Treating the New-Onset Epilepsy Patient

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Abstract New-onset epilepsy presents neurologists with profoundly unique challenges and specific management considerations. During the 67th Annual Meeting of the American Epilepsy Society, specialists in epilepsy discussed concerns that neurologists and other clinicians face in treating this population, including patient selection; choice of drug therapy; patient prognosis; and specific considerations related to the treatment of epilepsy in children, the elderly, and other patient subpopulations.

Treatment of new-onset epilepsy requires considerable medical expertise and depends upon accurate diagnosis, patient education about the disease and its prognosis, selection of optimal therapy, individualized management, and patient monitoring to detect recurrent seizures and adverse effects of therapy.

Unlike chronic epilepsy, new-onset epilepsy has yet to establish a clinical pattern. The patient may develop refractory seizures or never have another seizure. Evidence of a cortical lesion on magnetic resonance imaging (MRI) of the brain is associated with a greater chance of recurrence of seizures (Figure 1); such a finding also helps determine appropriate treatment.1

At a symposium on the treatment of new-onset epilepsy held during the 67th Annual Meeting of the American Epilepsy Society in Washington, DC, experts focused on timing the treatment of an initial seizure, the initial choice of therapy, considerations related to patient age and other factors, and prognosis. The symposium was chaired by Gregory Krauss, MD, Professor of Neurology at Johns Hopkins University in Baltimore, Maryland, and Scott Mintzer, MD, Associate Professor of Neurology at Thomas Jefferson University in Philadelphia, Pennsylvania.

TREATING NEW-ONSET EPILEPSY: PERSPECTIVE FROM A LONGITUDINAL STUDY

Based on a presentation by Bernd Pohlmann-Eden, MD, PhD, Co-Director of the Epilepsy Program and Professor of Neurology, Pharmacology and Psychology; Dalhousie University, Halifax, Canada, and Rupprechts-Karl-University, Heidelberg, Germany.

Does a first-time seizure warrant initiation of antiepileptic drug (AED) therapy? Does one seizure even qualify as “epilepsy?” If so, what factors lead to clinical epileptogenesis?

The widely accepted definition of epilepsy is the occurrence of two unprovoked seizures.2 However, it is reasonable to diagnose a person genetically predisposed to recurrent seizures as having epilepsy following the occurrence of just a single seizure.3 Furthermore, the terms “new-onset epilepsy” and “newly diagnosed epilepsy” are differentiated by a time domain. New-onset epilepsy is defined as an early stage of epilepsy often characterized by more than two seizures within a single year. In newly diagnosed epilepsy, subtle seizures may have gone unrecognized for several years before presentation.4

Differentiating patients presenting with a first seizure has implications for research in this area, since seizures in the newly diagnosed epilepsy group may not have begun as recently as those observed or reported in patients with new-onset epilepsy.5

Etiology

Response to treatment may depend on the underlying etiology of new-onset epilepsy. The highest seizure-free rates 1 year after initiation of treatment have been observed among patients who experienced seizures following diagnosis of a stroke or tumor, whereas the lowest rates were seen in individuals with seizures having a dual pathology or associated with hippocampal sclerosis.6 The specific factors responsible for clinical epileptogenesis are unknown but may be determined by syndrome-inherent characteristics, seizure activity, the timing and choice of therapy, and genetics, as well as by interactions among all these factors. In addition, why some patients have pharmacoresistant seizures is not well known, and more research in this area is needed.

Timing of Therapy

If the patient has risk factors that increase the risk of recurrence, such as imaging or electroencephalographic (EEG) evidence of an epileptogenic focus, initiating treatment is reasonable. Antiepileptic therapy also is in order if a second seizure would be medically or socially detrimental to patients, such as those with severe osteoporosis or a spinal cervical fracture.
or patients who could lose their jobs if they have a second seizure.  

