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Advancements in the Treatment of Epilepsy

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Abstract

Diagnostic tools and treatment options for epilepsy have expanded in recent years. Imaging techniques once confined to research laboratories are now routinely used for clinical purposes. Medications that were unavailable a few years ago are now first-line agents. Patients with refractory seizures push for earlier surgical intervention, consider treatment with medical devices, and actively seek nonpharmacologic alternatives. We review some of these recent advances in the management of epilepsy.

EEG/fMRI: concurrent electroencephalography and functional magnetic resonance imaging

MEG: magnetoencephalography

PET: positron emission tomography

INTRODUCTION

Epilepsy, operationally defined as having or being at risk of having recurrent unprovoked seizures, affects an estimated 1.1–2.3 million people in the United States. The diagnosis of epilepsy confers a greater likelihood of injury and sudden unexplained death, as well as a loss of independence and perceived stigmatization. Patients with epilepsy report poorer overall health-related quality of life, and exhibit activity limitations, psychiatric comorbidities, increased unemployment rates, and lower educational attainment and income than those without seizures (1–3). The goal of treatment is to attain seizure freedom without side effects and return patients to normal, healthy lifestyles.

The past several years have brought new diagnostic aids, medication options, and devices for the treatment of seizures. It is not just the armamentarium that has changed but also the way it is used. Imaging techniques once confined to research laboratories are now routinely used in clinics. Medications that were new and unfamiliar a few years ago are now first-line treatments. Patients and physicians push for earlier surgical intervention to treat refractory seizures and actively seek alternatives in diets and implantable devices. This is an exciting time in epileptology, and below we share some of the recent developments.

DIAGNOSIS

Successful treatment requires a precise diagnosis. Recent advances in imaging technology help to identify subtle lesions that may represent epileptogenic foci. Magnetic resonance imaging, for example, now with phased array surface coils (PA MRI) and field strengths of 3 Tesla (3T), has signal-to-noise ratios 6 to 8 times that of conventional 1.5T scans. PA MRI better defines the gray-white junction and creates a more uniform signal intensity of normal cortex, allowing better visualization of abnormalities such as cortical dysplasias. A study of 3T PA MRI detected brain lesions in 65% of patients with focal epilepsy and reportedly normal standard 1.5T scans. In addition, in 33% of patients with lesions revealed by 1.5T scans, abnormalities were better defined on the 3T images (4). A greater ability to detect or characterize subtle lesions may alter treatment strategies.

Although still largely a research tool, concurrent EEG and functional MRI (EEG/fMRI) is now used for clinical purposes at some centers. Functional MRI uses blood oxygenation level dependent (BOLD) pulse sequences, which map cerebral blood flow with millisecond temporal resolution (5). With simultaneous EEG, it is possible to correlate areas of altered blood flow with the occurrence of interictal or ictal discharges (6). This may help to identify foci or networks that are functionally abnormal during spikes and sharp waves, although they may not be recognized as structural lesions on standard MRI scans (7).

Whereas EEG detects electrical potentials, magnetoencephalography (MEG) senses magnetic fields created by activity of apical dendrites, providing a novel technique for the localization of ictal and interictal epileptiform activity (8). An advantage of MEG is the relative lack of signal attenuation by the skull and scalp compared with EEG. MEG, however, only measures those fields tangential to the scalp. It is most sensitive to discharges in the neocortical convexities and relatively poor at detecting more mesial sources. Although MEG may identify epileptiform discharges missed by routine scalp EEG, its utility continues to be debated.

Nuclear imaging modalities have also gained popularity, as a growing number of centers now have access to this technology. Positron emission tomography (PET) scanning, for example, is commonly used to aid in localization of seizure foci. Interictal injection with a radio-labeled tracer, most often fluorodeoxyglucose-18 (FDG), may reveal regions of cellular hypometabolism that signify underlying abnormal, potentially epileptogenic, brain tissue. In contrast, ictal

single-photon emission computed tomography (SPECT) uses injection of a technetium-99-labeled tracer at the start of a seizure. This lipophilic tracer is 90% extracted on first pass into lipid-rich tissue including brain in proportion to local perfusion. Uptake of the tracer by a brain region with actively firing cells, evident on the scan as a focal area of hyperperfusion, may indicate the region of seizure onset. SISCOM, a technique in which SPECT images obtained during ictal and interictal periods are subtracted and coregistered with MRI, further improves localization. The utility of ictal SPECT may be limited, however, by the logistics of appropriately timing the injection and by the sensitivity of various tracers. Nevertheless, this method is often useful in settings in which the MRI is unrevealing (9).

The availability of minimally invasive techniques provides additional tools for seizure localization. Older methods for focus identification, such as foramen ovale electrodes and epidural pegs, have seen resurgence. Foramen ovale electrodes are placed percutaneously through the foramen so that they lie along the inferomesial aspect of the temporal lobe. This allows recordings to be obtained from deep medial structures without the need for surgical placement of depth electrodes into brain tissue. Epidural pegs provide a method for obtaining recordings over the convexities through small burr holes, which eliminates the muscle artifact that may contaminate scalp leads. This technique may be used to plan for the optimal placement of grids or strips, or it may potentially obviate the need for further invasive recording. These methods, either separately or in conjunction, have been helpful in many cases in which scalp EEG data have been inconclusive (8).

