The goal of epilepsy treatment is to achieve seizure freedom with minimal adverse effects. The most important preventable cause of disability and poor health in patients with epilepsy probably is the toxicity related to antiepileptic drug (AED) therapy. Although epilepsy surgery and neuromodulation devices can limit the number of side effects associated with AEDs in carefully selected pharmacoresistant patients, they have their own untoward reactions. At a symposium on the fundamentals of epilepsy treatment held during the 2014 Annual Meeting of the American Epilepsy Society, five internationally recognized experts in the clinical and surgical management of epilepsy discussed the potential side effects of current epilepsy therapies, the acute treatment of status epilepticus, neurostimulation devices, the evaluation of patients for epilepsy and resective surgery, and complementary and alternative treatments such as dietary modification and hormonal therapy.

**Use of Questionnaires**

Patients tend to identify sequelae better when using structured questionnaires than when they are left to self-report events. Systematic screening for adverse events using standardized methods has several advantages: identification of high-risk populations, better recognition and quantification of adverse events, and reduction of AED toxicity by optimization of treatment. Most questionnaires take 5–10 minutes to complete, making them time-effective tools for busy clinical practices.

Perucca and colleagues performed a factor analysis on 19 adverse-event profile (AEP) items submitted to a large cohort of patients. The authors categorized adverse events into five biologically plausible classes: cognitive/coordination, mood/emotions, sleep, weight/cephalgia, and integument/mucosa. They believed that this focused classification system would allow clinicians to reduce adverse events better and thereby improve patient quality of life.

**Types of Adverse Events (Table 1)**

**Type A.** Augmented dose-related adverse events (type A) constitute the most common class of adverse events. These adverse events are related to the mechanisms of action of AEDs and are dose-dependent. Examples of common type A events associated with AEDs include drowsiness, diplopia, dizziness, and cognitive impairment.

Type A adverse events may be addressed in several ways. Administration of extended-release preparations may minimize side effects associated with peak serum drug concentrations. Use of a prodrug may optimize delivery patterns and...
minimize side effects. In addition, more frequent dosing and/or dose reduction may avoid type A adverse events.

Type B. Idiosyncratic events (type B) are uncommon and unrelated to a drug’s known mechanism of action. Idiosyncratic reactions are a major source of concern, because they encompass most life-threatening effects of AEDs. The most common type B events are cutaneous, hematologic, or hepatic.

Cutaneous hypersensitivity reactions have a yearly incidence of 1–2 cases per 100,000 patients treated. The AEDs most commonly associated with cutaneous side effects are carbamazepine, lamotrigine, phenytoin, and phenobarbital. Risk factors for cutaneous reactions include being very young or old, a history of drug reactions, exposure to certain human herpesvirus infections, and rapid titration. In addition, a genetic predisposition toward certain type B adverse events is evidenced by the association of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis with the genes for HLA-B*1502 in patients of Asian ancestry and HLA-A*3101 in Japanese and European populations.

For blood dyscrasias, the greatest concern is felbamate-associated aplastic anemia, which has an estimated incidence of 127 cases per 1 million patients per year. Patients with a history of cytopenia, previous autoimmune disorders, and a positive antinuclear antibody titer are at higher risk of developing this condition.

AEDs are the fourth most common drug type implicated in drug-induced acute hepatic necrosis. Use of felbamate, divalproex sodium, lamotrigine, or carbamazepine is commonly associated with hepatotoxicity. Among the newer AEDs, topiramate-associated acute angle-closure glaucoma, zonisamide-associated oligohidrosis, and retigabine-associated skin discoloration are further examples of type B events.

Given the low incidence of idiosyncratic adverse events, these occurrences are often not evident during initial drug studies with a limited number of exposed subjects. For example, to predict an adverse event with an incidence of 1:10,000 with a 95% risk, around 30,000 patients must be exposed to the drug of interest. Clinicians should be vigilant to recognize currently “unknown” adverse events when prescribing newer AEDs.

Type C. Chronic AED toxicities (type C) that are insidious in onset and related to the cumulative AED dose include weight gain (valproate, carbamazepine, gabapentin) or weight loss (felbamate, topiramate, zonisamide). Both enzyme-inducing and noninducing AEDs can impair bone health. Prevention with calcium and vitamin D supplementation, coupled with appropriate screening procedures, should be considered. An example of a serious, potentially irreversible type C effect is vigabatrin-induced visual-field loss.

Type D. Teratogenic and carcinogenic effects are examples of type D events. The risk of teratogenicity is increased with polytherapy, drug exposure during the first trimester, and use of certain AEDs (valproate, phenobarbital, topiramate). In utero exposure to valproate is associated with an increased risk of impaired cognitive function at 3 years of age.

