concussions, head injuries). The session was chaired by David Labiner, MD, Head of the Department of Neurology and Director of the Arizona Comprehensive Epilepsy Program at the University of Arizona in Tucson.

SURGERY VS RADIOSURGERY: SEIZURE FREEDOM AND COGNITIVE COST

Based on a presentation by Samuel Wiebe, MD, MSc, FRCPC, Professor of Clinical Neurosciences; Head, Division of Neurology; and Director of Clinical Research, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Mesial temporal lobe epilepsy (MTLE), a syndrome that typically occurs during adolescence, is characterized by specific complex partial seizures referred to as "limbic seizures." Many affected patients have not received benefit from several medications, and their seizures are considered refractory, making this condition the most common of the drug-resistant, surgically treatable epilepsies. The most prevalent pathologic feature of MTLE is hippocampal sclerosis, which was described as early as the 1800s. Removal of atrophied hippocampi was first popularized in the 1950s. Since then, localized surgical resection has progressed as more information about the focal pathology of the hippocampus has been published.

Investigators also have reported important evidence about seizure-onset zones outside the hippocampus. At least 56% of MTLE seizures occur beyond this region (eg, the amygdala, parahippocampus, and entorhinal cortex).[2] MTLE is a network disorder. Optimal resective surgical strategies need to take into account that important network components may reside in the extrahippocampal medial temporal cortex in some patients.

Results of a randomized clinical trial[3] and guidelines published by the AAN[4] have established anterior temporal lobe resection (ATLR) as the effective procedure of choice for patients with drug-resistant MTLE. More recently, alternative techniques and approaches have been developed for more selective resection or ablation. Selective amygdalohippocampectomy (SAH) and radiosurgery have gained popularity among neurologists and neurosurgeons hoping to reduce the risk of cognitive decline but maintain the rates of seizure freedom. The relative outcomes of seizure freedom and rates of cognitive decline related to these three interventions are subjects of great interest.

Examining Cognitive Function

When measuring cognitive decline in patients who undergo temporal lobe resections/ablations, the different dimensions of memory function must be considered. The four main categories of memory that may be impaired are episodic, semantic, procedural, and working memory. The temporal lobe primarily is involved with semantic and episodic memory.[5] Because cognitive decline varies between patients, measures that reliably show changes in specific memory domains tests must be used, and studies that use gross measures with grouped outcome data must be discounted.[6]

In ATLR, outcomes are well established; about 70% of patients remain free

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of seizures after 1–5 years of follow-up, and about 60% remain seizure-free thereafter.[7] A recent meta-analysis examined cognitive function after ATLR.[8] The investigators found intelligence quotient (IQ) declines in 8%–16% of patients and gains in 13%–18% for combined left and right temporal lobectomy groups; they also noted verbal IQ gains in 11%–12% of patients and losses in 11%–18% of all temporal lobectomy patients.

However, another systematic review of long-term (> 5 years) outcomes found that the IQ of patients who underwent ATLR generally was unchanged in the long term.[9] Reliable declines in word-finding ability occurred in 39% of patients after dominant ATLR. In terms of quality of life (QOL), over one half of patients achieved freedom from seizures and had improved QOL whether or not they experienced significant memory loss. Seizure outcome seemed to be more important to these patients' QOL than was verbal memory loss.[10]

The results of numerous cohort studies have shown that SAH and ATLR produce similar rates of seizure freedom[11]; however, these findings have not been shown in randomized, controlled trials. Patients who undergo SAH have cognitive and memory declines similar to those of individuals who undergo ATLR. However, in a meta-analysis, the results of 15 of 21 studies (71%) suggested that cognitive outcome following SAH may be better than that noted after ATLR.[12]

Radiosurgery involves the firing of targeted radiation beams to a particular area, resulting in radionecrosis and functional ablation. Patients tend to achieve freedom from seizures if they are treated with an adequate radiation dose (> 20 Gy). Further, patients tend to experience delayed adverse effects due to the edema and necrosis that occur about 10–12 months after the exposure. Given the limited number of radiosurgery studies reported, cognitive outcomes after this procedure are not well known. However, some early evidence suggests that up to one third of patients who have undergone radiosurgery experience cognitive decline.[13]

No randomized clinical trials have compared ATLR, SAH, and radiosurgery in MTLE patients, and an optimal therapeutic strategy still is unclear. Similar freedom from seizures (~ 70%) has been noted following ATLR and SAH; radiosurgical results with certain radiation levels have been competitive. As noted above, indirect evidence has suggested that cognitive outcomes are better after SAH than following ATLR. Cognitive outcomes following radiosurgery have not been established.

COGNITIVE DYSFUNCTION AND ITS COURSE IN EPILEPSY: IS IT PROGRESSIVE?

Based on a presentation by Bruce P. Hermann, PhD, Professor of Neurology, and Director, Charles Matthews Neuropsychology Laboratory, University of Wisconsin School of Medicine and Public Health, Madison

The cognitive effects of epilepsy over a lifetime are well known, but the relative contributions of prior neurodevelopmental factors and exact trajectory later in life are still conjectural. Two fundamental questions have yet to be fully answered. First, what is the time course of changes in cognition in people with epilepsy over their lifetimes? Second, how do neurodevelopmental factors contribute to cognitive impairment?

The Course of Epilepsy

Many studies have examined long-term cognitive outcomes in patients with childhood-onset epilepsy. However, many of these studies have been cross-sectional and have had inherent problems with assessing disease progression. Far fewer studies have included appropriate test-retest protocols in the same cohort over time. In a survey of longitudinal cognitive outcomes in adults and children with epilepsy, Dodrill[14] showed evidence of a decline in cognitive function over time that was more obvious in children than in older patients. Dodrill also demonstrated that the decline affected multiple cognitive domains, although the data were presented in a singular group average.

The results of subsequent studies suggest the existence of patient subgroups with different courses of impairment (mildly impaired, memory impaired, and memory plus executive impairment).[15] These phenotypes could be predicted by clinical epilepsy factors that included seizure frequency and the use of multiple antiepileptic drugs.

Neurodevelopment and Cognitive Impairment

Patients who have more severe epilepsy have worse outcomes, such as lower intellectual ability and educational difficulties. Predictors of cognitive impairment such as polytherapy, seizure frequency, and age of onset have been fairly consistent across studies. But how do children get to this point? To detect clues, several studies included a baseline assessment at diagnosis and followed patients for a prolonged period to study potential influences of antecedent neurodevelopmental problems and the long-term effects of epilepsy in these patients. This research resulted in evidence demonstrating that these patients had significantly more academic problems prior to their first seizure.[16] Another study that had more detailed cognitive dimensions and included patients with different epilepsy syndromes showed patterns of cognitive dysfunction, even in patients with more "benign" syndromes such as benign childhood epilepsy with centrotemporal spikes (BECTS).[17]

Comorbidities observed before the onset of epilepsy include psychiatric manifestations such as major depression (45%), behavioral issues such as attention deficit hyperactivity disorder (ADHD), academic problems (16% vs 4% among control subjects), and cognitive difficulties. Use of quantitative MRI (qMRI) performed at the time of the diagnosis of epilepsy has provided emerging radiologic evidence of these potential influences.

Thus, differences in cognitive function and/or physiologic structures as found using qMRI provide important clues about epilepsy. In addition, evidence that antecedent neurodevelopmental factors contribute to these consequences also exists.[18]

Later Status and Trajectory

One case-control study of long-term outcomes in patients with adolescent-onset temporal lobe epilepsy (TLE) dem-

onstrated dysfunction in regions beyond this area of the brain. In addition, bilateral dysfunction has been noted in patients with unilateral TLE.[19]

Lin et al[20] showed radiologic evidence of cortical thinning in extratemporal and bilateral areas of patients with unilateral TLE. In one study, they divided a large cohort of TLE patients into three subgroups according to severity of cognitive decline to find an anatomic correlation. The investigators noted a trend toward increased cortical thinning over the groups.

But do the cognitive effects progress? Approximately 20%–25% of patients with TLE have progressive epilepsy or experience worsening of their symptoms with time. A 4-year prospective study of cognitive ability showed that TLE patients had a decreased test-retest improvement effect when compared with controls.[15] In particular, this subgroup had problems with confrontational naming, verbal memory, and psychomotor speed.

In summary, a substrate antecedent to the onset of epilepsy apparently contributes to cognitive decline. In addition, subsequent neurodevelopmental effects contribute to cognitive difficulties, and a chronicity of these effects has been documented in a patient subgroup.

EPILEPSY AND AUTISM

Based on a presentation by Deborah Hirtz, MD, FAAN, Program Director, Clinical Trials and Studies, Division of Extramural Research, National Institutes of Health/National Institute of Neurological Disorders and Stroke, Bethesda, Maryland

Autism was first described by Kanner[21] and Asperger[22] in the 1940s. Once considered a rare condition, autism previously was ascribed to schizophrenia and "poor mothering." We now know it is a common biologic disorder that is being increasingly recognized and is represented by a spectrum of phenotypes.

The latest data from the Centers for Disease Control and Prevention (2008) show that 1 in 88 children has an autism spectrum disorder (ASD).[23] Recently, the media have covered the rapid increase in the number of children with autism who have needed specialized medical and educational services.

The diagnosis of autistic disorder requires that patients meet the following *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition) criteria: qualitative impairment in (1) social interaction and (2) communication and (3) restricted repetitive and stereotyped patterns of behavior or activities.[24] Approximately four times more boys than girls are diagnosed with autism.