Selecting an AED Regimen

The preferred AEDs for partial-onset epilepsy are lamotrigine, levetiracetam, and carbamazepine. The preferred AEDs for primary generalized epilepsy are lamotrigine, levetiracetam, and topiramate.

In the Halifax First Seizure Clinic (HFSC), the new-onset epilepsy patient often is started on phenytoin by a physician in the emergency room. Over one-third of the new-onset epilepsy group at HFSC underwent a switch to a second AED, most often due to safety concerns and side-effect profiles. After 6 months, 64% of patients in the AED arm and 2% of patients not given an AED were seizure-free. Further, 11% were pharmacoresistant, as suggested by failure of two or more AEDs to control seizures (unpublished data).

The HFSC study also revealed various patterns of pharmacoresistance: patients having persistently frequent breakthrough seizures, patients who experienced a single seizure every year, and patients who exhibited rare clusters of seizures.

These variations in treatment response and pharmacoresistance emphasize the need for continued prospective, longitudinal research and development of an individualized treatment plan.

Case Study of New-Onset Epilepsy

In one interesting case, a 42-year-old man with new-onset epilepsy was treated with levetiracetam. After experiencing a breakthrough seizure, he had one dose increase and remained seizure-free for 3 years. Imaging of this patient revealed periventricular heterotopias.

Contrary to what would be expected, interim analysis of HFSC data presented at the 2012 Annual Meeting of the American Epilepsy Society suggested that the likelihood of seizure freedom was excellent with or without AEDs in the setting of seizures and MRI evidence of congenital malformations.

DRUG CHOICE IN NEW-ONSET EPILEPSY

Based on a presentation by Tracy A. Glauser, MD, Director, Comprehensive Epilepsy Center, Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio.

When initiating AED therapy, neurologists need to consider the variables among patients, AEDs, and even countries. Patient-specific variables include the patient’s genetic background, age, gender, comorbidities, and medications being used. AED-specific variables include differences in efficacy in controlling certain types of seizures or syndromes, pharmacokinetics, dose-dependent adverse effects, teratogenicity, and interaction potential. Country-specific variables include differences in availability of AEDs, cost, and insurance coverage.

The culture of medicine relies heavily on randomized controlled trials (RCTs). Although the outcomes of RCTs can influence the basis of a treatment decision, the treatment plan still needs to be individualized to accommodate these variables.

The International League Against Epilepsy (ILAE) categorizes clinical trials into class I, II, and III/IV studies. Class I studies are defined by prospective RCTs demonstrating superiority or a sample size large enough to show noninferiority with treatment lasting at least 48 weeks and data showing >24 weeks of freedom from seizures. Class II RCTs are similar to class I studies, but they have a shorter duration or are failed superiority trials or noninferiority trials. Class III/IV studies are RCTs or meta-analyses not meeting criteria for class I or II studies or are expert reports.

Level of evidence is determined by a letter grade system. Level A evidence, which is established by more than either one class I or two class II studies, reflects the established efficacy of a particular treatment. Level B evidence suggests probable efficacy, whereas level C evidence suggests possible efficacy.

For partial-onset seizures in adults, several class I studies offer level A evidence that supports the efficacy of carbamazepine, phenytoin, levetiracetam, and zonisamide. Only one class I study examining partial-onset seizures in children demonstrated level A efficacy of oxcarbazepine. Likewise, only one class I study is available for the elderly, and this study established lamotrigine and gabapentin as effective options.

For generalized-onset seizures, only one class I study referred to the trat-
ment of absence seizures. This study established valproate and ethosuximide as effective options. Cumulatively, only seven class I studies exist for all partial and generalized seizure types in adults, children, and the elderly.

Future RCTs may provide information with minimal bias and impact of variability. However, these trials may not ask the correct questions; they also may create an artificial environment, and the management of the patient may be predetermined by the study protocol and not individualized therapeutic decisions. The ultimate treatment choice should depend upon available evidence-based guidelines, patient factors, and available resources. Figure 2 reflects the many factors involved in appropriate management of new-onset epilepsy.