Although initial studies of phenytoin and phenobarbital in animals resulted in concerns about carcinogenicity, results of clinical studies were inconclusive. Long-term treatment with phenytoin and carbamazepine has been implicated in the development of pseudolymphoma, which mimics malignant lymphoma both clinically and histologically and resolves after drug discontinuation.

Type E. Drug interactions constitute the fifth type of adverse events associated with AEDs. They largely can be minimized by careful drug selection, being continuously aware of what other drugs patients may be taking and their potential for drug interactions, avoiding polytherapy, and monitoring serum drug levels.

### TREATMENT OF STATUS EPILEPTICUS

Based on a presentation by David M. Treiman, MD, Newsome Chair in Epileptology and Director of the Epilepsy Center, Barrow Neurological Institute, Phoenix, Arizona.

Generalized convulsive status epilepticus (GCSE) is a relatively common, potentially life-threatening medical emergency. A commonly accepted definition of GCSE is more than 5 minutes of continuous seizure activity or two or more seizures with incomplete recovery to baseline. Approximately 5% of adults and 10%–25% of children with epilepsy have at least one episode of status epilepticus, whereas 13% of all patients with status epilepticus have recurrent episodes. The overall mortality related to status epilepticus is about 20%.

The initial steps in treating status epilepticus involve stabilization and supportive care, with emphasis on airway management. Once a patient is stabilized, overall goals of treatment include aborting ongoing seizures and preventing recurrence. Protocols for treating status epilepticus vary, but a widely used approach involves use of a benzodiazepine to achieve rapid, yet relatively short-lasting, control and of an AED such as intravenous fosphenytoin to achieve long-lasting control. Use of other newer AEDs such as levetiracetam or lacosamide for treating status epilepticus has been proposed but is currently off-label.

Benzodiazepines are most frequently
used for initial treatment of status epilepticus. Both diazepam and lorazepam work through the γ-aminobutyric acid (GABA) receptor and are effective. When compared with IV diazepam, which has a duration of action of 20–30 minutes, lorazepam has more favorable pharmacokinetics and a duration of action of more than 12 hours. Commonly reported adverse events include respiratory suppression, hypotension, and cardiac dysrhythmia.

A meta-analysis of eight small, observational studies investigating levetiracetam as a first-line, long-acting AED reported a mean efficacy of 68% in treating benzodiazepine-refractory status epilepticus. In a large, retrospective study, levetiracetam was associated with a higher rate of failure to control seizures (48%) than valproate (25%) when used as a second-line treatment for status epilepticus.

A 2013 review article estimated the overall efficacy of lacosamide among 136 patients with status epilepticus to be 56%. Sedation was the most common side effect; rare but serious adverse events included hypotension, atrioventricular block, and possible angioedema.

**Refractory Status Epilepticus**

Approximately 1 in 3 cases of status epilepticus cases becomes resistant to an adequate dose of benzodiazepine and initial AED therapy. There is little consensus on the drug of choice for treating refractory status epilepticus. In most cases, midazolam, propofol, or pentobarbital is administered. In one systematic review, pentobarbital titrated to background suppression was associated with a lower frequency of breakthrough seizures (4% vs 53%) when compared with midazolam or propofol titrated to seizure suppression; however, pentobarbital also was associated with a higher frequency of hypotension (76% vs 29%).

Treatment of status epilepticus is time-sensitive, and earlier treatment correlates with greater effectiveness. To minimize the time to treatment, much attention has been given to prehospital administration of parenteral therapy. The efficacy of both IV lorazepam and diazepam for status epilepticus is long established. In a double-blind, randomized clinical trial, intramuscular (IM) midazolam was not inferior to IV lorazepam when administered by paramedics for status epilepticus. On arrival at the hospital, patients receiving IM midazolam had a higher rate of seizure control (73% vs 63%) than did patients receiving IV lorazepam, with no significant difference in adverse effects.

The side effects of agents commonly used to treat status epilepticus are summarized in Table 2.

### TABLE 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Sedation, respiratory depression</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Cardiac dysrhythmia, hypotension, injection-site reaction</td>
</tr>
<tr>
<td>Valproate</td>
<td>Hypotension, pancreatitis (rare)</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Sedation, third-degree atrioventricular block, possible angioedema (rare)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Somnolence, postural dizziness, behavioral irritability</td>
</tr>
<tr>
<td>Propofol</td>
<td>Respiratory depression, hypotension</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Respiratory depression, hypotension</td>
</tr>
</tbody>
</table>

### Neurostimulation Devices

Based on a presentation by Robert S. Fisher, MD, PhD, Maslah Saul Professor of Neurology and Director, Stanford Epilepsy Center, Stanford University School of Medicine, Stanford, California.