Asperger's disorder has been acknowledged to be a separate condition from autism in the *DSM-IV,* but there are few studies to support this delineation. Childhood disintegrative disorder is rare and associated with global regression. The typical age at diagnosis is about 2–3 years for autistic disorder and 5–6 years for Asperger's disorder.

Proposed changes for the new 5th edition of the *DSM* include a category known as ASD, which is based on only two criteria: (1) qualitative impairment in social interactions/communications and (2) repetitive behavior/fixated interests.

> Children who have seizures early in life, symptomatic seizures, or infantile spasms are at highest risk of autism.

At-risk groups for having autism include premature infants and children who have siblings with autism, genetic disorders, or epilepsy.

Coincidental Prevalences?

The reported rate of epilepsy among children with autism varies from 5% to 46%, with a higher incidence seen among individuals with an intellectual disability. In a meta-analysis of children with autism and epilepsy, the pooled prevalence was 21.4%.[25] Seizure onset peaks both at an early age (< 5 years) and during adolescence.

Many controversies surround the prevalence of autism among those with epilepsy. Children who have seizures early in life, symptomatic seizures, and infantile spasms are at highest risk of autism. When the true rate of autism in patients with epilepsy is assessed, however, referral bias is an important confounder. In a population-based study with prospective and long-term follow-up, 5% of individuals with epilepsy had "primary" autism.[26] Among those with epilepsy, autism is more common in patients with intellectual disability and in those diagnosed with epilepsy during the first year of life, possibly due to the high prevalence of West syndrome and infantile spasms and their association with ASD.[25] Overall, 14% of patients with infantile spasms have ASD.[27]

Dravet syndrome is a severe epileptic encephalopathy that initially appears during the first year of life and is associated with multiple seizure types and refractory cognitive decline. One cohort of 37 children with Dravet syndrome included 9 patients with autism.[28]

Landau-Kleffner syndrome (LKS), a rare but severe focal epilepsy, is characterized by a rapid decline in language function, which may result directly from seizures and is not a "primary" autism. However, developmental regression occurs in up to one third of patients with autism, usually about 18–24 months after its onset.[29]

Neurologic Testing and Autism

Epileptiform activity in the absence of seizures has been reported. However, no population-based studies using electroencephalography (EEG) have been done in patients with autism.[30] In one study, about 60% of patients had epileptiform discharges during sleep.[31] No guidelines currently recommend routine EEG testing in patients with autism.[32]

Genetics

Numerous genes have been linked to autism and epilepsy. It is possible that commonly affected developmental pathways in synaptic plasticity are related to common genetic variation. Certain genetic defects could result in molecular derangements in ion channels and subsequently enhance neuronal excitation and inhibition. These same genetic defects

could contribute to both EEG changes and autism.

One of the most important known genetic syndromes associated with autism and epilepsy is tuberous sclerosis. It involves increased activity of the mTOR (mammalian target of rapamycin) gene, which is used as a mouse model for both autism and epilepsy. Mutations in sodium-channel genes occur in both autism and epilepsy. *Cntnap2*-deficient mice exhibit both autistic behavior and epileptic seizures.[33]

Treatment

No available pharmacologic interventions target both ASD and epilepsy. Further, there is no evidence that treating interictal spikes ameliorates the social or behavioral aspects of ASD. Likewise, there is no clear evidence that the use of antiepileptic drugs provides any benefit on mood and behavior.[29]

Thus, epilepsy and autism are both neural network disorders. Both of these conditions could be secondary to genetic defects that disrupt normal neuronal networks. Seizures or abnormal electrical activity may impact the developmental trajectory. However, there is no clear evidence that autism is caused by epilepsy.

CONCUSSION AND OTHER MINOR HEAD INJURIES: DO THEY CAUSE EPILEPSY?

Based on a presentation by Georg A. Hishaw, MD, Assistant Professor of Neurology, University of Arizona Health Sciences Center, Tucson

Mild traumatic brain injury (TBI) or concussions are common, resulting in about 500,000 emergency room visits yearly. However, this statistic likely underestimates the number of patients who experience a mild TBI every year. The majority of TBIs occur during motor vehicle accidents and falls, with sports injuries representing only 10% of the total. But is there a link between TBI and epilepsy? What EEG changes are associated with risk of post-traumatic seizures? What do post-traumatic seizures look like? And what other behaviors in the setting of TBI can be mistaken for seizures?

In one study, the incidence ratio (IR) of seizures among more than 4,000 patients who experienced trauma was 1.5 after a mild TBI, 2.9 after a moderate TBI, and 17.0 after a severe TBI.[34] A similar study at the Southern Arizona Veterans Administration registry showed a seizure IR of 3, 5, and 32 for mild, moderate, and severe TBI, respectively. The more severe the injury, the more likely the patient was to have post-traumatic seizures.

Etiology of Seizures Following Injury

Two main types of injury are related to seizure occurrence: direct trauma, which causes contusions, hemorrhage, and lacerations; and diffuse axonal injury (DAI), which involves the deep white matter.[35] In the above studies, seizures were more common among patients with penetrating injuries or skull fractures, which may have been due to the direct irritation of the cortical gray matter, where seizures usually originate.

Certain EEG findings seen early after TBI may not be associated with epilepsy. In animal models, immediate EEG changes include high-amplitude spikes and sharp waves, followed by suppression of background impulses. However, these changes do not necessarily correlate with seizure activity. In human studies, little evidence of EEG changes after TBI has been noted. One study of boxers reported evidence of reduced EEG amplitude and irregular theta activity within about 15–30 minutes of a fight. In another study of patients who had sustained a TBI, generalized slowing was found in 43%, and focal slowing was noted in 32%.[36] These patterns resolved after an average of 3 months. Generalized slowing takes longer to resolve than does focal slowing, which indicates the presence of a structural lesion; it commonly is seen among individuals with penetrating injuries and also may result from secondary diffuse axonal injury.

After trauma, the most common type of seizure seen is complex partial seizures. These occurrences commonly are preceded by an aura and have a wide variety of presentations, which depend on the origin of the seizure. However, several other disorders associated with episodic symptoms can mimic complex partial seizures. Affected patients often suffer stress and psychological damage from the injury, and they may experience dissociative events. In addition, they may have post-traumatic stress disorder (PTSD) along with paroxysmal nightmares, flashbacks, and panic attacks which could be mistaken for seizure activity. In addition, PTSD or acute stress may result in development of a conversion disorder or nonepileptic seizures/spells.[37] Furthermore, complicated migraine headaches that may or may not result from an injury can have focal neurologic signs and symptoms, including focal weakness and sensory and autonomic manifestations that may resemble seizures.[38]

Thus, the risk of epilepsy or post-traumatic seizures is higher following severe head injuries than after mild TBI or concussions. The likelihood that seizures will also occur depends upon the type of injury sustained. Complex partial seizures occur most commonly following significant TBI; this phenomenon has diverse presentations. Finally, many conditions can mimic post-traumatic seizures.

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Potential New Measures to Manage Partial-Onset Seizures

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Abstract Despite the availability of numerous antiepileptic drugs (AEDs) on the market, the quest to achieve seizure freedom in patients with epilepsy remains frustrating for many physicians. Clinical investigators recently discussed findings of two AEDs that may show particular promise in treating this patient population. In the first study described, investigators compared once-daily zonisamide monotherapy with twice-daily carbamazepine monotherapy in newly diagnosed patients with partial-onset epilepsy. In the second study, researchers analyzed the results of three clinical trials evaluating perampanel in patients with partial-onset seizures to assess the usefulness of time-to-event analysis, a proposed outcome measure that may speed the return of results and reduce patient exposure to a less effective drug.

Epilepsy affects nearly 3 million Americans and ranks third after Alzheimer's disease and stroke as the most common neurologic condition in the United States.[1] The treatment of epilepsy remains challenging. Almost 20 drugs are available for its treatment, yet most of these agents are indicated for add-on, or adjunctive, therapy of partial-onset seizures. Despite the variety of medications available, approximately one third of patients will not respond to antiepileptic therapy.[2] Thus, there is a continued need to develop new antiepileptic drugs (AEDs) and to expand the indications of existing medications, if possible.

During the 64th American Academy of Neurology (AAN) annual meeting in New Orleans, experts in epilepsy management discussed recent studies on novel and traditional AEDs and new measures of efficacy that may improve patient management.

ZONISAMIDE VS CARBAMAZEPINE FOR NEWLY DIAGNOSED PARTIAL SEIZURES

Zonisamide, a benzisoxazole derivative that is chemically unrelated to other AEDs, has multiple mechanisms of action, including inhibition of sodium channels and reduction of T-type calcium currents. Zonisamide has a prolonged half-life (about 63 hours), which enables it to be given once a day. Carbamazepine is an older-generation anticonvulsant that acts on voltage-gated sodium channels to reduce neuronal excitability. In the United States zonisamide is currently indicated only as adjunctive therapy for the treatment of partial-onset seizures in adults with epilepsy.

Baulac and colleagues[3] reported on the results of a phase III, randomized, double-blind, noninferiority trial that compared zonisamide monotherapy with carbamazepine monotherapy in previously untreated adults with newly diagnosed partial-onset epilepsy. This international, multicenter trial involved sites in Europe, Asia, and Australia.