NEW-ONSET EPILEPSY IN CHILDREN

Based on a presentation by Dave F. Clarke, MBBS, ABPN (Child Neurology and Sleep), ABCN, Associate Professor of Pediatric Neurology, University of Texas Southwestern, and Director, Dell Children’s Comprehensive Epilepsy Program, Dell Children’s Medical Center of Central Texas, Austin, Texas.

One challenge facing clinicians treating pediatric patients is recognition of seizures versus nonepileptic paroxysms. In addition, children diagnosed with childhood epilepsy syndromes and constellations must be treated with the appropriate AEDs.

As suggested by a study performed at a tertiary-care first seizure clinic, the diagnosis of seizures in children can be difficult. In this series, one fourth of the children were incorrectly diagnosed as having seizures, and the diagnosis of epilepsy was missed in one third. Further, children exhibit numerous nonepileptic mimics of seizures, such as myoclonus, cataplexy, syncope, daydreaming, hyper-exkplexia, or infantile colic, to name a few.

When choosing AEDs for use by children, the same patient and environmental factors as used for adults must be considered. In addition, consideration of seizure type, epilepsy syndrome, and other specific factors must be identified, because particular AEDs are more targeted toward certain syndromes than others.

Choosing Therapy for Different Types of Seizures

Neonatal seizures are characterized by enhanced network excitability and immature cortical circuits, which often lead to focal seizures; migrating or multifocal seizures; and, rarely, generalized tonic-clonic seizures. Following neonatal seizures, the risk of epilepsy is 22% within 12 months and 33.8% within 48 months. Traditional AEDs, such as phenobarbital or phenytoin, are < 50% efficacious in neonates.

In the acute setting, the consensus is to use intravenous (IV) benzodiazepines, phenytoin, and phenobarbital. Animal studies have suggested that topiramate may be neuroprotective. However, use of topiramate in the acute setting is limited by the lack of suspension or IV formulations. On the other hand, a survey of pediatric neurologists in 2007 revealed that even though evidence of safety and efficacy of newer AEDs is lacking, the use of levetiracetam and topiramate is recommended for neonatal seizures. These findings reflect the urgent need for further clinical trials to fully evaluate the long-term safety of these AEDs in neonates.
Infantile spasms (West syndrome) are manifested by clusters of repetitive flexor spasms, sometimes called "salaams," and head nods. The etiology of this syndrome can be cryptogenic or due to tuberous sclerosis or other brain abnormalities. The distinct EEG pattern demonstrates hypsarrhythmia, a high-voltage slowing pattern with chaotic multifocal spike waves and electroencephalographic seizures. The American Academy of Neurology Practice Guidelines on treating this syndrome are not absolute, but they suggest that adrenocortical thyroid hormone (ACTH) or vigabatrin is possibly effective, although in the setting of tuberous sclerosis, neither of these treatments was superior. The Infantile Spasms Working Group suggests that ACTH is effective as first-line therapy for infantile spasms, although the dose and duration of treatment are undetermined. Vigabatrin also is recommended as a first-line option but should be tapered or discontinued after 6–9 months due to concern for visual-field constriction.

The United Kingdom Infantile Spasms Study (UKISS) was a multicenter randomized controlled trial comparing vigabatrin to hormonal therapy (prednisolone or tetracosactide). Hormonal therapy initially showed better efficacy, but there was no difference between the two treatment groups at 14 months. Several case reports have shown that a ketogenic diet is possibly effective.

Focal seizures in children have been studied in two randomized controlled trials and one meta-analysis. Oxcarbazepine and phenytoin had class I evidence for efficacy, and oxcarbazepine had differential efficacy in one study. In the United States, oxcarbazepine, carbamazepine, lamotrigine, and levetiracetam are believed to be appropriate for initial monotherapy of focal seizures. The recommendations, however, vary slightly between the United States and Europe (Table 1).