MEDICATIONS

Historically, treatment options for epilepsy have been limited. Major pharmacologic options included carbamazepine, phenobarbital, phenytoin, primidone, ethosuximide, and valproic acid. Though often effective, relatively affordable, and familiar, these older medications carry the risks of hepatic dysfunction, drug interactions, and other significant side effects. Between 1978, when valproic acid was introduced, and 1993, when felbamate was approved, no new anticonvulsants were approved by the US Food and Drug Administration (FDA). In contrast, in the past decade, eight new anticonvulsants have been approved in the United States. These agents typically offer equal efficacy but may have fewer adverse effects and drug interactions than the older generation of medications (9a, 9b). Newer anticonvulsants (listed in reverse order of FDA approval) include pregabalin, oxcarbazepine, zonisamide, levetiracetam, tiagabine, topiramate, lamotrigine, gabapentin, and felbamate.

What may be more striking than the number of new medications, however, is how quickly these drugs have become first-line therapies. In 2005, Karceski et al. (10) surveyed 43 epileptologists regarding their prescribing practices. Lamotrigine was considered a first-line treatment for idiopathic primary generalized tonic-clonic, absence, simple partial, and secondarily generalized tonic-clonic seizures, and it was the treatment of choice for complex partial seizures. Topiramate was a first-line medication for treatment of idiopathic primary generalized tonic-clonic seizures. Oxcarbazepine had become the treatment of choice for simple partial and secondarily generalized tonic-clonic seizures, and levetiracetam was also an acceptable initial option for treatment of these partial-onset seizure types. The survey also marked a shift in thinking from as little as five years earlier, when lamotrigine, topiramate, and levetiracetam were often considered to be second-line agents.

With new treatments, however, often comes confusion and a lack of consensus regarding prescribing practices. The American Academy of Neurology (AAN) and American Epilepsy Society (AES) have published recommendations for use of many of the newer

SPECT: single-photon emission computed tomography

AAN: American Academy of Neurology

AES: American Epilepsy Society

medications (11–13). The choice in a given patient, however, continues to be guided by seizure type, patient characteristics and side effect profiles. Below we summarize the indications, associated adverse events, mechanisms and pharmacokinetic properties of the more recently approved anticonvulsants. These drugs are discussed in the reverse order of their approval in the United States (**Table 2**).

Pregabalin

Pregabalin is the newest anticonvulsant. It is structurally similar to gabapentin but has a slightly longer half-life. Although structurally related to gamma-amino-butyric acid (GABA), the drug does not have GABA-ergic activity. Pregabalin binds to the alpha$_2$-delta subunit of voltage-gated calcium channels, reducing calcium influx and thereby decreasing release of several neurotransmitters, including glutamate.

Clinical experience with pregabalin is limited because it was only approved by the FDA in June 2005. The drug is currently indicated for adjunctive treatment of partial-onset seizures in adults, on the basis of studies demonstrating seizure frequency reduction up to 47.8%–54% in this population (14–16). Our experience suggests that pregabalin may worsen idiopathic generalized epilepsy.

Initial studies suggest a few potential advantages of pregabalin. The drug is reasonably well tolerated at starting doses up to 600 mg/day (14), although many patients complain of dizziness at initial doses above 100–150 mg/day. In urgent situations, steady state can be achieved in as little as 48 h. Pregabalin is renally excreted, so it is suitable for patients with hepatic disease. A lack of hepatic enzyme induction or inhibition is also advantageous in that the drug poses little risk for interaction with other medications.

In addition, pregabalin is generally safe. Serious adverse events included a maculopapular rash in one patient, which resolved after discontinuation of the drug, as well as isolated reports of cholestatic jaundice. There is no known association of pregabalin with cardiovascular dysfunction; cases of peripheral edema have been reported, but detailed cardiac testing of those patients has not been described (16). These adverse events are typically dose-related. They tend to occur shortly after the medication is started, often within one week of initiation, and are generally self-limited, even if the drug is continued. Weight gain has been reported in a substantial fraction of patients chronically treated with pregabalin.

Oxcarbazepine

Oxcarbazepine is FDA approved for use as monotherapy and adjunctive treatment in children (17, 18) and adults (19–21) with partial seizures. Oxcarbazepine has rapidly become a first-line agent for those with partial seizures and is often preferred in patients with psychiatric comorbidities because of its apparent mood-stabilizing effects. Studies comparing oxcarbazepine monotherapy with phenytoin (22, 23), valproic acid (24), and carbamazepine (25) demonstrate equivalent rates of seizure freedom in populations with both partial-onset and primary generalized tonic-clonic seizures. The AAN/AES guidelines suggest that although oxcarbazepine monotherapy is appropriate inpopulations that include patients with newly diagnosed partial and/or generalized seizure disorders, there is insufficient evidence to determine efficacy for those with primary generalized seizures alone.

The drug was developed as a structural variant of carbamazepine, designed to eliminate the carbamazepine epoxide metabolite thought to cause side effects. Carbamazepine and oxcarbazepine are distinct drugs, with separate metabolic pathways and somewhat different modes of action and side effect profiles (26).

Oxcarbazepine exerts much of its effect through 10-monohydroxy metabolite (MHD), an active metabolite not present

with carbamazepine. Oxcarbazepine blocks voltage-sensitive sodium channels, stabilizing neuronal membranes and inhibiting repetitive firing at lower concentrations than that required by carbamazepine. Increased potassium conductance and modulation of voltage-activated calcium channels may also play a role in its anticonvulsant effect. The interaction occurs at the N-, P-, and R-type calcium channels rather than the L-type channels affected by carbamazepine.