Patients and Methods

A total of 583 patients were randomly assigned to receive either zonisamide once daily or controlled-release carbamazepine twice daily. Adults 18–75 years of age were eligible to participate. Patients in both treatment groups were equivalent in types of seizures experienced, with most having complex partial-onset seizures with secondary generalization. The frequency of seizures was similar between the two groups. The majority of patients (> 65%) had cryptogenic seizures.

Zonisamide was started at 100 mg/d once daily and then uptitrated to a target dose of 300 mg/d over 4 weeks. Carbamazepine was started at 200 mg/d twice daily and then increased to 600 mg/d over this same period. Patients then entered a flexible dosing period lasting 26–78 weeks. Doses were increased if seizures occurred and decreased if side effects were reported. The permissible dosing range was 200–500 mg/d of zonisamide and 400–1,200 mg/d of carbamazepine.

After the patients were seizure-free for 26 weeks, they entered a 26-week maintenance phase, which was followed by a transition to either a double-blind extension study or weaning from medication. Criteria for removal from the study included a need for a medication dose that was outside the proscribed range or the occurrence of seizures during the maintenance phase.

Results

In all, 161 of 282 patients (57.1%) given zonisamide and 192 of 301 patients (63.8%) given carbamazepine completed the trial. The primary efficacy endpoint of the study was seizure freedom for at

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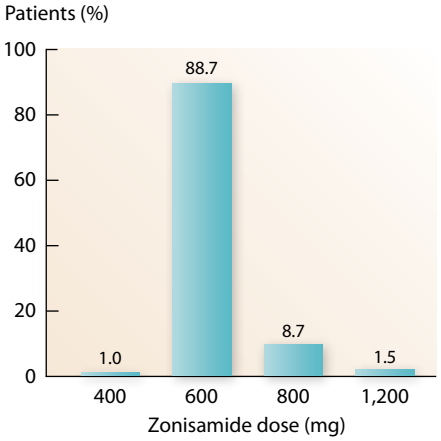

FIGURE 1 Zonisamide dose at which 26-week seizure freedom was achieved. Adapted, with permission, from Baulac et al.[3]

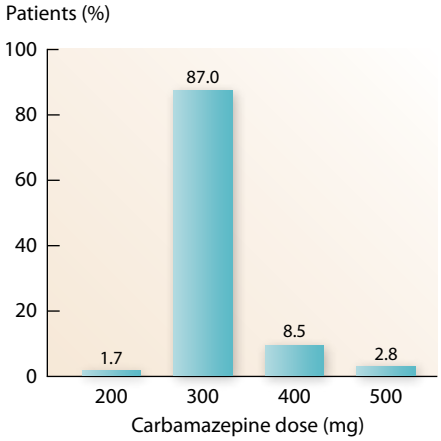

FIGURE 2 Carbamazepine dose at which 26-week seizure freedom was achieved. Adapted, with permission, from Baulac et al.[3]

least 26 weeks. This endpoint was met by 177 of 223 patients in the zonisamide group (79.4%) and 195 of 233 patients in the carbamazepine group (83.7%). The adjusted absolute treatment difference was –4.5% (95% confidence interval [CI], –12.2 to –3.1); the lower limit of the CI just exceeded the prespecified margin of noninferiority. However, the lower limit of the CI of relative difference (–14.7%) was within the relative –20% margin required by the International League Against Epilepsy (ILAE) guidelines.[4]

The 52-week seizure-freedom rate was 67.6% for the zonisamide group and 74.7% for the carbamazepine group. The vast majority of patients who achieved seizure freedom at 26 weeks in both groups did so at the initial target dose (Figures 1 and 2).

The frequency of treated-associated adverse events was in between the two groups. The overall incidence of adverse events was 60.5% for patients given zonisamide and 61.7% for those using carbamazepine; most of these reactions were mild to moderate. Headache was the most common adverse event in both groups. Weight loss and decreased appetite were more common in patients using zonisamide. Dizziness was more common with carbamazepine therapy. The incidence of adverse events leading to discontinuation of therapy was similar in the two groups. Discontinuation due to fatigue was more common in the zonisamide group, whereas the carbamazepine group was more likely to cease therapy because of rash. No laboratory abnormalities, including decreased bicarbonate serum levels, or electrocardiographic anomalies were observed.

The authors concluded that zonisamide or carbamazepine monotherapy leads to high seizure-freedom rates at 26 weeks in patients with new-onset partial-onset seizures. The lower confidence limit of absolute difference between treatments just exceeded the predetermined margin for noninferiority, and the relative difference between the two treatment groups did not exceed the margin required by the ILAE. Most patients achieved seizure freedom at the lowest target dose. Both drugs were well tolerated, and no troubling safety issues were noted.

Comments

Although this study shows that single-agent use of zonisamide or carbamazepine is essentially equivalent in controlling partial-onset seizures in newly diagnosed patients, other factors need to be considered before starting a specific anticonvulsant.[2]

Compliance with a given medication regimen decreases with increased frequency of dosing.[5–8] Thus, the ability to give zonisamide on a once-daily basis likely will allow for greater compliance in the long term when compared with the need for twice-daily carbamazepine dosing.

Caution must be taken when using carbamazepine in certain generalized epilepsy syndromes. Use of this drug has been reported to exacerbate absence seizures in children.[9] Zonisamide, in contrast, has shown promise in treating idiopathic generalized epilepsy and epilepsy syndromes in pediatric patients[10,11]; however, it is currently approved in the United States only for the adjunctive treatment of partial seizures in adults.

Carbamazepine is a known inducer of cytochrome P450 (CYP450); thus, caution must be used when prescribing a significant number of medications, including oral contraceptives, concomitantly with this drug. Zonisamide, on the other hand, does not interact with CYP450, making its use more attractive, particularly in patients who need to be transitioned from monotherapy.

The choice of anticonvulsants for use in women of childbearing age is challenging. The use of carbamazepine during pregnancy has been associated with neural tube defects.[12] Zonisamide treatment has not been clearly associated with birth defects, but limited data have been collected to date.[13] All women with epilepsy who are on AEDs should receive supplementation with 0.4 mg/d of folic acid.[14]

PERAMPANEL AND TIME TO SEIZURE RECURRENCE

Perampanel is a selective, noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonist. AMPA plays a key role in seizure generation in animal models of epilepsy.[15] Perampanel is the first glutamatergic antagonist to demonstrate clinical efficacy with an acceptable side-effect profile.

A recently published phase III trial showed a dose-dependent decrease in seizure frequency among patients with refractory partial-onset seizures who were treated adjunctively with perampanel.[16] The median percent change from baseline in seizure frequency for patients given 2, 4, or 8 mg/d of perampanel or placebo was –13.6%, –23.3%, –30.8%, and –10.7%, respectively. The difference from placebo was statistically significant for patients

who received 4 mg/d (P = 0.0132) or 8 mg/d (P = 0.0003) of the drug.

In three multicenter, randomized, double-blind, placebo-controlled trials (studies 304, 305, and 306), perampanel demonstrated efficacy when given at doses of 4–12 mg/d.[17] Fifty-percent responder rates were 22.4%, 30.8%, 37.6%, and 39.5% with perampanel doses of 2, 4, 8, and 12 mg/d, respectively, and 18.4% with placebo; further, 75% responder rates were 10.6%, 12.6%, 18.8%, 20.2%, and 5.7%, respectively. Proportions of patients achieving seizure freedom during the trial were 1.9%, 5.0%, 3.8%, and 4.4% with perampanel doses of 2, 4, 8, and 12 mg/d and 1.1% with placebo. Side effects reported with perampanel use have been mild to moderate, with headache, somnolence, and dizziness the most commonly seen in a pair of phase II trials[18]; dizziness was the most frequent adverse event noted in the aforementioned phase III trial.[16]

> Time-to-event analysis may be useful for gathering results more quickly and reducing patient exposure to a poorly effective drug.

Details of these three randomized controlled clinical trials are discussed by Jeffrey D. Kennedy, MD, on page 26 of this issue of *The Neurology Report*.

Different outcome measures used in clinical trials of AEDs include the percentage of patients who are seizure free with treatment and the percentage of patients experiencing a 50% reduction in seizures. A new parameter, time-to-event analysis, may be useful for gathering results more quickly and reducing patient exposure to a poorly effective drug. Laurenza and coworkers[19] pooled the results of the three previously discussed phase III perampanel trials to evaluate time-to-event endpoints (median time to 1st, 3rd, 6th, 9th, and 12th seizure). An individualized time to event was also determined, representing the median time for patients to reach their individual baseline seizure rate (N^{th} seizure).

Methods

The prior clinical trials recruited patients at least 12 years of age who experienced treatment-resistant partial-onset seizures despite treatment with one to three AEDs. The trial was conducted in three phases: a 6-week prerandomization (baseline) phase, a double-blind phase with a 6-week titration period (2 mg/d to start, followed by a 2-mg dose escalation every week), and then a 13-week maintenance period in which 2, 4, 8, or 12 mg of perampanel or placebo was given. Dose reductions were permitted for intolerability.

Time to 1st, 3rd, 6th, 9th, and 12th seizure events were prespecified exploratory endpoints in the phase III trials; the median time to N^{th} seizure, defined as the rounded number of seizures per 28 days at baseline for each patient, was an ad hoc analysis.