Benign rolandic epilepsy often presents at a young age, generally between 3 and 13 years of age. Atypical events of tongue and facial twitching often progress to secondary generalized tonic-clonic seizures. In one case, a 7-year-old boy experienced left facial twitching with occasional difficulties with articulation and no history of secondary generalized tonic-clonic seizures. The events mostly occurred in the early morning hours. The diagnosis often may be made by taking a detailed history coupled with the results of a sleep EEG. Although these events qualify as epilepsy, treatment is not always necessary, and the evidence for effective treatment also is not definitive.

There are no level A or B treatment recommendations from the ILAE for rolandic epilepsy; carbamazepine and valproate have level C evidence. Results of RCTs suggest the use of sulfisoxame and gabapentin. The expert US consensus recommends use of oxcarbazepine or carbamazepine as initial monotherapy for rolandic epilepsy, followed by lamotrigine, levetiracetam, and gabapentin. However, whether treatment is necessary for benign rolandic epilepsy remains unclear. In a population study comparing 43 treated and 36 untreated patients, the overall seizure outcome was the same.

Generalized epilepsy syndromes include childhood and juvenile absence seizures. Level A evidence is available from the ILAE supporting initial treatment with ethosuximide, valproate, and lamotrigine. There also is consensus in this recommendation from the United Kingdom and Europe.

Juvenile myoclonic epilepsy is a syndrome affecting children 12–18 years of age. It is related to myoclonic seizures, generalized tonic-clonic seizures, and absence seizures. Valproate has been the drug of choice historically for treating juvenile myoclonic epilepsy; however, its use is limited by its side-effect profile and risks of teratogenicity. No level A, B, or C evidence for optimal treatment is available from the ILAE. Results of class 4 studies have suggested the usefulness of treatment with clonazepam, lamotrigine, levetiracetam, topiramate, valproate, and zonisamide. Data from the United Kingdom have recommended the use of valproate, lamotrigine, topiramate, and levetiracetam. However, juvenile myoclonic epilepsy may be exacerbated if treated with phenytoin, carbamazepine, gabapentin, vigabatrin, tiagabine, or oxcarbazepine.

Lennox-Gastaut syndrome (LGS) is characterized by a slow spike-and-wave EEG pattern. It has been reported in 1%–4% of juveniles with childhood epilepsy and accounts for 10% of those < 5 years of age. This syndrome is related to multiple seizure types (eg, tonic, atonic, myoclonic, generalized tonic-clonic, and atypical absence seizures) that are often pharmacoresistant. Valproate has previously been the drug of choice. The Felbamate Study Group and other research teams determined that felbamate was effective in LGS, even though its use was
limited by side effects and organ toxicity. The Scottish Intercollegiate Guidelines Network also recommended use of valproate, lamotrigine, topiramate, and felbamate and specifically recommended treatment with clobazam and rufinamide. The US consensus for treatment of this syndrome, however, involves use of valproate, topiramate, lamotrigine, and, sometimes, zonisamide.

Landau-Kleffner syndrome, syndrome of continuous spike and wave activity in sleep, and malignant rolandic epilepsy are related to neurocognitive deficits, language impairment, and continuous epileptiform activity during sleep. The key to diagnosis of these syndromes is the history and results of prolonged EEG, including sleep without rapid eye movements. The recommended AEDs for initial treatment of these syndromes are high-dose diazepam, valproate, corticosteroids, ACTH, and, sometimes, IV immunoglobulin. For treating epilepsy with electrical status epilepticus during slow sleep and its related disorders, high-dose valproate or a combination of valproate and ethosuximide is recommended.

In general, the treatment of many pediatric epilepsy syndromes needs further study, especially as there may be an influence of genetics and EEG patterns as well as clinical symptoms.