Metabolites of oxcarbazepine, unlike those of carbamazepine, are excreted in the urine, so dosing must be adjusted in patients with renal disease. The effect on P-450 hepatic enzyme subtypes is minimal, causing only limited drug interactions (see **Table 1**). Of particular concern, however, is the induction of CYP3A4 and CYP3A5 enzymes, which may reduce concentrations of oral contraceptives. Nevertheless, oxcarbazepine is associated with fewer hepatic enzyme and drug interactions than carbamazepine or other older agents.

In general, oxcarbazepine carries lower risk of adverse events than the prior generation of anticonvulsants. Clinical experience, however, suggests that oxcarbazepine does have adverse effects, often causing headache (26a). Side effects are typically dose-related, and slow titration is recommended to minimize risk. Serious side effects include rash and hyponatremia. Rash, when it occurs, generally appears within one month of use. Because cross reactivity of allergic reactions occurs in up to 27% of patients, those with exfoliative dermatitis from use of carbamazepine should not receive oxcarbazepine. The incidence of hyponatremia is greater with oxcarbazepine than with carbamazepine, and is of particular concern in the elderly and those on sodium-wasting agents. The hyponatremia is most often chronic and asymptomatic, developing gradually over the first six weeks of treatment. Sodium levels typically normalize with reduction or cessation of oxcarbazepine treatment and may respond to fluid restriction. Sodium levels should be obtained prior to initiating treatment and should be monitored during the first three months of use in those at risk. No consensus exists as to a threshold for discontinuation of the drug, although levels less than 128 mEq/L and a continuing downward trend are worrisome.

Zonisamide

Zonisamide is FDA approved for adjunctive treatment of partial seizures in patients 16 years of age and older (27, 28). Although some studies demonstrate efficacy in children with partial and generalized epilepsy (29), including infantile spasms (30) and myoclonic seizures (31), AAN/AES guidelines caution that there is insufficient evidence to recommend use of zonisamide in children or patients with primary generalized seizures. Further data are also required to confirm utility as monotherapy, although zonisamide is often used as such for treatment of partial seizures in adults.

Zonisamide contains a sulfonamide chemical structure, precluding its use in patients with a sulfa allergy. It produces its anticonvulsant effect by blockade of sodium and T-type calcium channels, thereby stabilizing neuronal membranes. Zonisamide also has weak carbonic anhydrase–inhibiting activity, but this does not appear to substantially contribute to its antiseizure properties.

The medication offers several advantages. First, although the drug undergoes primarily hepatic elimination, it does not alter hepatic metabolism. Hence, zonisamide has fewer drug interactions than older medications do. Second, estimates of the half-life are as great as 24–60 h. This long duration enables once-per-day administration, improving compliance. Third, the drug may cause weight loss, as opposed to weight gain caused by many alternative medications. The drug is now available as a generic formulation, potentially making it more affordable. Finally, open-label data and anecdotal experience suggest that zonisamide may have antimigraine properties, providing a reasonable option for those with comorbid headaches.

Table 1 Properties of new anticonvulsants[a]

Medication	Half-life	Mechanism	Clearance	Hepatic enzyme effects	Notable drug interactions	Cautions
Pregabalin	6 h	Likely related to effects at voltage-gated calcium channels	Renal	None	None	None
Oxcarbazepine	4–9 h	Sodium channel blockade; possible contribution of effect on potassium and calcium channels	Renal and hepatic	Minimal induction and inhibition of subtypes	Decreases levels of: carbamazepine dihydropyridines oral contraceptives lamotrigine (?) Increases levels of: phenobarbital phenytoin MHD decreased by: verapamil carbamazepine phenobarbital phenytoin valproate	Cross reactivity of hypersensitivity to carbamazepine; risk of hyponatremia
Zonisamide	24–60 h	Sodium and calcium channel blockade	Hepatic more than Renal	None	Levels decreased by hepatic enzyme-inducing medications: carbamazepine phenytoin phenobarbital	Do not use if patient has sulfa allergy or history of nephrolithiasis
Levetiracetam	6–8 h	Binding at SV2A synaptic vesicle protein and high-voltage calcium channels, modulation of GABA and glycine receptors	Renal, hydrolysis	None	None	Risk of psychiatric side effects
Tiagabine	4–9 h	Inhibition of GABA reuptake	Hepatic	None	Levels decreased by hepatic enzyme-inducing medications: carbamazepine phenytoin phenobarbital	Risk of "spike-wave" stupor

Table 1 (*Continued*)

Medication	Half-life	Mechanism	Clearance	Hepatic enzyme effects	Notable drug interactions	Cautions
Topiramate	15–23 h	Blockade of voltage-dependent sodium channels, inhibition of carbonic anhydrase, antagonizes AMPA/kainate glutamate receptors, and modulates GABAa-mediated chloride activity	Renal more than hepatic	Induction and inhibition	Decreases levels of: oral contraceptives (no effect with topiramate doses <200 mg/d) lithium digoxin valproate Increases levels of: haloperidol phenytoin Levels decreased by hepatic enzyme-inducing medications: carbamazepine phenytoin valproate	Do not use if patient has sulfa allergy or history of nephrolithiasis Potential side effects include cognitive impairment, open-angle glaucoma, metabolic acidosis, weight loss
Lamotrigine	15–35 h	Likely related to inhibition of voltage-sensitive sodium channels	Hepatic	Minimal induction	Decreases levels of: valproate oral contraceptives Levels decreased by: phenytoin oral contraceptives Levels increased by: valproate	Risk of rash, particularly with concurrent use of valproate
Gabapentin	4–6 h	Unknown; may be related to voltage-activated calcium channels	Renal	None	Levels decreased by: Maalox-TC	None
Felbamate	20–23 h	Antagonist of glycine recognition site of NMDA receptor	Renal and hepatic	Induction and inhibition	Increases levels of: valproate phenytoin carbamazepine epoxide[b] phenobarbital Decreases levels of: carbamazepine oral contraceptives Levels increased by: valproate Levels decreased by: phenytoin carbamazepine	Risk of aplastic anemia, hepatic failure, and rash

[a]Abbreviations: MHD, 10-monohydroxy metabolite; GABA, gamma-amino-butyric acid.
[b]Elevated levels of the epoxide may cause toxicity.

