NEW ANTIEPILEPTIC DRUGS

The Food and Drug Administration (FDA) recently approved 3 new AEDs, and a fourth AED may be near approval. Lacosamide (LCS) is approved by the FDA for adjunctive treatment for partial-onset seizures. It has novel mechanisms of action, enhancing the slow inactivation of voltage-gated sodium channels and binding collapsing response mediator protein 2. LCS has a low potential for drug–drug interactions, is renally excreted, and is dosed twice daily. It does not affect plasma concentrations of concomitant AEDs. The most common adverse effects were dizziness, headache, diplopia, nausea, and vomiting, which were mild or moderate. Small increases in the PR interval were observed, but were not of clinical consequence. In a recent randomized, double-blinded, placebo-controlled trial of adjunctive treatment with LCS for medically refractory partial-onset seizures at doses of 400 to 600 mg daily, median reductions in seizure frequency were 37.3% for the 400 mg/day and 37.8% for the 600 mg/day groups. For secondarily generalized tonic-clonic seizures, median reductions in seizure frequency were more robust at 59.4% for the 400 mg/day group and 93.0% for the 600 mg/day groups. In addition, 8% of the patients in the 600 mg/day group became seizure-free.¹

Rufinamide (RUF) is FDA-approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). This new AED adds to the AEDs already used for LGS including valproic acid, lamotrigine, felbamate, and topiramate. Its mechanism of action includes limiting the excessive firing of sodium-dependent action potentials, but RUF also exhibits a broad spectrum of activity in animal models. It does not affect the plasma concentrations of other AEDs. The most frequent adverse effects were vomiting and somnolence. Status epilepticus has been reported but is uncommon (0.9%). A recent randomized, double-blinded, placebo-controlled trial of RUF in patients with LGS and generalized seizures, including atypical absence and tonic-atonic seizures, showed a 32.7% median percentage reduction in total seizures and a 42.5% median percentage reduction in tonic-atonic seizures. RUF also significantly reduced seizure severity.² RUF has been studied as adjunctive treatment for partial seizures in adults and adolescents. The most common adverse effects occurring with RUF in this study were dizziness, nausea, diplopia, and ataxia.³

Vigabatrin (VGB) was recently FDA-approved for treatment of refractory partial seizures and infantile spasms. Although it has been used in other countries for 20 years, the FDA withheld approval of VGB in 1997 pending further research on VGB-induced peripheral visual field defects. It has been shown to be highly effective in treating infantile spasms in patients with tuberous sclerosis and cryptogenic patients. The mechanism of action of VGB is an irreversible inhibition of GABA-transaminase responsible for the catabolism of GABA. Three specific side effects have been reported with VGB: intramyeloclinic edema in animals, psychosis (<1%), and...
VGB-induced peripheral visual field defects. Regarding visual field defects, the prevalence in adults has been estimated to range from 25% to 50% and consists of a bilateral concentric visual field defect causing constriction of visual fields. Recommendations include obtaining a baseline peripheral visual field test and every 6 months thereafter. The VGB-induced visual field defect is largely irreversible but not progressive. A previous multicenter, double-blind, placebo-controlled trial of adjunctive VGB therapy for medically refractory complex partial seizures demonstrated a 39.5% median seizure reduction and therapeutic success in 43% of patients (i.e., 50% reduction from baseline in mean monthly seizure frequency); 6.5% of patients became seizure-free. The most common adverse effects were somnolence, fatigue, and lightheadedness. Depression developed in 12% of patients. There were no significant cognitive adverse effects.4

Elicarbazepine acetate (ESL) is a new AED not yet approved by the FDA, which has demonstrated efficacy and safety in adjunctively treating adults with medically refractory partial-onset seizures. The mechanism of action is blockade of voltage-gated sodium channels. This medication may be more effective in patients who have failed other sodium channel blockers due to the development of pharmacoresistance from an alteration in sodium channel receptor protein subunits. There is a low incidence of drug interactions. The most common adverse effects were dizziness, headache, diplopia, somnolence, and nausea. Adults with medically refractory partial epilepsy treated adjunctively with ESL had a 43% responder rate, 45% median relative reduction in seizures, and 8% seizure freedom for patients on the highest dose (1,200 mg daily).5

**REFRACTORY EPILEPSY** A new definition of drug-resistant epilepsy has been proposed which is “defined as failure of adequate trials of 2 tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”6 In those medically refractory patients, additional treatments for epilepsy including resective epilepsy surgery, vagal nerve stimulation, ketogenic diet, modified Adkins diet, or low glycemic index diet are other potential options to consider. Of all of these other treatment options, epilepsy surgery has the highest overall rate of seizure freedom (approximately two-thirds).