Results

A total of 1,318 patients were included in the pooled intention-to-treat analysis, with 180 patients given 2 mg/d of perampanel, 172 patients given 4 mg/d, 372 patients given 8 mg/d, 201 patients given 12 mg/d, and 393 patients given placebo. The median baseline seizure frequency in these patients (10.0–13.7 seizures over a 28-day period) was comparable across treatment groups (Table 1). The average number of AEDs used at baseline was 2.3 per patient.

Placebo-treated patients reached their individual N^{th} seizure at approximately 30 days. Perampanel-treated patients given 4, 8, and 12 mg/d consistently took longer to reach their N^{th} seizure when compared with the placebo group (Table 2). The group given 12 mg/d did not differ from patients given 8 mg/d, probably because these patients reached their N^{th} seizure before reaching the 10- or 12-mg/d dose levels at weeks 5 and 6 of the titration phase.

Pooled data from the three studies for time to event (1st through 12th seizure) favored the 2-mg/d perampanel dose. This was surprising, given the lack of efficacy of this dose in analyses of primary and secondary outcome measures.

This post hoc analysis was challenging given the high median baseline seizure frequency. Early seizure events (such as 1st through 12th seizure) tend to occur early, before patients have sufficient exposure to necessary drug doses. In this study, the 1st through 12th seizure events occurred too early for patients to have reached a therapeutic dose.

Using an individualized baseline seizure rate (ie, time to N^{th} seizure) led to more consistent results, with perampanel-treated subjects taking longer to reach that point than did patients given placebo. This phenomenon was not seen at higher doses of the drug, because the N^{th} seizure occurred before that dose was reached during the scheduled titration.

Comments

Before licensing approval is granted, new AEDs must provide superior efficacy when compared with placebo in double-blind, randomized, controlled trials.[2] In regulatory studies in Europe, a ≥ 50% reduction in seizure frequency as compared with placebo is required. Median reduction in seizure frequency is the primary endpoint of concern in the United States.

This study demonstrated that time to event (preselected 1st through 12th seizure) was not useful as an outcome measure.

TABLE 1

Baseline Seizure Frequency During 28 Days of Adjunctive Perampanel Therapy[a]

		Perampanel dose			
	Placebo (n = 393)	2 mg/d (n = 180)	4 mg/d (n = 172)	8 mg/d (n = 372)	12 mg/d (n = 201)
Median frequency (min, max)	10.2 (3.3, 569.1)	10.1 (3.2, 429.6)	10.0 (2.9, 4,503.9)	12.0 (2.4, 1,030.8)	13.7 (1.4, 1,083.1)

[a] Pooled intention-to-treat dataset, excluding patients from Central and South American regions

Source: Laurenza et al[19]

TABLE 2
Kaplan-Meier Analysis of Time to N^{th} Seizure Event in Three Phase III Studies of Perampanel[a]

Time to seizure event, median days (95% CI)	Study 304			Study 305			Study 306			
		Perampanel dose			Perampanel dose			Perampanel dose		
	Placebo (n = 121)	8 mg/d (n = 133)	12 mg/d (n = 133)	Placebo (n = 136)	8 mg/d (n = 129)	12 mg/d (n = 121)	Placebo (n = 184)	2 mg/d (n = 180)	4 mg/d (n = 172)	8 mg/d (n = 16)
Time to baseline seizure frequency per 28 days (N^{th} seizure)	32.0 (29.0, 37.0)	36.0[b] (30.0, 43.0)	36.0[b] (31.0, 42.0)	28.0 (26.0, 32.0)	36.0[c] (31.0, 43.0)	33.0[b] (31.0, 40.0)	30.0 (27.0, 33.0)	32.0 (28.0, 33.0)	33.0[d] (29.0, 37.0)	36.0[c] (33.0, 42.0)
Time to 1st seizure	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	3.0[d] (2.0, 4.0)	2.0 (2.0, 3.0)
Time to 3rd seizure	6.0 (5.0, 8.0)	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	6.0 (4.0, 8.0)	6.0[b] (5.0, 10.0)	6.0 (4.0, 7.0)	8.0 (6.0, 10.0)	9.5 (7.0, 11.0)	8.0 (7.0, 11.0)	8.0 (6.0, 10.0)
Time to 6th seizure	14.0 (11.0, 18.0)	16.0[d] (11.0, 22.0)	14.0 (10.0, 18.0)	13.0 (9.0, 15.0)	15.0[d] (11.0, 20.0)	12.0 (10.0, 16.0)	16.0 (13.0, 20.0)	19.0 (16.0, 22.0)	18.0 (14.0, 21.0)	17.0 (12.0, 21.0)
Time to 9th seizure	21.0 (15.0, 26.0)	27.0[d] (18.0, 34.0)	22.0[d] (16.0, 30.0)	18.0 (13.0, 26.0)	22.0[d] (16.0, 33.0)	18.0 (15.0, 24.0)	26.0 (19.0, 32.0)	31.0 (23.0, 34.0)	28.0 (20.0, 33.0)	28.0 (20.0, 33.0)
Time to 12th seizure	27.0 (20.0, 33.0)	35.0[d] (24.0, 46.0)	31.0[d] (24.0, 40.0)	27.0 (18.0, 33.0)	31.0[d] (21.0, 45.0)	28.0 (16.0, 39.0)	34.0 (26.0, 41.0)	37.0 (31.0, 47.0)	38.0 (27.0, 46.0)	41.0 (30.0, 46.0)

[a] Intention-to-treat dataset; [b] $P < 0.01$ vs placebo; [c] $P < 0.001$ vs placebo; [c] $P < 0.05$ vs placebo
Source: Laurenza et al[19]

The frequency of seizures at baseline was too variable. However, the time to N^{th} seizure (individualized baseline) appeared to be a useful statistic to include as an outcome measure in future studies.

Perampanel shows promise as a novel anticonvulsant. This drug is the first AED to selectively and effectively inhibit a glutamatergic ion channel implicated in epilepsy and to have a favorable tolerability profile. The drug is currently under review by the US Food and Drug Administration.

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Promising New Directions in Epilepsy Management

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Abstract Although the majority of patients derive benefit from antiepileptic therapy, nearly one third of patients continue to experience seizures. At a session held during the 2012 Annual Meeting of the American Academy of Neurology, experts in the treatment of epilepsy discussed advances in the medical and surgical management of this often difficult-to-control condition. Among subjects covered were novel antiepileptic drugs, methods of predicting toxicity and following patient progress, and techniques to identify and study unusual brain activity.

Despite the availability of more than 20 antiepileptic drugs (AEDs) approved by the US Food and Drug Administration (FDA), nearly one third of patients with epilepsy have refractory seizures, and many more experience various adverse effects. Potentially curative epilepsy surgery has been available for decades to selected refractory epilepsy patients, yet many affected individuals continue to have seizures after surgery, and some experience new cognitive dysfunction postoperatively. Clearly, improved medical and surgical treatments for patients with epilepsy are needed.

At a session held during the 2012 Annual Meeting of the American Academy of Neurology, four experts discussed emerging techniques in epilepsy management, including recent marketing approval for novel AEDs, advances in monitoring, and use of magnetic resonance imaging (MRI) for patient assessment. The session was chaired by William H. Theodore, MD, FAAN, Chief of the Epilepsy Section at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

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MEDICAL THERAPY: CLINICALLY RELEVANT ADVANCES IN BASIC SCIENCE

Based on a presentation by Jaideep Kapur, MD, PhD, Professor and Vice Chair, Department of Neurology, University of Virginia School of Medicine, Charlottesville

Ezogabine

Recently approved by the FDA for adjunctive therapy of partial seizures, ezogabine (also known as retigabine) has a truly novel mechanism of action that is different from that of all previously approved AEDs. Ezogabine acts on voltage-gated potassium channels and promotes channel opening, which results in hyperpolarization of neurons due to potassium ion movement out of the cell. The drug promotes potassium-channel opening in various ways, including prolonging the duration of opening and shifting voltage dependence for activation, leading to more rapid and increased levels of channel opening.[1]

Ezogabine acts on potassium channels encoded by the gene *KCNQ2-5*; these channels primarily are found in the central nervous system at the axon initial segment of neurons. The drug does not affect cardiac KCNQ1 channels, which lack a key amino acid residue for ezogabine binding.[1]

Clobazam

Clobazam, another drug recently approved by the FDA to treat epilepsy, is indicated for the adjunctive treatment of Lennox-Gastaut syndrome. Although clobazam is a benzodiazepine, its structure differs from that of traditional drugs of this class. It features nitrogen atoms at the 1 and 5 positions of the benzodiazepine ring rather than at the 1 and 4 positions, as seen in traditional benzodiazepines.[2] The anticonvulsant action of clobazam is mediated by γ-aminobutyric acid type A ($GABA_A$) receptors, which are pentamers composed of subunits from 16 different gene families.[2] Specifically, each $GABA_A$ receptor is composed of two α, two β, and one γ, σ, or ε subunit. The presence of a γ_2 subunit is required for receptor sensitivity to benzodiazepines, and the sensitivity to individual benzodiazepines depends upon an α subunit type.[2] The specificity of the α subunit of clobazam is not yet fully established, but it is being studied actively.

Intramuscular Midazolam for Convulsive Status Epilepticus

The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), a double-blind trial of intramuscular (IM) midazolam versus intravenous (IV) lorazepam, recently demonstrated the noninferiority of midazolam.[3] Although the trial was designed to test noninferiority rather than superiority in patients experiencing seizures, 73.0% of the IM midazolam group and 63.4% of the IV lorazepam group ($P < 0.001$ for superiority) did not have seizures upon arriving at the emergency department.