Table 2 FDA-approved indications for new anticonvulsants

Medication	Use in partial seizures (simple, complex, secondarily generalized)—adjunctive	Use in partial seizures (simple, complex, secondarily generalized)—monotherapy	Use in absence seizures—monotherapy	Use in primary generalized tonic-clonic seizures—adjunctive	Use in primary generalized tonic-clonic seizures—monotherapy	Use in Lennox-Gastaut (tonic/atonic and tonic-clonic seizures)—adjunctive	Use in myoclonic seizures of JME[a]—adjunctive
pregabalin	adults						
oxcarbazepine	adults, children ≥ 2 years of age	adults, children ≥4 years of age					
zonisamide	adults						
levetiracetam	adults, children ≥ 4 years of age			adults, children ≥6 years of age			adults, children ≥12 years of age
tiagabine	adults, children ≥ 12 years of age						
topiramate	adults, children ≥ 2 years of age	adults[b], children ≥10 years of age[b]		adults, children ≥2 years of age	adults[b], children ≥10 years of age[b]	adults, children ≥2 years of age	
lamotrigine	adults, children ≥ 2 years of age	adults[c],(d)	(children)	adults, children ≥2 years of age	(adults[d])	adults, children ≥2 years of age	
gabapentin	adults, children ≥ 3 years of age, ≥12 years of age if secondary generalization	(adults and adolescents[b])					
felbamate[e]	adults	adults				adults, children ≥2 years of age (≥4 years per AAN)	

[a]Juvenile myoclonic epilepsy.
[b]For initial monotherapy.
[c]Only FDA approved for conversion to monotherapy in patients receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate.
[d]For initial monotherapy of partial and mixed (partial and generalized) seizure types.
[e]According to AAN guidelines, children with partial or generalized epilepsies and patients with Lennox-Gastaut syndrome under age 4 years who are unresponsive or intolerant to first-line agents may also consider use in certain situations when risk/benefit ratio unclear; data limited.
( ) = Appropriate for use based on AAN/AES guidelines but not FDA approved for this indication.

Adverse reactions are typically dose-dependent. Most commonly, patients report cognitive clouding. Nephrolithiasis may be associated with zonisamide use. Concomitant administration of other carbonic anhydrase inhibitors, such as acetazolamide or topiramate, may increase the risk for renal stone formation. The drug should be avoided in patients with a history of nephrolithiasis, and those taking the medication should be encouraged to drink sufficient amounts of water. Another serious risk is that of hypohydrosis with resultant hyperthermia, a rare side effect that occurs primarily in children. Zonisamide may also cause a rash and, rarely, Stevens-Johnson syndrome.

Levetiracetam

Levetiracetam is indicated for adjunctive treatment of partial epilepsy in adults (32, 33) and children aged 4 years and older (34, 35) with refractory seizures. Data also support conversion to monotherapy in patients with refractory partial epilepsy (36). In clinical practice, levetiracetam is often prescribed as monotherapy on the basis of its success as an add-on treatment. Use as monotherapy, however, is not currently FDA approved or AAN/AES recommended owing to insufficient data regarding efficacy. Levetiracetam is indicated for add-on therapy of myoclonic seizures in patients aged 12 years and older with juvenile myoclonic epilepsy (37, 38). Most recently, levetiracetam also received FDA approval for adjunctive treatment of primary generalized tonic-clonic seizures in adults and children aged 6 years and older with idiopathic generalized epilepsy.

Levetiracetam has rapidly gained popularity owing to its ease of administration. Taken orally twice per day, the drug is at steady state within three doses and can be rapidly titrated to therapeutic levels. A new intravenous formulation is available, indicated for adjunctive treatment of partial seizures in adults and as an alternative when oral administration is temporarily prohibited. Access to intravenous levetiracetam may increase its off-label use in acute situations, as case reports have indicated benefit in status epilepticus (39). Because it has no hepatic effects, levetiracetam is a first-line medication for those with liver dysfunction. The lack of hepatic effects also minimizes the potential for drug interactions, making levetiracetam a preferred agent for patients taking multiple medications, such as those who are elderly, HIV-positive, or on chemotherapy.

Levetiracetam's mechanism of action is unknown. It does not act at the receptors typically affected by antiepileptic medications. The drug binds to a presynaptic protein, SV2A, located on synaptic vesicles. The protein is probably involved in vesicle fusion to the presynaptic membrane and may reduce neurotransmitter release, but the relationships between SV2A binding and anticonvulsant properties are unclear. The anticonvulsant effect of levetiracetam may also be related to other atypical mechanisms, such as reduction of current through neuron-specific high voltage–activated calcium channels and modulation of the effects of zinc and beta-carbolines on inhibitory GABAa and glycine receptors.

No serious adverse reactions to levetiracetam have been reported. Common side effects include irritability and behavioral changes, and in some patients these adverse effects may be treatment limiting.