## NEW-ONSET EPILEPSY IN THE ELDERLY

**Based on a presentation by Ilo E. Leppik, MD, Professor of Neurology and Pharmacy, College of Pharmacy and Department of Neurology, University of Minnesota Medical School, Minneapolis, Minnesota.**

The overall incidence of epilepsy increases sharply after age 50 (Figure 3). In terms of epilepsy etiology, most cases in patients over 65 years of age are cryptogenic, although stroke and degenerative processes are common (Figure 4). At least one unprovoked seizure occurs in 7%–21% of patients with Alzheimer’s disease. In most cases, patients present to neurologists for evaluation and treatment of convulsive seizures, even though these events probably were preceded by subtle, unrecognized focal seizures. Early onset of Alzheimer’s disease is related to a higher incidence of seizures; the risk ratio (RR) for onset at 50–59 years of age is 87, compared with a RR for onset at 70–79 years of age of 3.

The incidence of epilepsy in nursing homes (1,642/100,000 person-years) is about 10-fold higher than in the outpatient setting. Seizures in nursing home residents tend to be related to the occurrence of injury, stroke, and neurodegenerative disorders, although there is a high incidence of unknown predisposing factors. Among the general population, the incidence of epilepsy increases with age; however, the prevalence of epilepsy among residents of nursing homes actually decreases as patients become older.

The most prevalent seizure type among the elderly is complex partial seizures followed by generalized tonic-clonic seizures.

### Risk Factors for Recurrent Seizures

Multiple factors must be considered to appropriately manage geriatric epilepsy, including the presence of medical comorbidities such as mood disorders, visual impairment, osteoporosis, and/or memory loss. In addition, clinicians need to consider the social implications of epilepsy in the elderly, including the loss of driving privileges, a possible lack of spousal support, the emotional response to the stigma associated with epilepsy, the cost of medication, a fear of recurrent seizures, and the impact of role reversal with adult children.

Arguments for initiating treatment after one seizure focus on the medical risk of a second seizure occurring or the possibility of an underlying stroke or neurodegenerative process. Concerns for cognitive side effects and falls are also reasons to defer treatments until absolutely necessary.

In a prospective 2000–2011 observational study, the risk of a second seizure at 1 year was 53% (95% confidence interval
[CI], 45%–62%) in older patients and 48% (95% CI, 44%–51%) in younger patients. In this study, the predictors of recurrent seizures were remote symptomatic etiology, first seizures occurring out of sleep, EEGs showing epileptiform abnormalities, and partial seizures, but not the person’s age.45

In a separate study investigating seizures in patients who had experienced a stroke,44 the incidence of recurrent seizures was 43%. The risk of recurrence increased with late onset of a first seizure after the stroke, a hemorrhagic component of the stroke, occipital location, and low Rankin score after the initial seizure.

Drug Therapy

A multicenter, randomized, double-blind parallel study in 593 elderly patients found a similar level of seizure control among groups assigned to treatment with gabapentin, lamotrigine, or carbamazepine.46 However, the group assigned to treatment with carbamazepine had the highest rate of discontinuation for adverse effects. These results suggest that lamotrigine or gabapentin use is the ideal initial therapy for new-onset epilepsy in the elderly. However, this study was also performed before levetiracetam became available, and sustained-release carbamazepine was not used.

Smaller studies comparing the use of levetiracetam with that of carbamazepine in the elderly have found a similar degree of seizure control, with levetiracetam causing fewer side effects than carbamazepine.46 In another study, lamotrigine use seemed to cause less dysphoria than did administration of carbamazepine.47 Further, zonisamide use has resulted in a better tolerability profile in the elderly than in nonelderly adults.48