Midazolam is a benzodiazepine with a unique feature: In addition to binding to $GABA_A$ receptors and enhancing their actions, it also binds to the peripheral benzodiazepine receptor, a translocator protein on the mitochondrial membrane.[4] This translocator protein binds to cholesterol, then transports it into mitochondria, where it is converted into neurosteroids.[4] These neurosteroids enhance GABA activity on benzodiazepine-insensitive $GABA_A$ receptors.[4] Thus, midazolam enhances the action of both benzodiazepine-sensitive and benzodiazepine-insensitive $GABA_A$ receptors via direct and indirect mechanisms.

Perampanel

A promising drug in development, perampanel has a unique anticonvulsant mechanism of action, and it may have antiepileptogenic properties. Perampanel blocks α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type ionotropic glutamate receptors, thereby preventing passage of sodium or calcium ions through the receptor when glutamate binds. This action reduces excitatory postsynaptic potentials.[5] In a rat model, AMPA-receptor blockade attenuated posthypoxia susceptibility to neuronal damage independent from the anticonvulsant action, suggesting a possible neuroprotective effect.[6]

Targeting Epileptogenesis

Although all of the current FDA-approved AEDs are able to control seizures, none has truly antiepileptogenic properties. An antiepileptogenic agent ideally would work either to prevent the occurrence of seizures after an epileptogenic event (eg, a high-risk head injury) or potentially even reverse existing cellular or network pathology that contributes to seizures. Possible targets for antiepileptogenic therapy include known mediators of epileptogenesis that are under active investigation (Table 1).[7–9]

Before true antiepileptogenic therapy can become a reality, further research is needed to better understand these pathways and to test possible treatments in animal models.

TABLE 1
Mediators of Epileptogenesis

- Calcium entry into neurons via NMDA receptors, AMPA receptors, and other mechanisms
- Tyrosine kinase B activation and brain-derived neurotrophic factor release
- Mammalian target of rapamycin (mTOR) signaling
- Activation of cyclic AMP/CREB/inducible cyclic AMP repressor pathway
- Inflammatory response via IL-β, TNF-α
- Neuron restrictive silencer factor

NMDA = N-methyl-D-aspartic acid; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMP = adenosine monophosphate; CREB = cyclic AMP response element-binding; IL-β = interleukin-beta; TNF-α = tumor necrosis factor-alpha

TABLE 2
Biologic Sources of Variability in AED Efficacy and Adverse Effects

DNA
- Single nucleotide polymorphisms
- Copy-number variants
- Cytogenetic rearrangements
- DNA modifications (eg, methylation)
- Insertions/deletions

RNA
- Expression levels
- MicroRNA levels
- Processing (eg, splicing and editing)

Proteins

Metabolites

AED = antiepileptic drug; DNA = deoxyribonucleic acid; RNA = ribonucleic acid

AEDs: PHARMACOGENETICS AND PHARMACOGENOMICS

Based on a presentation by Tracy Glauser, MD, Professor of Pediatrics and Neurology; Director, Comprehensive Epilepsy Center; and Co-Director, Genetic Pharmacology Service, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Drug toxicity is a major problem for hospitalized patients in the United States, accounting for approximately 100,000 deaths in 1994.[10] Various biologic and environmental factors contribute to the interindividual variability in drug efficacy and adverse effects, including among AEDs. The sources of this biologic variability are multiple, ranging from DNA to metabolites (Table 2).

Pharmacogenetics is the study of the effect of patients' DNA variations on their clinical response to a drug, and pharmacogenomics is the systematic study of drug effects on the entire genome. Pharmacogenomics has the potential to significantly reduce severe adverse drug reactions: 59% of the 27 medications with the highest frequency of adverse reactions are metabolized by enzymes with a variant allele known to cause poor metabolism.[11] This group of medications includes two commonly prescribed AEDs: phenytoin and carbamazepine.[11]

A classification system for known pharmacogenetic associations has been defined by the FDA using the concept of biomarkers.[12] This classification includes one known valid biomarker and a few probable valid biomarkers for AED efficacy or adverse effects (Table 3). As the only known valid biomarker for AEDs, human leukocyte antigen (HLA)-B*1502 is associated with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) among populations in China, Thailand, and Malaysia but not Europe or Japan.[13,14] The HLA-B*1502 allele is associated with a highly significant odds ratio of 84.75 for SJS/TEN.[13] There is additional evidence of an association between other aromatic anticonvulsants (namely, phenytoin, oxcarbazepine, and lamotrigine) and severe cutaneous reactions.[15]

Among the probable valid AED biomarkers is another HLA allele that also is associated with carbamazepine toxicity. The presence of the HLA-A*3101 allele increased the risk of carbamazepine-induced hypersensitivity reactions from 5% to 26% among subjects with Northern European ancestry.[16] This allele is found in 2%–5% of Northern Europeans; if further studies validate the association, routine clinical testing of selected patients may be indicated in the future, as it is for HLA-B*1502.

Other probable valid biomarkers include transporters, drug-metabolizing enzymes, and ion channels. In 2003, an association was found between a polymorphism of the ABCB1 drug-efflux transporter protein and resistance to AED treatment.[17] However, findings from

TABLE 3
AED Pharmacogenetic Biomarkers

Known valid AED biomarkers
- HLA-B*1502

Probable valid AED biomarkers
- Transporters: ABCB1
- Drug-metabolizing enzymes: CYP2C9 and CYP2C19
- Ion channels: SCN2A
- HLA-A*3101

AED = antiepileptic drug; HLA = human leukocyte antigen

subsequent studies have been mixed; a meta-analysis of 11 case-control studies found no significant association.[18]

A single-dose study of the pharmacokinetics of phenytoin among healthy Turkish volunteers showed that mutant alleles of *CYP2C9* were a major determinant of phenytoin plasma levels.[19] This same study found a smaller, but significant, effect of the *ABCB1* transporter polymorphism on phenytoin levels.

A different study among Japanese participants found that particular mutations of *CYP2C9* were associated with high plasma levels of phenytoin, even at low daily doses of the medication.[20] This Japanese study also found a smaller effect of mutations in *CYP2C19*, with significantly higher plasma phenytoin levels seen at higher daily doses.

AED efficacy was associated with another type of probable valid biomarker, namely, voltage-gated sodium channels. Among Chinese epilepsy patients, there was an association between an allele of *SCN2A* and AED resistance.[21]

NEW ELECTROPHYSIOLOGIC TECHNIQUES

Based on a presentation by Brian Litt, MD, Associate Professor of Neurology and Bioengineering, University of Pennsylvania, Philadelphia

Resection currently is the most efficacious treatment for some individuals with refractory partial seizures, but a number of patients may still experience recurrent seizures after surgery. In clinical practice, surgical techniques for epilepsy (including the placement of intracranial electrodes for phase II monitoring) have remained relatively static for a number of years. However, recent novel techniques in intracranial recording have revealed possible new electrophysiologic features of the epileptogenic zone, and novel flexible microelectrode arrays may allow monitoring of previously unreachable cortical areas with unprecedented detail.

High-Frequency Oscillations

Neuronal oscillations span a wide range of frequencies, extending beyond the recording range of traditional electroencephalography.[22] Studies have suggested that high-frequency oscillations (HFOs) in the ripple (80–250 Hz) and fast ripple (250–1,000 Hz) range may be involved in the generation of seizures, but most of these studies were done with microwire electrodes rather than traditional clinical intracranial electrodes.[22]

Worrell et al[22] obtained simultaneous microwire electrode and traditional macroelectrode recordings from custom mesial temporal depth electrodes and compared characteristics of HFOs recorded from each type of electrode. Ripples and fast ripples were recorded from both types of electrodes, and increases in HFOs were noted in seizure-generating brain regions relative to control regions. The clinical macroelectrodes recorded mostly ripple frequencies rather than fast ripples, with lower average frequency than the HFOs recorded by the microwire electrodes. Fast-ripple recordings were most commonly restricted to a single microwire, suggesting that fast ripples may be generated by highly localized groups of neurons that are best sampled using microwire electrodes.

To further assess for clinical significance of HFOs, Jacobs et al[23] studied 20 patients who underwent surgical resection for intractable epilepsy after intracranial electroencephalographic monitoring. HFOs were identified visually during a few minutes of slow-wave sleep, and rates of HFOs in resected and nonresected areas were compared according to surgical outcome. After a mean follow-up of 22 months post surgery, patients with a good surgical outcome had a significantly larger proportion of HFO-generating areas resected than did those having a poor postoperative seizure outcome.

These results are promising, but before HFO measurement can become part of routine clinical practice, the results need to be replicated and new, less labor-intensive methods of identifying HFOs need to be developed. As an initial step in improving HFO identification, Blanco et al[24] developed an automated algorithm for detecting and classifying HFO signals from long-duration micro- and macroelectrode intracranial recordings.

Microseizures

Techniques such as the use of microwire electrodes and wide-bandwidth electrophysiologic recordings have allowed for identification and study of HFOs in human intracranial recordings. They also have led to the discovery of microseizures—seizure-like events not detectable using clinical macroelectrodes.[25]

Stead et al[25] recorded microseizure events in patients with epilepsy and control subjects who had intractable facial pain, demonstrating that these events can occur in patients without a diagnosis of epilepsy. However, the microseizures were more frequent in brain regions that generated seizures and among epilepsy patients versus control subjects. The microseizures also sporadically evolved into larger scale clinical seizures. It is possible that frequent microseizures may be markers of a patient's epileptogenic zone, but further study is needed to determine the significance of these electrophysiologic findings, particularly since they were seen in control subjects without a diagnosis of epilepsy.