Levetiracetam has a particularly wide therapeutic range. Hence, levetiracetam levels are typically not clinically useful, except to determine compliance.

Tiagabine

Tiagabine exerts its anticonvulsant effect via a novel mechanism involving inhibition of GABA reuptake into neurons and glia. The medication is indicated as adjunctive therapy in patients aged 12 years and older for the treatment of partial seizures (40–42). However, little evidence supports

its use as monotherapy, in younger children, or for treatment of generalized-onset seizures.

There are four reasons why tiagabine is not commonly prescribed. First, the drug may not be as effective as others (40–42). Although it is not possible to directly compare trials owing to differences in study populations, dosages, and design, tiagabine seems to have somewhat lower responder rates than the other newer medications. Second, tiagabine undergoes hepatic elimination. This makes it a less desirable option for patients with liver disease. Tiagabine itself does not alter hepatic enzyme function, but its metabolism may be affected by enzyme inducers and inhibitors, which raises concern about drug interactions. Third, the medication takes several weeks to titrate to a therapeutic dosage. Fourth and most important, the drug carries the potential for serious side effects.

Use of tiagabine may cause a paradoxical increase in seizure activity. New seizure types may develop, along with an increased incidence of nonconvulsive status epilepticus (NCSE) or so-called spike-wave stupor. In a recent retrospective study of patients with refractory partial seizures, 7.8% of those treated with tiagabine experienced episodes of NCSE, confirmed by spike- and polyspike-wave discharges on EEG that resolved after discontinuation of the drug (43). In fact, the FDA has issued a safety alert in response to reports of new-onset seizures and status epilepticus in patients without epilepsy who were prescribed tiagabine for other indications. Some patients on tiagabine have developed an encephalopathy that is probably related to seizure activity. These effects do not appear to be dose-related and may develop more than three months after treatment is initiated. Assertions that frontal lobe epilepsy increases these risks are controversial and not well documented in the literature. The mechanism for development of encephalopathy is uncertain, but is probably related to GABA-mediated pathways.

Topiramate

Topiramate blocks voltage-dependent sodium channels, inhibits carbonic anhydrase, acts as an antagonist of 2-(aminomethyl) phenylacetic acid (AMPA)/kainate glutamate receptors, and modulates GABAa-mediated chloride activity. The mode of action underlying its anticonvulsant effect, however, remains unknown.

Topiramate is approved by the FDA as initial monotherapy for partial-onset or primary generalized tonic-clonic seizures in patients 10 years of age and older. Studies supporting this indication have shown that patients with partial (44) and primary generalized tonic-clonic (45) seizures randomized to higher doses of topiramate had significantly greater rates of seizure freedom than those on lower doses of the drug. Topiramate is also approved as adjunctive therapy for patients 2 years of age and older with refractory partial seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. Randomized double-blind add-on studies support its use in these populations, demonstrating greater reduction in partial-onset seizures (46), primary generalized tonic-clonic seizures (47), and drop attacks (48) compared to placebo. Efficacy and safety of conversion from another antiepileptic medication to topiramate monotherapy have not been adequately studied.

Topiramate is advantageous in its broad range of efficacy. It may also help prevent migraines and is at times favored for patients with comorbid headaches and seizures. The medication also has mood-stabilizing effects. Topiramate may be less preferable as a first-line agent, however, owing to its long list of potential side effects.

Common adverse reactions to topiramate include cognitive dysfunction, often associated with word-finding difficulties. Paresthesias of fingertips and toes may occur shortly after the medication is initiated, probably related to carbonic anhydrase inhibition. Paresthesias are typically self-limited, resolving

over weeks. If bothersome or prolonged, isolated case reports indicate that potassium supplementation at 20–40 mEq per day may be helpful (49), although no placebo-controlled trials have been published to date. Serious side effects include nephrolithiasis in 1%–5% of patients, and the drug should be avoided in those with a history of renal stones. The acute onset of diminished visual acuity or ocular pain should prompt concern about open-angle glaucoma associated with topiramate use, typically occurring within the first month of treatment. Other possible side effects include hypohydrosis, particularly in children, and a hyperchloremic, nonanion gap metabolic acidosis. Transient but significant weight loss may also occur. The risk of the above side effects appears to be dose-related and may be minimized by slow titration. Despite the mood-stabilizing properties of topiramate, there are reports of rare topiramate-induced suicidality. In addition, the drug is a sulfa derivative and is contraindicated in patients with sulfa allergies.

Lamotrigine

Lamotrigine has rapidly become a first-line agent for many seizure types and patient populations. It is currently FDA approved as adjunctive therapy for partial (50–53) and primary generalized tonic-clonic (54) seizures, as well as generalized seizures of Lennox-Gastaut syndrome (55), in patients 2 years of age and older. Lamotrigine is also indicated for conversion to monotherapy in adults with partial seizures receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate (56). Conversion to monotherapy from other anticonvulsants or from multiple anticonvulsants is not currently approved. Nor is the drug approved for initial monotherapy, although there is evidence of efficacy in this situation (57–59). In practice, lamotrigine is often used as initial monotherapy for partial-onset and primary generalized tonic-clonic seizures. The AAN/AES guidelines also indicate that lamotrigine is effective for newly diagnosed absence seizures in children (60), although it is not FDA approved for this indication. Anecdotal reports suggest that in some patients, lamotrigine may worsen myoclonic jerks (61).