A recent meta-analysis of surgical outcomes in lesional and nonlesional epilepsy provides guidance to the clinician in counseling the patient regarding the prognosis for seizure freedom after epilepsy surgery. In studies using MRI or histopathology to define the presence of a lesion, the proportion of patients seizure-free was 43% in nonlesional epilepsy and 68% in lesional epilepsy. Additionally, the odds of being seizure-free for 1 year or later after epilepsy surgery were 2.5–2.8 times higher in patients with a lesion defined on MRI or by histopathology than in nonlesional patients. Seizure freedom was higher in adults with temporal lobe epilepsy (45% nonlesional vs 72% lesional) than with extratemporal epilepsy (26% nonlesional vs 53% lesional).7

Another predictor of surgical outcome is the type of hippocampal sclerosis (HS) or lack of HS found on pathologic examination. Typical HS is defined as patterns of neuronal loss primarily involving both CA1 and CA4 subfields, while atypical HS involves focal or restricted neuronal loss (i.e., CA1 only or CA4 only). One recent study identified atypical HS cases from a large surgical series of adults who had undergone anterior temporal lobectomy and hippocampectomy for refractory temporal lobe epilepsy. The study correlated pathologic findings with clinical outcomes after epilepsy surgery, defined as seizure freedom at 2 years follow-up. Atypical patterns of HS were seen in 30% of patients (including end folium sclerosis, CA1 predominant pattern, and indeterminate HS). Those with the poorest outcomes were those with the CA1 subtype (33% seizure freedom) and with absence of HS (44% seizure freedom). Those with the best outcomes included those with end folium sclerosis (100% seizure freedom), total HS (i.e., CA1–CA4 loss, 71% seizure freedom), classic HS (i.e., sparing CA2, 69% seizure freedom).8

The postoperative EEG has been used as a predictor of seizure freedom after epilepsy surgery. A recent meta-analysis pooled data from 18 published studies \((n = 1,345)\) and 2 unpublished data sets \((n = 503)\) of postsurgical patients with interictal epileptiform discharges (IEDs) on postoperative EEGs and seizure outcome. The postoperative EEGs in the published studies were performed at a mean of 6.3 months after surgery \((\text{SD}, 3.1 \text{ months})\) and in the unpublished datasets, at 3 and 12 months after surgery. Mean prevalence of IEDs on postoperative EEGs was
31.5%. Presence of postoperative IEDs was associated with a higher risk of seizures (odds ratio [OR] 3.3). An abnormal postoperative EEG had a modest positive predictive value (52%) but a very good negative predictive value (71%). Therefore, the absence of IEDs on a postoperative EEG was associated with a high chance of good seizure outcome.9

**NEW DEVICE TRIALS** Vagal nerve stimulation was FDA-approved in 1997 for the treatment of medically refractory epilepsy (both partial and generalized). Potential new stimulation treatments (i.e., responsive neurostimulation [RNS] and deep brain stimulation [DBS]) have been developed for epilepsy.10

RNS (NeuroPace, Inc.) is an investigational device implanted in the calvarium with detection/stimulation electrodes implanted on the cortical surface or within deeper structures (e.g., hippocampus) via depth electrodes. The location of the seizure onset zone has to be precisely known, and may include 2 separate foci. The device detects ictal discharges and applies brief electrical stimulation to attempt termination of the discharges. An unpublished randomized, double-blind, sham-controlled clinical trial involving 191 patients demonstrated safety and efficacy. There were no serious unanticipated adverse events. Anticipated adverse events were infection, skin erosion, increased seizures, falling, and the need for cranial reconstruction.10

DBS (Medtronic, Inc.) is another investigational device, already approved for the treatment of PD and essential tremor. This device was examined in epilepsy using 2 4-contact deep brain electrodes placed in both anterior nuclei of the thalamus designed to provide scheduled stimulation to that region. The pulse generator is implanted below the clavicle. The mechanism of action is thought to relate to stimulation of the limbic system, but the precise mechanism of action is unknown.10 Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy trial was a prospective, randomized, double-blind trial involving 110 patients with medically refractory partial epilepsy implanted with a bilateral DBS device. Seizure frequency and severity were reduced, and quality of life was improved. The proportion of seizure-free patients was 12.7% for at least 6 months in open-label long-term follow-up. Adverse effects overall included paresthesias (18.2%), implant site pain (10.9%), implant site infection (9.1%), hemorrhages (4.5%), infection (12.7%), and status epilepticus (4.5%). There was a statistically significant difference between patients in the active vs control group regarding the proportion of patients who reported depression or memory impairment (14.8% vs 1.8%, \( p = 0.02; 13.0\% \text{ vs } 1.8\%, \ p = 0.03 \), respectively). There were 5 deaths, none of which were thought to be related to the device.11 The use of DBS in the generalized epilepsies is unknown.