Flexible, High-Density Electrode Arrays

Microwire depth electrodes and small penetrating electrode arrays such as the Utah array permit high-resolution intracranial recordings. However, these electrodes cannot record over the large areas of brain surface required for clinical recording, and they have other drawbacks, including deterioration of signal quality over time and insertion-related inflammatory tissue response or hemorrhage.[26] High-density electrode arrays covering larger areas of the cortical surface are needed.

Viventi et al[26] developed new, high-

density, flexible microelectrode arrays composed of silicon nanomembrane transistors that can record visual evoked potentials and seizures in felines. The seizure recordings from this high-density array revealed a recurrent spiral-wave ictal pattern. Recordings of interictal spikes demonstrated vastly different microscale spatial patterns among spikes that were indistinguishable based on macroelectrode recordings. These novel microelectrode arrays have the potential to advance our understanding of seizure electrophysiology, and they may be clinically useful in the future.

FUNCTIONAL MRI FOR ASSESSMENT OF LANGUAGE AND MEMORY IN EPILEPSY

Based on a presentation by William Gaillard, MD, Professor of Neurology and Pediatrics, George Washington University, and Chief, Division of Epilepsy, Neurophysiology, and Critical-Care Neurology, Children's National Medical Center, Washington, DC

One of the most worrisome risks of epilepsy surgery is postoperative decline in memory or language function. Accurately predicting this risk before surgery requires knowledge of hemispheric language dominance and the different brain areas involved in particular cognitive tasks. For patients with epilepsy, it is important to know whether brain organization differs from that seen in most normal controls to better predict the risk of postoperative deficits.[27]

The intracarotid amobarbital procedure (Wada test) is the current gold standard for assessing hemispheric dominance of language and memory. However, this procedure entails some risk to the patient and does not provide information on brain regions activated in response to a specific cognitive task.[27]

Functional MRI (fMRI) is a promising, noninvasive, indirect measure of neuronal synaptic activity that can be used in patients over 4 years of age and that offers potential advantages over Wada testing. Specifically, fMRI allows for whole-brain temporal and spatial resolution, thereby providing information on both lateralization and localization of eloquent functions that should be spared during surgery. In addition, fMRI may be repeated, and multiple tasks are available to assess various cognitive functions.[27]

Language fMRI

Language fMRI testing entails the use of simple tasks targeted to different language functions, with particular attention paid to expressive (frontal) and receptive (temporal) functions.[28] Frequently tested fMRI language paradigms include verbal fluency, semantic decision tasks, reading comprehension, and auditory comprehension.[28] Activation of a cortical region by an fMRI language paradigm suggests involvement of that area in language function; however, critical areas for language function are not *necessarily* activated during fMRI studies.[28]

Functional MRI is a promising, noninvasive, indirect measure of neuronal synaptic activity in patients over 4 years of age that offers potential advantages over Wada testing.

Language fMRI has been validated by comparison with the Wada test; in fact, one study demonstrated a 91% overall fMRI agreement with the Wada test.[27] The discrepancies identified between Wada and fMRI results arose for a variety of reasons, but disagreement among patients whose language fMRI showed bilateral activation was most common.[27]

Despite these discrepancies, temporal lobe language laterality on fMRI may correlate with postoperative language function following anterior temporal lobectomy, perhaps to a greater degree than does Wada testing.[29] Sabsevitz et al[29] showed that higher levels of right temporal language activation on fMRI among left anterior temporal lobectomy patients correlated with better postoperative performance on the Boston Naming Test. A similar, but slightly weaker, correlation was seen with the degree of right language lateralization on Wada testing.

Why some patients with epilepsy have atypical language lateralization (right lateralization or bilateral) is not well understood, but factors including handedness, MRI findings, and age at onset of epilepsy are associated with atypical language lateralization. Gaillard et al[30] studied 102 patients with left hemisphere seizure onset and found that nearly 30% of patients had atypical language dominance. Atypical language lateralization was more common among patients with atypical handedness (left handed or ambidextrous), onset of seizures before age 6, stroke on MRI, or normal MRI.[30] Patients with mesial temporal sclerosis or focal cortical lesions such as dysplasia, tumor, or vascular malformation were less likely to have atypical language lateralization.

Memory fMRI

Memory fMRI may help in identifying patients at risk for amnesia after epilepsy surgery, but research in this area is much less well developed than is the study of language fMRI. There is some evidence suggesting a correlation between hippocampal activation patterns and risk of memory decline among patients with mesial temporal lobe epilepsy.

Bonelli et al[31] studied 72 patients who had memory fMRI studies prior to anterior temporal lobe resection. Greater ipsilateral *anterior* hippocampal activation predicted greater postoperative visual memory decline among patients with right mesial temporal lobe epilepsy and greater verbal memory decline among individuals with left mesial temporal lobe epilepsy. In contrast, greater ipsilateral *posterior* hippocampal activation correlated with better postoperative memory function—specifically, visual memory in the right temporal lobe epilepsy group and verbal memory among the left temporal lobe epilepsy group.

CONCLUSION

Recent work on fMRI, intracranial microelectrode recording techniques,

pharmacogenomics, and the basic science of epileptogenesis and AED efficacy has uncovered valuable information relevant to the medical and surgical treatment of epilepsy patients. With future advancement in these areas of investigation, there is a potential for a significant impact on clinical care.

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Emerging Developments in Antiepileptic Drug Therapy

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Abstract Nearly two out of five patients with epilepsy continue to have seizures despite treatment with antiepileptic drugs or surgery. This dismal record has prompted the reevaluation of current therapies in underserved special populations, such as children with epileptic disorders, and the identification of new antiepileptic compounds with novel mechanisms of action and a tolerable side-effect profile. At the 64th Annual Meeting of the American Academy of Neurology, researchers presented data from the CATZ study, a recently completed phase III, double-blind, placebo-controlled trial evaluating the safety and efficacy of zonisamide in pediatric patients with partial-onset seizures. Other presenters described the results of three separate phase III randomized clinical trials exploring the clinical benefits and tolerability of perampanel as adjunctive therapy in adult patients with refractory focal or partial-onset seizures.

The past few decades have produced several exciting developments in our understanding and management of epilepsy, including renewed enthusiasm for surgery, trials of new therapeutic neurostimulation devices, and several new antiepileptic drugs (AEDs). This research effort is providing practitioners with an expanding array of therapeutic choices, allowing them to tailor medication regimens according to patient response and side-effect profiles. However, these advances have so far produced little improvement in patients achieving seizure freedom.[1,2] Nearly 40% of patients with epilepsy remain refractory to AEDs.[3] At best, current surgical treatment offers long-term seizure freedom in 60%–70% of selected ideal patients.[4]

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For many other individuals with epilepsy, however, surgery is not an option, and neurostimulation offers little more than a palliative option.

Contemporary research is focusing on identifying novel therapeutic targets or mechanisms of action for antiepileptic therapy and developing new preclinical evaluation methods to pinpoint more effective treatments that reduce or prevent epileptogenesis. Additional emphasis is being placed on reevaluating current therapies in special populations, improving the design and efficacy of neurostimulation devices, treating common comorbidities associated with epilepsy, and refining clinical trial designs.[1,5,6]

In light of the renewed emphasis on developing novel treatments for epilepsy, physicians are optimistic that more effective therapies may be just over the horizon. At the forefront is a new generation of AEDs with novel mechanisms of action such as perampanel (which is discussed later in this article) and ezogabine (also known as retigabine). Ezogabine, which was recently approved by the US Food and Drug Administration (FDA) for adjunctive treatment of partial-onset seizures, is a first-in-class AED that activates voltage-gated potassium channels in the brain, reducing excitability through the stabilization of neuronal potassium channels in an "open" position.[7,8] Whether perampanel, ezogabine, and other such drugs with novel mechanisms of action represent a revolutionary new class of AEDs or just another therapeutic choice with efficacy similar to that of currently available medications is not yet known; head-to-head comparisons of new AEDs with traditional AEDs are conspicuously absent in the literature.

ZONISAMIDE EFFICACY IN PEDIATRIC PATIENTS

Based on a presentation by Anna Rosati, MD, PhD, Paediatric Neurology Unit, Children's Hospital Anna Meyer, University of Florence, Florence, Italy

Zonisamide, which was approved by the FDA in 2000 for the adjunctive treatment of partial seizures in adults, has several mechanisms of action. It acts as a sodium-channel antagonist; reduces inward T-type calcium-channel currents; and inhibits neurotransmitters primarily by affecting γ-aminobutyric acid, serotonin, and dopamine levels.[9,10]

Epilepsy treatments generally remain underinvestigated in the pediatric population. Several AEDs, including zonisamide, have been tested in phase II clinical trials to establish a pharmacokinetic profile and determine the adverse effects of adjunctive therapy when these drugs are used in pediatric patients. However, their efficacy has not been studied in a young population.[10,11]

Data from the CATZ trial, a recently completed, phase III, double-blind, placebo-controlled, multicenter study,

were presented at the 2012 Annual Meeting of American Academy of Neurology (AAN) by Rosati et al.[12] The investigators assessed the efficacy and safety of zonisamide in 207 young patients aged, 6–17 years old with partial-onset seizures who were being treated with one or two AEDs. The patients were randomized to receive either placebo (n = 100) or zonisamide (n = 107); the zonisamide dosage was titrated from 1 mg/kg/d to 8 mg/kg/d over a period of 8 weeks. Patients were then maintained on that dosage for 12 weeks and subsequently either continued taking 8 mg/kg/d of the drug as part of an extension study or were gradually withdrawn from zonisamide therapy.