Lamotrigine has become a preferred agent for women planning pregnancy. In multiple pregnancy registries, the rate of fetal malformations in children born to mothers on lamotrigine monotherapy has been low, 2.5%–2.9%. A single report suggests that within that rate, there may be an overrepresentation of a specific malformation, cleft lip or palate (62). Because this finding has not been confirmed in other pregnancy registries, many epileptologists consider lamotrigine to be a first-line agent in pregnancy. This issue is likely to generate further discussion as additional data become available.

Lamotrigine offers several advantages. The drug is considered to be effective and generally well tolerated. Although it is metabolized by the liver, lamotrigine elicits little hepatic enzyme induction and no enzyme inhibition. Hence, there are relatively few drug interactions, making lamotrigine a reasonable option for the elderly, patients with HIV, and patients with other underlying medical problems in whom polypharmacy is an issue. Owing to its mood-stabilizing effects, the drug has also become a popular choice for patients with comorbid depression or bipolar disorder. Lamotrigine is a first-line agent for patients with renal or hepatic dysfunction, as well. Although its metabolism may be affected by hepatic disease, the drug itself causes little renal or hepatic toxicity.

A few notable drug interactions, however, do exist. Lamotrigine causes a modest reduction in levonorgestrel levels, and ethinyl estradiol may decrease lamotrigine levels. Adequate lamotrigine levels may be difficult to attain in the presence of phenytoin, as this drug induces the metabolism of lamotrigine. Very high dosages of lamotrigine may be required to yield therapeutic blood levels with concomitant phenytoin use. In

contrast, valproate may significantly increase lamotrigine blood levels. When converting to lamotrigine monotherapy from these anticonvulsants, lamotrigine levels should be monitored carefully. The therapeutic range begins at 4–6 mcg/ml. Some patients may benefit from higher levels, although our clinical experience suggests that levels in the teens pose a greater risk for side effects.

Although the drug is typically well tolerated, a few potential side effects deserve mention. Use of lamotrigine carries a risk of rash. The risk appears similar to that associated with phenytoin and carbamazepine, but if a lamotrigine associated rash occurs, it may be very serious and patients should be encouraged to contact a physician immediately. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. The risk is highest for children and those on concurrent valproate. Uncommon side effects also include cough and insomnia.

Risks are minimized by slow titration. It takes several weeks to properly attain a therapeutic dosage; the titration schedule may be confusing for some patients, and various blister starter packets are available to simplify the regimen. An even slower titration schedule should be employed for those also taking valproate, and separate starter packets are available for that purpose.

The chemical structure of lamotrigine is unrelated to those of the other anticonvulsants. The mechanism underlying lamotrigine's anticonvulsant effect is uncertain. The drug is postulated to act by inhibiting use- and voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and modulating release of excitatory neurotransmitters such as glutamate.

Gabapentin

Although gabapentin is structurally related to GABA, the drug does not act via GABAergic mechanisms. The mechanism of its anticonvulsant activity is unknown. Animal data suggest that it binds to a subunit of voltage-activated calcium channels, but the functional importance of this is unclear.

Gabapentin is FDA approved as adjunctive therapy for partial seizures in patients aged 3 years and older and for seizures with secondary generalization in those aged 12 years and older. These indications are supported by double-blind randomized placebo-controlled studies (63–65). According to the AAN/AES evidence-based guidelines, gabapentin is also a reasonable option as initial monotherapy for adolescents and adults with newly diagnosed partial-onset seizures (66), although it is not yet FDA approved for this indication. Insufficient evidence exists to support its use as monotherapy in those with refractory partial seizures. The drug has not been shown to be effective for primary generalized epilepsies and may in fact worsen myoclonic jerks (67), absence, and primary generalized tonic-clonic seizures.

Gabapentin is typically quite well tolerated with few drug interactions. Our clinical experience suggests, however, that it is less efficacious than other available anticonvulsants.

Felbamate

Felbamate, an N-methyl-D-aspartate (NMDA) receptor antagonist, was approved by the FDA in 1993 for use as adjunctive treatment (68) or monotherapy (69–71) in adults with partial-onset seizures, and as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older (72). In addition, limited data suggest efficacy as add-on treatment for typical and atypical absence seizures (73, 74), partial seizures in children (75), and generalized tonic-clonic seizures in adults (76). Although one study demonstrated efficacy as monotherapy or adjunctive treatment for myoclonic, typical absence, and generalized tonic-clonic seizures associated with juvenile myoclonic epilepsy in adolescents and adults (77), the results must be interpreted with caution given the small sample size.

The drug appeared to be well tolerated and to cause less sedation than other anticonvulsants. In 1994, however, a "Dear Doctor" letter proposed that physicians discontinue use of the drug owing to cases of aplastic anemia, with recent estimates suggesting a prevalence of 27–209 cases per million. The course of aplastic anemia depends on the severity of bone marrow suppression. Reports also identified instances of hepatic failure and rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, associated with felbamate use. Although rare, these reactions were serious and prompted many physicians to discontinue felbamate therapy in their patients.

In light of these findings, the AAN issued a guideline for felbamate use (78). The guideline suggests that felbamate may be an appropriate choice for patients over age 4 with Lennox-Gastaut syndrome, and for patients over age 18 with partial seizures refractory to first-line anticonvulsants. One may also consider use of felbamate in certain situations for children with partial or generalized epilepsies and patients with Lennox-Gastaut syndrome under age 4 who are unresponsive to or intolerant of first-line agents. Data suggested a better risk/benefit ratio for treatment with monotherapy and for continuation in patients who have taken the drug for more than 18 months.