When to consider the use of the above devices and the appropriate subjects in whom to consider device usage will need to be delineated in the future.

**PSYCHIATRIC ISSUES** Depression is common among patients with epilepsy and the association may be bidirectional. Patients with epilepsy have an increased incidence of depression, and those with depressive disorder are at risk for a more severe seizure disorder. In addition, suicidality, depression, and epilepsy may share common pathophysiology; however, the mechanisms relating epilepsy and AEDs to depression and suicidality are not yet understood.12,13 In January 2008, the FDA issued an alert regarding the increased risk of suicidality (1.8-fold increased risk) in patients on all AEDs for 3 different indications, including epilepsy. The alert was based on a meta-analysis of 199 clinical trials of 11 AEDs involving 43,892 patients treated for epilepsy, psychiatric conditions, and pain. AEDs were associated with a greater risk of suicidality in epilepsy (OR 3.53) than in psychiatric disorders (OR 1.51) or other disorders (OR 1.87).14 The FDA accepted a recommendation from the advisory board to not issue a black box warning; however, the board cautioned that all AEDs increase the risk of suicidality, and recommended that a handout describing this risk should be given to patients along with the prescribed AED. Concerns have been raised about the FDA analyses and interpretation.14 First, trials without suicidality were excluded from the analysis, leaving only 33 out of 199 trials in the main analysis. Additionally, the data on suicidality were not prospectively and systematically collected, thereby increasing the risk of reporting bias. Also, the alert treats suicidality as a class effect rather than applying it to select AEDs. Eight out of 11 AEDs showed increased risk of suicidality; however, statistical significance was only achieved with lamotrigine and topiramate. In fact, carbamazepine and valproate had a nonsignificant protective effect on suicidality. Finally, the risk of uncontrolled seizures needs to be balanced against the risk of suicidality.
The risk of increased suicidality may not have a class effect with AEDs, but rather a group effect. A recent case-control study of 44,300 patients with epilepsy treated with AEDs examined the risk of suicidality in patients on 4 different groups of AEDs. Newer AEDs with a high potential of causing depression (levetiracetam, tiagabine, topiramate, and vigabatrin) were associated with a 3-fold risk of self-harm/suicidal behavior as compared with no AED use. Other classes of AEDs including barbiturates, conventional AEDs, or low-risk newer AEDs were not associated with increased risk.15

Finally, contrary to the findings reported by the FDA at the advisory committee meeting in July 2008, a recent cohort study of 5.13 million patients with or without epilepsy, bipolar disorder, depression, or the use of AEDs found that the use of AEDs was not associated with an increased risk of suicide-related events among patients with epilepsy, but was associated with increased risk in patients with depression and those without epilepsy, depression, or bipolar disorder.16

PREGNANCY ISSUES Management issues related to caring for women with epilepsy (WWE) are challenging; however, 3 recent AAN practice parameter updates were published in 2009.17–19 These articles addressed teratogenesis, perinatal outcomes, obstetric complications, change in seizure frequency, use of vitamin K, folic acid, blood levels of AEDs, and breastfeeding. In terms of teratogenesis, one important finding was that it was deemed highly probable that intrauterine first-trimester valproate exposure has higher risk of major congenital malformations compared to carbamazepine and possibly compared to phenytoin or lamotrigine. AED polytherapy should also be avoided during the first trimester.18 WWE who smoke during pregnancy possibly have a substantially increased risk of premature contractions and premature labor and delivery. Also, WWE who have been seizure-free for at least 9 months prior to pregnancy probably have a high likelihood (84%–92%) of remaining seizure-free during pregnancy.17

In terms of cognitive outcomes in children of WWE treated with AEDs during pregnancy, recommendations include avoiding valproate and AED polytherapy (Level B), and avoiding phenytoin and phenobarbital (Level C) during pregnancy.18 A study since the guidelines examined IQs of mother/child pairs from the United States and United Kingdom; it found that fetal valproate exposure was significantly associated with a lower IQ (92) at 3 years of age as compared to carbamazepine (98; \(p = 0.04\)), lamotrigine (101; \(p = 0.009\)), and phenytoin (99; \(p = 0.04\)).20

Important points to remember about managing AEDs in WWE of childbearing potential include using monotherapy at the lowest doses when possible, making changes in AEDs before pregnancy, avoiding valproate if possible and using valproate at the lowest possible doses only if the benefits clearly outweigh the risks, monitoring AED levels throughout pregnancy and adjusting as needed, and administering at least 0.4 mg of folate before conception, and additional folate during pregnancy. It is unclear if higher doses provide greater benefit.19

DISCUSSION

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