Endpoints were ≥ 50% seizure frequency reduction and median percent change from baseline in 28-day seizure frequency during the 12-week maintenance period and the entire double-blind period (ie, titration plus maintenance). A total of 93 patients treated with zonisamide and 90 patients receiving placebo completed the study.

The results are summarized in Table 1.[12] A ≥ 50% reduction in seizure frequency was achieved in 50.5% of patients given 8 mg/kg/d of zonisamide and 31.0% of those given placebo. The secondary endpoint, the median percent change in baseline 28-day seizure frequency, was –50.0% for the zonisamide group and –24.5% for the placebo group during the maintenance phase (between-group difference, 25.2%) and –42.2% for zonisamide and –20.4% for the placebo group during the entire double-blind period (between-group difference, 25.3%).

Adverse effects (most commonly, headache, decreased appetite, nasopharyngitis, and upper abdominal pain) were reported in 55.1% of patients receiving zonisamide and 50.0% of those given placebo. Adverse effects that were associated with zonisamide therapy to a significantly greater extent than with placebo use included decreased appetite, weight loss, somnolence, vomiting, and diarrhea. Severe adverse effects and those leading to withdrawal from the study occurred more often among patients using placebo than among those using zonisamide, whereas serious adverse effects were seen in four patients treated with zonisamide and two using placebo.

This study demonstrated that zonisamide is an effective adjunctive treatment for partial-onset seizures in children ≥ 6 years of age when compared with placebo. Further, use of zonisamide in this pediatric population was not associated with serious or new adverse effects or safety concerns.

TABLE 1
Improvement in 50% Responder Rate and 28-Day Seizure Rate with Zonisamide vs Placebo

Parameter	Zonisamide	Placebo
≥ 50% Reduction in seizures	50.5%	31.0%
Median 28-day seizure rate		
Double-blind phase	–42.2%	–20.4%
Maintenance phase	–50.0%	–24.5%

Source: Rosati et al[12]

PERAMPANEL ESTABLISHES EFFICACY IN STAGE III CLINICAL TRIALS

Based on presentations by Gregory Krauss, MD, Associate Professor and Director, Adult Epilepsy Clinic, Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland; Antonio Laurenza, MD, Executive Director, Eisai Medical Research, Woodcliff Lake, New Jersey; Jacqueline French, MD, Professor of Neurology and Co-Director of Epilepsy Research and Epilepsy Clinical Trials, New York University Comprehensive Epilepsy Center, New York, New York; Ziad Hussein, PhD, Senior Director of Modelling and Simulation, Eisai Ltd, Hatfield, Hartfordshire, United Kingdom; and Lynn Kramer, MD, FAAN, President of Eisai Neuroscience Product Creation Unit, Ridgefield Park, New Jersey

Perampanel, a noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist, is a novel investigational compound being developed to treat patients with epilepsy. Glutamate, the predominate excitatory chemical neurotransmitter, has been long studied for its role in acute seizures and epilepsy. Until recently, clinical investigators focused on the link between N-methyl-D-aspartate receptors and glutamate. More recently, studies have been directed toward AMPA receptors, which transmit the majority of fast glutaminergic signaling and may play a central role in seizure generation and spread.[13]

Following promising preclinical and early clinical studies, phase III trials of perampanel have been completed. The drug effectively reduced seizure frequency when given as adjunctive therapy to patients with refractory partial-onset epilepsy. During the 2012 annual AAN meeting, several investigators summarized data from three multicenter, double-blind, parallel-group phase III trials (studies 304, 305, and 306), which were performed in three phases: prerandomization (baseline period), a double-blind phase, and a follow-up period.[14–18]

> Perampanel effectively reduced seizure frequency when given as adjunctive therapy to patients with refractory partial-onset epilepsy.

Patient Population and Treatment Schema

A total of 1,478 patients (age ≥ 12 years) with uncontrolled focal or partial-onset seizures while taking up to three AEDs were randomized to receive adjunctive therapy with 8 or 12 mg/d of perampanel or placebo (studies 304 and 305) *or* 2, 4, or 8 mg/d of perampanel or placebo (study 306) over 6 weeks. The dosage was titrated upward by 2 mg/wk until the target dose was reached; patients then continued on maintenance therapy for 13 weeks. Patients with primary generalized epilepsy, Lennox-Gastaut syndrome, or a history of status epilepticus within the previous year were excluded from the study. Seizures were recorded daily in a patient diary and normalized to 28 days for analysis.

TABLE 2
Responder Rates from Three Pooled Phase III Trials of Perampanel

		Perampanel dose			
Responder rate	**Placebo (n = 348)**	**2 mg/d (n = 161)**	**4 mg/d (n = 159)**	**8 mg/d (n = 46)**	**12 mg/d (n = 114)**
50%	18.4	22.4	30.8	37.6	39.5
75%	5.7	10.6	12.6	18.8	20.2
100%	1.1	1.9	5	3.8	4.4

Source: Krauss et al[14]

TABLE 3
Median Time to Baseline 28-Day Seizure Rate with Perampanel Therapy

		Perampanel dose			
	Placebo	**2 mg/d**	**4 mg/d**	**8 mg/d**	**12 mg/d**
Days	30	32 ($P = 0.0672$)	33 ($P = 0.0019$)	36 ($P < 0.0001$)	34 ($P < 0.0001$)

Source: Laurenza et al[15]

TABLE 4
Prolonged Time to Next Seizure over Baseline with Perampanel Therapy

		Perampanel dose			
	Placebo	**2 mg/d**	**4 mg/d**	**8 mg/d**	**12 mg/d**
Days	32	33 ($P = 0.0723$)	38 ($P = 0.0003$)	41 ($P < 0.0001$)	38 ($P < 0.0001$)

Source: Laurenza et al[15]

Response Rate and Freedom from Seizures

To determine the dependency of response rate on perampanel dosage, Krauss et al[14] evaluated 50%, 75%, and 100% responder rates in patients given 2, 4 , 8, or 12 mg/d of perampanel. Data were pooled from previously described phase III trials with a 6-week titration period and 13-week maintenance period (n = 442). Latin-American patients were excluded due to a regional effect that resulted in a high placebo response. Responder rates were defined as the proportion of patients having a lower seizure frequency as compared with the 28-day baseline seizure rate (median, 10.2–18.9).

Responder rates and last medication dose determined during the maintenance period (Table 2)[14] suggested that use of 4–12 mg/d of perampanel significantly increased 50% and 75% responder rates in a dose-dependent manner. Additionally, a trend toward seizure freedom with increasing perampanel exposure was observed.

Time to Seizure Recurrence

Laurenza et al[15] employed a novel study design, measuring median and individualized "time to event," which was intended to reduce baseline variability and to allow patients to complete studies with less exposure to the drug. Endpoints were median time to 1st, 3rd, 6th, 9th, and 12th seizure; the individualized temporal endpoint was the median time for patients to reach their baseline 28-day seizure rate (N^{th} seizure).

Data were pooled from the phase III studies 304, 305, and 306 and excluded patients from Central and South America. Adjunctive therapy with perampanel prolonged the median times to baseline, 28-day seizure rate (Table 3)[15]; median time to next seizure over baseline (Table 4)[15]; and median times to 6th, 9th, and 12th seizure events.

These results suggested that administration of 4–12 mg/d of perampanel effectively prolonged the 28-day seizure rate and time to next seizure. In addition, they supported the outcomes of previous investigations, showing that 4–12 mg/d of perampanel is effective as adjunctive therapy of partial-onset seizures. The lack of seizure-rate prolongation with the 12-mg/d dose was attributed to most patients reaching a 12th seizure before receiving the full 12-mg daily dose.

These results supported the use of an individualized "time to event" in future studies. Additionally, the investigators suggested that adequate evaluation of later or higher drug exposure would be better reflected by endpoints involving long titration periods and/or high baseline event frequency.

Efficacy with Concomitant AEDs

French et al[16] analyzed the effect of concomitant AED administration on perampanel efficacy via assessment of seizure frequency and responder rate. This study included 1,478 pooled phase III trial participants. After randomization, 180 patients were given 2 mg/d of perampanel, 172 were given 4 mg/d of perampanel, 431 were given 8 mg/d of perampanel, 254 were given 12 mg/d of perampanel, and 441 were given placebo. Endpoints were median percent change in 28-day seizure frequency (Table 5)[16] and 50% responder rate (Table 6).[16] Patients used an average of 2.2 concomitant AEDs, most commonly carbamazepine (n = 491), valproate (n = 478), lamotrigine (n = 457),

TABLE 5
Median Differences of Median Percent Change in 28-Day Seizure Frequency with Perampanel Therapy[a]

Perampanel dose			
2 mg/d	**4 mg/d**	**8 mg/d**	**12 mg/d**
7.7% to –7.8%	–3.0% to –12.7%	–8.9% to –20.8%	–12.4% to –16.7%

[a] In patients receiving concomitant antiepileptic drugs vs placebo
Source: French et al[16]

TABLE 6
50% Responder Rate Ranges for Perampanel vs Placebo

	Perampanel dose			
Placebo	**2 mg/d**	**4 mg/d**	**8 mg/d**	**12 mg/d**
13.6%–23.1%	13.8%–21.4%	19.6%–34.7%	29.7%–38.3%	30.6%–43.0%

Source: French et al[16]

TABLE 7
Perampanel Inducers and Adverse Effects[a] with Increasing Exposure

Perampanel inducers	Adverse effects
Phenytoin	Fatigue
Oxcarbazepine	Somnolence
Carbamazepine	Gait disturbances
Topiramate (mild)	Dizziness
	Weight gain
	Irritability
	Dysarthria
	Euphoric mood

[a] Adverse effects are listed in decreasing order of occurrence.