Generally, some practitioners believe in avoiding AEDs that have significant drug-drug interactions or highly protein-bound metabolites in favor of drugs having long half-lives or alternative formulations such as IV options. Among elderly patients, drug-drug interactions usually involve an AED with another medication. Among the few studies that have evaluated AED drug interactions, one showed that carbamazepine use resulted in a lower simvastatin level when compared with placebo.49 In addition, the therapeutic window for AEDs decreases with age due to the risk of toxicity at lower serum concentrations. Although the serum concentration needed to control seizures also may decrease slightly, it does not fall to the same degree as does the threshold for toxicity; thus, the therapeutic window of AEDs decreases with age.50,51

Serum concentrations of AEDs can vary dramatically among the elderly. In a study measuring serum phenytoin levels without any change in dosing, serum levels varied by up to 200% on repeat testing, compared with < 20% in the community setting.52

Summary

Elderly patients have a moderate risk of new-onset epilepsy. When initiating therapy for this group of patients, clinicians must remember that the elderly often have multiple comorbidities that are being treated simultaneously. Consequently, the risk of drug interactions is substantially higher than it would be in the general population. Clinicians may opt to initiate therapy after just one seizure due to the etiology of that event and the likelihood of its recurrence. Large swings in serum drug levels, as evidenced by the high variability in serum phenytoin concentrations in the elderly, may confound therapeutic drug monitoring and complicate management. In addition, the therapeutic window of AEDs may be narrower for older patients than for younger adults, so the elderly must be closely monitored for potential toxicities.

PROGNOSIS FOR NEW-ONSET EPILEPSY

Based on a presentation by Scott Mintzer, MD, Associate Professor of Neurology and Director, Epilepsy Monitoring Unit and Epilepsy Surgery Program, Jefferson Comprehensive Epilepsy Center, Thomas Jefferson University, Philadelphia, Pennsylvania.

Multiple studies have reported that an average of 68% of patients with new-onset epilepsy are free of seizures > 1 year after treatment is initiated.53–56 The prognosis for primary generalized epilepsy may be slightly better, with studies reporting a seizure freedom of 94% among children, 64% in adults, and 76% in adolescents.56–58 Of the primary generalized epilepsies, childhood absence epilepsy has a better remission rate than does juvenile absence epilepsy.59–63 For juvenile myoclonic epilepsy, the 2- and 5-year remission

![FIGURE 5 Cumulative probability of being seizure-free from the start of treatment by the number of antiepileptic drug regimens tried. Adapted, with permission, from Brodie et al.53](image-url)
rates are 75% and 68%, respectively.\textsuperscript{94,65} The percentages of patients weaned off of AEDs in these studies were 9% and 19%. For patients with juvenile myoclonic epilepsy, the rates of pharmacoresistance or pseudoresistance resulting in recurrent seizures due to provocation (such as lack of sleep or alcohol intake) are 17% and 18%, respectively.\textsuperscript{18} Symptomatic generalized epilepsies are more resistant, with rates of remission ranging from 14% to 42%.\textsuperscript{56,67,68}

For focal epilepsy due to benign rolandic epilepsy, a 96% remission rate at 5 years has been suggested.\textsuperscript{69} Mesial temporal sclerosis reportedly has a poorer chance of becoming seizure-free on one AED, what are the chances that they will be seizure-free on another? Wang et al\textsuperscript{74} compared the seizure rates of patients who switched AEDs and 20% of controls who did not switch AEDs. Of patients who were not seizure-free at enrollment, only 30% of patients who switched AEDs and 20% of controls achieved seizure freedom.

**Summary**

Overall, about two thirds of patients with epilepsy are free of seizures after the first year of treatment. Childhood absence epilepsy and benign rolandic epilepsies have a more favorable prognosis. Juvenile absence epilepsy, symptomatic generalized epilepsy, and mesial temporal sclerosis have a worse prognosis for seizure freedom. Major predictors of seizure freedom are the number of seizures experienced and the number of AEDs previously attempted. The number of seizures preceding diagnosis may indicate vulnerability and an increased propensity for further seizures.

**REFERENCES**