The AAN guideline notes that the risk/benefit ratio should be examined carefully in each patient, however, and that patients should be counseled regarding possible side effects and the recommendations for monitoring. Routine laboratory studies had not been shown to be useful, but the manufacturer and FDA do recommend liver function tests and blood counts. Because the risk of aplastic anemia declines after one year of treatment, the value of routine monitoring after this time period is less clear. The drug should not be used in patients with a history of hematologic abnormalities, liver disease or systemic lupus erythematosus, patients who cannot comply with close follow-up, or patients and guardians unable to provide informed consent. Should physicians choose to prescribe felbamate, they are encouraged to register their patients in the Felbatol Registry (**http://www.guideline.gov**, 78a).

Vigabatrin

Vigabatrin is a derivative of the inhibitory neurotransmitter GABA and irreversibly inhibits GABA transaminase, preventing breakdown of the neurotransmitter. The drug was initially intended to treat partial seizures in adults. Used in Europe since the late 1980s, it was found to be effective, particularly as adjunctive therapy for complex partial seizures and partial seizures with secondary generalization (79, 80). The medication appeared to be relatively well tolerated with minor side effects. After several years on the market in Europe, however, it was discovered that vigabatrin caused visual field defects in up to nearly 50% of adults (81), with additional case reports in children (82). Some patients also developed diminished visual acuity, deficits in color vision, and other retinal abnormalities (81). When FDA approval was sought in 2004, it was denied because of these potential visual effects. As a recent AAN practice parameter suggests, however, the drug may be effective for treatment of infantile spasms, including spasms in the setting of tuberous sclerosis, for which there are few other treatment options (83). Many physicians and parents of these patients obtain the drug from outside the United States despite the potentially serious side effects.

Drugs in Development

Several new compounds are currently in development, and the following drugs are quickly moving along the pipeline (84). Brivaracetam, an SV2A ligand related to levetiracetam, recently acquired orphan drug status for symptomatic myoclonus and is undergoing evaluation for add-on treatment of partial seizures and Unverricht-Lundborg

disease. Eslicarbazepine acetate, structurally related to carbamazepine and oxcarbazepine, is in phase III clinical trials for the adjunctive treatment of partial seizures in adults, with results expected this year. Lacosamide, in both intravenous and oral formulations, is under phase III investigation for the treatment of partial seizures. Thought to be effective in partial-onset seizures, ritigabine and carisbamate are also in phase III trials (85). A New Drug Application has been submitted to the FDA for rufinamide, a compound believed to be efficacious for adults and adolescents with refractory partial seizures as well as for adults and children with Lennox-Gastaut syndrome. Each new drug provides additional hope for seizure freedom in patients with epilepsy.

Drug Monitoring

Routine monitoring of anticonvulsant levels is not recommended except during pregnancy, when an increased volume of distribution causes levels to fall and changes in dosage are often required. Levels should be used to address specific concerns, e.g., to document compliance, assess for toxicity, or aid in management when changing drug regimens or when breakthrough seizures occur.

ALTERNATIVES TO PHARMACOLOGIC MANAGEMENT

A 2001 study of patients with newly diagnosed epilepsy found that 47% become seizure-free with the first anticonvulsant prescribed (86). The probability of successful treatment diminishes with successive trials of different medications. Typically patients are considered to be refractory to medications when they have failed three or more anticonvulsants. Failure is defined as breakthrough seizures of any frequency, often quantified in the literature as at least one seizure within the past year. For these patients, ~30% of those with epilepsy, alternatives to pharmacologic management should be considered.

The utilization of surgical approaches for refractory epilepsy has increased. Resection is an effective treatment with little associated morbidity. In the first randomized controlled trial of epilepsy surgery, 64% of those who underwent anteromesial temporal lobectomy for refractory complex partial seizures were free of seizures that impaired consciousness, compared to 8% of those who received medical management alone. Moreover, 42% of the surgical patients were completely seizure-free (87). A review of the literature regarding anteromesial temporal lobectomy and neocortical resections yielded similar results (88). On the basis of these data, the practice parameter set by the AAN and AES in 2003 states that referral to a surgical center should be considered for patients with refractory, disabling, complex partial temporal lobe seizures. A more recent report demonstrated even more impressive statistics, with 73% of those undergoing resection for mesial temporal lobe epilepsy rendered seizure-free (89). Unfortunately, many potential surgical candidates are not referred for evaluation or are referred after long delays.

The appropriate timing of surgical intervention remains in question. A trial to assess outcomes of early surgery (the Early Randomized Surgical Epilepsy Trial, or ERSET) was unable to recruit a sufficient number of subjects. Anecdotal reports and small case series suggest a role for urgent resection in refractory status epilepticus, although randomized controlled trials have not been performed. This highlights the need for studies of treatment strategies for medically refractory seizures.

Implantable devices are an alternative for patients who are not candidates for, or do not desire, resection. Vagus nerve stimulation (VNS) was the first implantable device developed for treatment of seizures. Its mechanism of action remains unknown. Electrodes wrap around the left vagus nerve and connect to a generator placed subcutaneously in the

chest wall. The stimulator delivers preprogrammed intermittent electrical pulses to the vagus nerve. It may also be activated by the swipe of a magnet to abort a seizure. During stimulation, however, patients may experience cough, hoarseness, or throat pain. Moreover, VNS requires surgical implantation, a costly procedure that poses a risk of injury to the nerve and carotid sheath. Very few adult patients (only isolated case reports) are rendered seizure-free by the device, and the risks must be weighed against the low probability of significant benefit. Overall, VNS is not believed to be useful in adults, although some success has been reported in children with refractory seizures. The AAN practice guidelines state that VNS is indicated for those aged 12 years and older with refractory partial seizures who are not candidates for resection (90).