Source: Hussein et al[17]

and levetiracetam (n = 435).

The findings suggested that 4–12 mg/d of perampanel is an effective adjuvant therapy for reducing seizure frequency and increasing responder rates. Further, the efficacy of this drug was not influenced by the concomitant use of other AEDs.

Effect of Concomitant AEDs on Perampanel Pharmacokinetics and Pharmacodynamics

Hussein and colleagues[17] studied the pharmacokinetic and pharmacodynamic effects of perampanel as they related to demographic factors and concomitant AED administration. In addition, the authors performed an analysis of predicted exposure/efficacy with the last dose achieved in a model.

Patients in studies 304, 305, and 306 were randomized and treated with perampanel as described previously. Of the 1,478 participants in the phase III trials, 1,109 patients were included in the pooled pharmacokinetic/pharmacodynamic study (770 patients in the pharmacokinetic study alone, including 745 in the last-dose analysis). Investigators compared blood samples taken at baseline with those obtained during the double-blind treatment phases, maintenance therapy periods, and at the end of the follow-up phases or upon discontinuation of perampanel therapy. Perampanel levels were determined via liquid chromatography and mass spectroscopy.

Investigators reported that 12 concomitant AEDs (carbamazepine, lamotrigine, valproate, levetiracetam, topiramate, oxcarbazepine, clobazam, zonisamide, phenytoin, clonazepam, pregabalin, and phenobarbital) were used by at least 50 patients in the pharmacokinetic/pharmacodynamic population analysis. Furthermore, 71% of patients were prescribed at least one perampanel inducer (Table 7).[17]

Mean plasma perampanel concentrations remained linear over the dose range, regardless of concomitant AED use. The pharmacokinetic/pharmacodynamic analysis demonstrated that seizure frequency decreased and 50% responder rate increased in a linear fashion with increasing perampanel serum level at steady state, regardless of the presence of a concomitant perampanel inducer.

Adverse effects (Table 7)[17] increased with greater perampanel exposure and were not affected by demographic factors or use of concomitant AEDs, including perampanel inducers. No change in appetite or headaches related to perampanel concentration was seen. Demographic factors (age, sex, body mass, and race) did not affect the exposure/efficacy relationship, the probability of response to perampanel, or the occurrence of adverse effects.

Dose-Response Analysis

Kramer and others[18] assessed 28-day seizure frequency and 50% responder rate from patients enrolled in the three pooled phase III trials (studies 304–306) and an open-label extension study (OLE 307). This research involved 209 patients who completed double-blind phase III studies involving 8 mg/d of perampanel to start and then 12 mg/d during the conversion period of the OLE study. Another analysis was performed on patients randomized to receive 12 mg/d of perampanel by the conversion period. Latin-American patients were excluded from the analysis due to a regional placebo effect.

The findings suggested that improved perampanel efficacy via reduced seizure frequency and increased responder rate can be achieved with doses increased to 12 mg/d from 8 mg/d (Table 8).[18]

CONCLUSION

The relatively recent proliferation of new AEDs and treatments for intractable epilepsy has not had a significant impact on patients achieving seizure freedom. A critical shift in the development and assessment of therapies, however, has produced novel AEDs; this movement is leading to a reevaluation of current therapies for different target populations. Whether this new emphasis will improve the static efficacy facing current therapies is yet to be seen. Both zonisamide and perampanel have demonstrated promising efficacy in pediatric and adult patients, respectively, with refractory partial-onset seizures in medically refractory patients, with the potential to improve the current level of AED efficacy and provide new options for the treatment of epilepsy in these populations.

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TABLE 8
Median Percent Change in 28-Day Seizure Frequency and 50% Responder Rate with Perampanel Therapy

	Perampanel dose		
Parameter	8 mg/d	8 mg/d → 12 mg/d[a]	12 mg/d[b]
28-Day seizure frequency	–32.4%	–43.3%	–42.1%
50% Responder rate	37.8%	43.5%	42.9%

[a] Patients completing maintenance therapy with 8 mg/d of perampanel and then increased to 12 mg/d

[b] Patients randomized to and then maintained on 12 mg/d of perampanel

Source: Kramer et al[18]

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CME Post Test

Using this page 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 32 and see the instructions below it to obtain CME credit.

1. In two placebo-controlled phase II trials of adjunctive ezogabine therapy to control partial-onset seizures, patients using ezogabine were more likely to:
   a. Benefit from the drug if they were young
   b. Benefit from the drug if they were Hispanic or Asian
   c. Experience a 50% or greater reduction in seizure frequency than had they taken placebo
   d. Have adverse events if they were also taking sodium-channel blockers such as phenytoin or carbamazepine

2. In investigating the incidence and timing of adverse events in patients taking eslicarbazepine acetate, Sperling et al reported that 30% of all adverse events occurred during:
   a. Week 1 of therapy
   b. Week 2 of therapy
   c. Week 3 of therapy
   d. Week 4 of therapy

3. The procedure of choice for treating patients with drug-resistant mesial temporal lobe epilepsy is:
   a. Selective amygdalohippocampectomy
   b. Anterior temporal lobe resection
   c. Vagal nerve stimulation
   d. Gamma Knife surgery

4. Among patients with epilepsy, autism is more common in patients with intellectual disability and in those diagnosed with epilepsy:
   a. Before puberty
   b. From 4 to 7 years of age
   c. From 2 to 3 years of age
   d. During the first year of life

5. Which of the following statements about the use of zonisamide versus carbamazepine in patients with newly diagnosed partial-onset epilepsy is *true?*
   a. Both drugs are known inducers of cytochrome P450.
   b. Zonisamide, but not carbamazepine, has been shown to exacerbate absence seizures in pediatric patients.
   c. Zonisamide may be given once daily, whereas carbamazepine must be given twice daily.
   d. Treatment with both drugs has been associated with serious birth defects.

6. In analyzing the results of three clinical trials of perampanel in partial-onset seizures, Laurenza et al found that _____ is a useful outcome measure.
   a. Time to event (preselected 1st to 12th seizure)
   b. Time to *N*th seizure (individualized baseline)
   c. Frequency of seizures after 28 days of therapy
   d. Frequency of seizures after 16 weeks of therapy

7. Which of the following biomarkers is associated with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in China, Thailand, and Malaysia but not in Europe or Japan?
   a. HLA-B*3101
   b. HLA-B*1502
   c. The Leu359 allele in *CYP2C9*
   d. SCN2A IVS7-32A>G (rs2304016) A alleles

8. Which of the following statements about functional magnetic resonance imaging (fMRI) is *true?*
   a. fMRI cannot be used to localize eloquent functions to spare during surgery.
   b. fMRI can be used in patients as young as 1–2 years of age.
   c. fMRI may cause brain damage if repeated.
   d. fMRI permits whole-brain temporal and spatial resolution.

9. In a study of zonisamide adjunctive therapy in pediatric patients with partial-onset epilepsy:
   a. Adverse effects occurred in twice as many patients using zonisamide as those using placebo.
   b. Severe adverse effects and those leading to study withdrawal occurred more often among patients using placebo than those using zonisamide.
   c. Decreased appetite and weight loss occurred more commonly in patients using placebo than in those using zonisamide.
   d. New adverse events were seen in the pediatric population that were not anticipated from the drug's safety profile in adult patients.

10. Which of the following antiepileptic drugs reduces seizure frequency by antagonizing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors?
   a. Topiramate
   b. Zonisamide
   c. Perampanel
   d. Ezogabine

Evaluation

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

	Strongly agree	Agree	Disagree
1. As a result of this activity, I am more knowledgeable about the …			
a. Outcomes of clinical trials testing novel and established antiepileptic drugs (AEDs), alone and in combination, in the treatment of epilepsy.	❑	❑	❑
b. Advantages and disadvantages of surgical options for controlling seizures.	❑	❑	❑
c. Relationships of cognitive dysfunction, memory loss, and autism with respect to both the etiology of epilepsy and its treatment.	❑	❑	❑
d. Pharmacogenetics and pharmacogenomics of AEDs as they relate to the clinical management of epilepsy.	❑	❑	❑
e. Usefulness of technologic advances in helping predict the risk of memory loss or language dysfunction before surgery in patients with epilepsy and in the assessment of seizure activity and treatment response.	❑	❑	❑

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

	Yes	No	Don't know
3. Did the information you received from this CME activity:			
a. Confirm the way you currently manage your patients?	❑	❑	❑
b. Suggest new options for managing your patients that you might apply in the future?	❑	❑	❑

	Patient management	Board review	CME credit
4. I used the information in this issue for … *(check all that apply)*	❑	❑	❑

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

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