As the search for novel epilepsy treatments continues, devices for this purpose are emerging as a strong and viable option. Neurostimulation devices have several advantages over drug therapy, including novel mechanisms of action, better compliance, and avoidance of systemic side effects. When compared with AEDs, neurostimulation devices offer a unique adverse-event profile.

### Vagus Nerve Stimulation (VNS)

In 1997, VNS was approved by the US Food and Drug Administration (FDA) for adjunctive treatment of partial-onset seizures that are refractory to AED treatment in patients over 12 years of age. The intraoperative complication of most concern with initial placement of the device is VNS-induced bradycardia (1:1,000 cases). In addition, cases of asystole have been reported. Caution should be observed to detect and promptly address asystole. Airway compromise secondary to tissue injury and vocal cord dysfunction are the main adverse events noted during the immediate postoperative period.

Typically, the device is activated 2–3 weeks after it is implanted. Laryngopharyngeal side effects causing voice alteration are the most common adverse effect (≤66%). Obstructive sleep apnea (OSA) may occur with epilepsy, and VNS may worsen preexisting OSA. To minimize the risk of worsening OSA, polysomnography should be considered before VNS implantation. Continuous positive airway pressure titration may be hindered by VNS. Strategies to address this problem include minimizing stimulation frequencies and prolonging off-time.

### Deep Brain Stimulation (DBS)

DBS is not yet approved in the United States for use in patients with epilepsy. Adverse effects related to DBS are due either to the neurosurgical procedure or to stimulation.

In the SANTE study, the most serious potential side effects of DBS for epilepsy were death, infection, hemorrhage, and status epilepticus. Three of 110 patients (2.7%) died during the 3-year follow-up. None of the deaths was associated with surgery or occurred postoperatively (up to 3 months after implantation). In two cases, sudden unexplained death in epilepsy (SUDEP) occurred at an estimated rate of 5 per 1,000 person-years, which is lower than the SUDEP rate among candidates for epilepsy surgery. Fourteen patients (12.7%) experienced infectious complications. Intracranial hemorrhage, experienced by five patients (4.5%), was asymptomatic. This complication rate was similar to that for movement disorders treated with DBS.
Side effects associated with stimulation include paresthesia (22.7%), depression (3.5%), seizures different from preoperative ones, and memory disorders.26

Responsive Neurostimulation (RNS)

The NeuroPace® RNS® system (NeuroPace, Inc; Mountain View, CA) was approved by the FDA in 2013. Heck and colleagues27 reported no difference in the rate of serious adverse events or neuropsychologic status among 97 subjects in the treatment group and 94 subjects in the sham group. The most common adverse events were implant-site pain and headache. In a pooled analysis of 256 patients, notable adverse events included infection at the implant site (6.3%), battery depletion (4.3%), device removal (4.1%), and intracranial hemorrhage unrelated to seizures (2.7%). The rates of hemorrhage and infection for RNS were comparable with those of intracranial electrode placement.28,29

The side-effect profile of currently available neurostimulation devices differs from that of AEDs. This distinction is particularly important for patients who are responding inadequately to drug therapy or for whom further dose escalation or addition of another AED to their regimen is limited because of side effects, the potential for drug interactions, or both. With the exception of VNS, experience with neuromodulation devices to treat epilepsy is limited. Future research should identify optimal neurostimulation parameters that would maximize benefits and minimize side effects.

Evaluation for Epilepsy Surgery and Risks of Resective Surgery

Based on a presentation by Mary L. Zupanc, MD, Clinical Professor of Pediatrics, University of California at Irvine, and Neurology Chair and Director, Pediatric Comprehensive Epilepsy Program, Children’s Hospital of Orange County, Irvine, California.

Drug-resistant epilepsy is defined as a failure of two well-tolerated, appropriately chosen AEDs to achieve sustained seizure freedom.30 Uncontrolled epilepsy has many unwanted consequences, including loss of independence and increased risk of injury, depression, and suicide. In addition, this phenomenon is related to an increase in long-term mortality.31 Resective surgery in a carefully selected, pharmacoresistant epilepsy patient offers a substantially better chance of seizure control than does an additional trial of drug therapy. The risks associated with epilepsy surgery can be broadly divided into those associated with evaluation and others associated with surgery itself.

Risks Associated with Evaluation for Epilepsy Surgery

Evaluation for epilepsy surgery should be performed in experienced epilepsy centers using a multidisciplinary team approach. In most cases, the evaluation includes video/electroencephalographic (EEG) monitoring, radiographic imaging (magnetic resonance imaging, single-photon emission computed tomography, positron emission tomography), magnetoencephalography, and neuropsychology. These noninvasive evaluations have relatively low risk when compared with the surgery itself.