VNS has, however, paved the way for new device-driven therapies. A trial is under way to assess the efficacy of responsive or "closed loop" stimulators. These devices, implanted in the epileptogenic focus, detect epileptiform activity. They then deliver electrical stimulation to abort the abnormal discharges, thereby preventing the evolution of a clinical seizure. Some centers are also investigating use of deep brain stimulation for the treatment of epilepsy. Deep brain stimulation delivers "scheduled" or "open loop" stimulation to structures such as the thalamus, cerebellum, and hippocampus (91).

The implantation of any device poses a small risk of infection and hemorrhage. It also requires rigorous work-up, as would a surgical resection. For example, one must know the precise location of seizure onset in order to plan the placement of a closed-loop stimulator. This may require invasive EEG monitoring with recording grids, strips, or depth electrodes.

Dietary treatments provide an alternative, noninvasive approach for patients with refractory seizure disorders. The classic ketogenic diet, developed in the 1920s, recently gained popularity (92). It involves low carbohydrate and high fat intake, with resultant ketosis. The mechanism of action underlying its efficacy, however, remains unclear. Approximately 20% of children on the diet have a >90% reduction in seizure frequency, with 7% seizure-free at one year. Although the diet is most effective in children, adults have also attained good results. It is typically used for treatment of generalized seizures or multiple seizure types but may also be considered for any patient with refractory seizures or intolerance of medications. The diet requires monitoring of weight, lipid profiles, electrolytes, urinalyses, urine calcium, and creatinine every 3–6 months. The risk of hyperlipidemia, however, is relatively low. More common side effects include weight loss, gastrointestinal upset, and acidosis.

Unfortunately, the diet also tends to be restrictive and unpalatable. A low-glycemic-index diet, allowing more carbohydrates and less fat, provides a less restrictive alternative. The diet is limited to foods that produce relatively little increase in blood glucose levels. In a study of 20 patients, 50% of those treated with this diet had a >90% reduction in seizure frequency (93). A modified Atkins diet offers another less restrictive option. This diet yields seizure reduction rates comparable to that of the ketogenic diet but without the limitations on calories, fluid, and protein. At six months, 35% of 20 patients placed on the modified Atkins diet had a >90% improvement in seizure frequency, and particular efficacy was noted for absence seizures (94). Some suggest that this diet may be appropriate for patients with more recent-onset, less refractory seizures than those treated with the ketogenic diet. Overall, dietary therapies are good options for those resistant to or intolerant of anticonvulsants, with the goal of discontinuing or reducing medications. Our clinical experience with adults, however, suggests that diets are difficult to maintain.

OTHER TREATMENT ISSUES

Patients with epilepsy often demonstrate subtle or transient cognitive dysfunction in areas

such as attention, language, and memory, despite otherwise normal intelligence. Factors that may contribute to cognitive difficulties include seizure type, frequency, severity, and age of onset; side effects of treatment; and, perhaps most important, psychosocial and psychiatric comorbidities (95–97). Patients with seizures have a greater incidence of anxiety, depression, and bipolar disorder, with suicide rates ten times higher than that of the general population (3). These cognitive and emotional symptoms may be the most troublesome aspects of epilepsy for patients. It has become increasingly clear in recent years that those with epilepsy should be screened for concurrent cognitive and psychiatric disorders.

FUTURE DIRECTIONS

Further advancements in the diagnosis and treatment of epilepsy may stem from the study of genetics. It has long been accepted that many of the primary generalized epilepsies have a genetic basis. A recent trend in genetic studies of epilepsy has been the finding of gene mutations resulting in channelopathies. Mutations in genes encoding sodium channel subunits were found to underlie various epileptic syndromes of infancy, including generalized epilepsy with febrile seizures plus (GEFS+), severe myoclonic epilepsy of infancy, and benign familial neonatal-infantile seizures. The syndrome of benign familial neonatal convulsions has been traced to gene mutations causing aberrant voltage-dependent potassium channels, and mutations that alter voltage-gated chloride channels have been linked to childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand-mal seizures on awakening (98).

Recent studies have also revealed a genetic basis to various focal epilepsies. It is an intriguing notion that such a diffuse process results in a focal brain abnormality, as seen with nicotinic acetylcholine receptor gene mutations in autosomal dominant nocturnal frontal lobe epilepsy and LGI-1 mutations in familial lateral temporal lobe epilepsy (99).

The importance of these studies may lie in their implications for optimizing future treatment. For instance, genetic markers that predict anticonvulsant response would be invaluable. Genetic testing might also identify patients at risk for seizure recurrence, allowing more rapid initiation of treatment. Many of the genetic tests are now commercially available, although interpretation of results may be complicated by possible polygenetic mechanisms or variable penetrance. Currently such testing does not typically play a role in clinical management. If patients or their families desire such testing, referral to a genetic counselor should be considered.

SUMMARY

Recent years have brought new tools for the diagnosis of epilepsy, with advances in MRI techniques, the advent of MEG, increased availability of PET and SPECT, and use of multimodal imaging studies such as EEG/fMRI. Minimally invasive means of intracranial EEG monitoring are more commonly employed, such as epidural pegs and foramen ovale electrodes. A wider range of treatment options also exists, including new anticonvulsants, dietary therapies, implantable devices, and earlier surgical interventions. Great strides have been made in the management of epilepsy, as many of today's standard diagnostic procedures and first-line therapies were not available just a few years ago.

DISCLOSURE STATEMENT

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