The first step in considering epilepsy surgery often is video/EEG monitoring in a dedicated epilepsy monitoring unit (EMU). The goal of the EMU stay is to capture seizures, so withdrawal of AEDs and stimulus provocation, such as sleep deprivation, are frequently used. EMU admission has a favorable risk/benefit ratio. Although uncommon, the risk of seizure-related injuries due to falls, uncontrolled behavior, and status epilepticus does exist.32 These risks can be minimized by having an in-house registered technologist reviewing live data, training nursing staff, and having rescue medication readily available. Risks associated with neuroimaging usually are minimal and related to radiation exposure and sedation, especially in children and cognitively impaired individuals.

Complication rates increase with invasive monitoring. Subdural grids are associated with a complication rate of 5%–30%, and permanent morbidity occurs in 2%–5% of patients. Placement of depth electrodes usually is associated with a lower complication rate (1%–5%) when compared with the subdural grid. Complications include hemorrhage, infection, transient neurologic deficit, and electrode malfunction.33 Another review estimated a much lower risk associated with invasive monitoring, with 7.7% of patients experiencing minor complications and 0.6% having major complications.34

Risks Associated with Resective Epilepsy Surgery

Minor and major medical complications were reported in 5.1% and 1.5%, respectively, of patients undergoing focal epilepsy surgery.34 Most commonly, leakage of cerebrospinal fluid was involved. Minor neurologic complications occurred in 10.9% of patients who underwent resection and were twice as frequent in children than in adults (11.2% vs 5.5%, respectively). Minor visual-field defects were most common (12.9%). Major neurologic complications were noted among 4.7% of patients, with the most common being major visual-field defects (2.1%). Perioperative mortality was uncommon after epilepsy surgery, occurring in only 0.4% of temporal-lobe patients and 1.2% of those undergoing extratemporal surgery.

Alternative Treatment Modalities

Based on a presentation by Kristen L. Park, MD, Assistant Professor of Pediatrics and Neurology, University of Colorado School of Medicine, Denver, Colorado.

Alternative treatment measures offer a unique side-effect profile, compared with
that of AEDs or surgery, and should be discussed with patients before treatment is initiated.

**Dietary Modification**

Dietary therapy for epilepsy dates back to the pre-phenytoin era. In the ketogenic diet, 87%–90% of calories consumed are derived from fat.29 A ketogenic diet was the mainstay of treatment for epilepsy in the 1920s and 1930s. In general, it is relatively well tolerated. Early side effects associated with initiation of this diet include acidosis, hypoglycemia, gastrointestinal (GI) distress, dehydration, and lethargy.37

In most cases, these side effects are short-lasting and can be managed without discontinuation of the dietary regimen.

In patients who stay on a ketogenic diet for a prolonged period, both common and somewhat uncommon late-onset side effects may occur. Lack of weight gain and GI distress commonly occur during the late phase. Uncommon but worrisome side effects include the development of kidney stones, dyslipidemia, osteopenia, and growth impairment.37,38 The risk of developing kidney stones due to chronic acidosis, urine acidification, hypercalciuria, and hypocitraturia is approximately 6% on a ketogenic diet.

Urinary alkalinization by consuming citrate salts should be considered for high-risk populations, such as those who use carbonic anhydrase inhibitors concomitantly or who have a family history of renal stones.29 In addition, close monitoring, including laboratory tests, should be accomplished during the initiation phase and thereafter. Vitamins and mineral supplements should be prescribed to prevent known deficiencies.

**Hormonal Treatment**

Administration of adrenocorticotrophic hormone (ACTH) is a mainstay in treating infantile spasms.40 Although ACTH is a naturally occurring hormone, supplementation causes several important side effects. Commonly, irritability (37%–100%), hypertension (0%–37%), and cerebral atrophy (62%) may occur.41,42 The risk of infection via immunosuppression is probably most notable; it affects at least 1 in 10 patients on ACTH.43 Five deaths in 304 cases (1.6%) have been reported; in one study, two of three deaths from sepsis were directly attributable to treatment with ACTH.44,45 Systemic implementation of a vigorous monitoring protocol is important in mitigating these side effects. Close monitoring of blood pressure, electrolyte concentrations, and urinary glucose levels should be considered.

The role of sex steroids in the pathophysiology of catamenial epilepsy has been studied extensively. A protective role for progesterone in animal models is long established.46 The underlying mechanism for catamenial epilepsy in humans appears to be cyclic hormone fluctuations in progesterone levels. Results of a randomized, controlled trial showed that cyclic progesterone treatment in women with intractable epilepsy is ineffective. However, a post hoc analysis suggested that progesterone therapy may be effective in a subset of women with higher levels of perimenstrual seizure exacerbation.47 The potential side effects of progesterone treatment include irregular bleeding, a decrease in bone mineral density, and weight gain. However, the side-effect profile of cyclic progesterone therapy was comparable to that of placebo in one randomized clinical study.47

**REFERENCES**


