Great progress has been seen in the treatment of epilepsy during the past decade, with the marketing of 8 new anticonvulsants and an innovative neurostimulation device. This plethora of options creates dilemmas for physicians faced with treatment decisions. This article reviews recent advances in epilepsy treatment, in the context of available evidence.

UNCERTAINTIES ABOUT RESEARCH DESIGNS

Randomized controlled trials are the essential evidence on which to judge the efficacy of a treatment. All new antiepileptic drugs (AEDs) or devices have been marketed only after rigorous randomized controlled trials. The most common designs for initial AED efficacy trials are “add-on” trials in which patients with refractory epilepsy receiving stable AED therapy are randomized to addition of a study drug or a placebo. This approach is open to criticism. Patients with refractory disease represent a small segment of the epileptic population, and results may not be generalizable. Furthermore, partial epilepsy is not a homogeneous entity. Drug interactions can also be a difficult confounding element in add-on trials.

Monotherapy trials, usually performed after add-on trials are successful, often include newly diagnosed patients and offer the best way to assess efficacy and tolerability of a drug. However, as monotherapy with available anticonvulsants controls complex partial seizures in up to 40% to 50% of patients,1 placebo-controlled monotherapy trials are considered unethical. Equivalence monotherapy trials,2 in which a new study drug is compared with a standard AED (both at therapeutic dosages), are an option but unfortunately do not meet current regulatory requirements (because it might be construed that both treatments were “equally ineffective”). Regulatory authorities (the US Food and Drug Administration) require demonstration of superiority rather than equivalence for proof of efficacy. Hence, acceptable studies compare a therapeutic dosage of a study drug with a pseudoplacebo (ie, a low dose of the study drug or a low dose of a standard AED). To protect patients, exit criteria are used as outcome measures or end points (eg, the patients continue in the study until a fixed point in time, or until first seizure, or until seizure frequency doubles, or some other fixed criterion). Concerns have been expressed over these trial designs as well, with the claim that they are on the borderline of ethical practice.3

Other problems encountered in AED drug trials include incorrect dosing (leading to underestimation of efficacy), suboptimal titration rates (leading to increased adverse effects), variability of seizure frequency requiring statistical manipulation for data analysis, inclusion of heterogeneous epilepsy syndromes with differential sensitivity to various drugs (and resulting failure to show a global beneficial effect), lack of power to demonstrate an effect or lack of difference, and emphasis on adults (but not children, women, or elderly patients).4 Nevertheless, many trial designs have established the place of newer therapies for epilepsy to some degree. In this review, approval refers to action of the US Food and Drug Administration unless otherwise stated.
PHARMACORESPONSIVE EPILEPSIES

Initiation of Treatment

Whether to treat at all is a question. Wiebe reviewed available literature on the risk of recurrence after a first unprovoked seizure and found only 18 relevant articles on the prognosis of adults with a first seizure (16 re-grouped into a meta-analysis and 2 controlled trials). Berg and Shinnar estimated the overall 2-year risk for recurrence at 42%. Patients with partial seizures, neu- rologic abnormalities, or electroencephalogram with epileptiform abnormalities had a 2-fold higher recurrence risk. The First Seizure Trial Group estimated the cumulative risk of recurrence at 2 years at 51% for untreated patients and 25% for patients treated after their first seizure. After a second seizure, the risk increases to 74%, which is why AED treatment is often initiated at this stage. The informed patient and physician must consider the specific syndrome, cause, age, concomitant illnesses, oc- cupation, driving, costs, and compliance in making this decision.

Choice of AED

Treatment should be initiated with a drug known to be efficacious for the specific seizure types. If the initial drug fails to control seizures, an alternate AED (as monotherapy) is the next step. Despite the introduction of newer AEDs, the “ruling dichotomy”—generalized epi- lepsies should be treated with divalproex sodium and focal seizures with carbamazepine—remains valid.

Primary Generalized Seizures. Most in this group respond to valproate, and only a few randomized studies are available for the newer AEDs. In a double-blind, placebo-controlled, parallel study, Chadwick et al found a tendency for gabapentin to reduce the frequency of general- ized tonic-clonic seizures to a greater degree than placebo; the difference may not have achieved statistical signifi- cance because of the low gabapentin dose (1200 mg). Biton et al, in a randomized, double-blind, placebo-controlled trial, showed a significant reduction in primary generalized tonic-clonic seizures in the topiramate treat- ment group (56.7% vs 9.0%). Most reports of positive ef- fects of lamotrigine in primary generalized seizures are case reports or open-label studies. In the study by Frank et al, an open-label dose escalation was followed by placebo- controlled double-blind testing of lamotrigine in patients with typical absence. Significantly more patients re- mained free of seizures when treated with lamotrigine (62%) than with placebo (21%). Vigabatrin and tiaga- bine hydrochloride do not seem to have a favorable effect on most forms of primary generalized seizures. No randomized studies compared the new AEDs with each other or with older drugs in primary generalized epilepsy.

Partial Seizures. All newly marketed AEDs were efficacious in add-on randomized controlled trials for partial seizures. Only a few randomized studies directly com- pared newer with older AEDs, and a single study com- pared 2 newer AEDs with one another. Oxcarbazepine was as efficacious as, but better tolerated than, carba- mazepine and as efficacious as phenytoin and valproate. In comparison trials of lamotrigine and carba- mazepine in adults and the elderly, more patients continued taking lamotrigine because of fewer adverse effects, but no differences in efficacy were found for partial seizures. A lamotrigine and phenytoin comparison trial had the same conclusions. Chadwick et al randomized patients to 1 of 3 masked dosages of gabapen- tin (300, 900, or 1800 mg/d) or open-label carbamaze- pine and found longer time to reach an exit event (defined as a total of 3 simple or complex partial seizures, 1 general- ized tonic-clonic seizure, or status epilepticus) for pa- tients taking 900 or 1800 mg/d than 300 mg/d. A recent study showed gabapentin to be similarly effective to la- motrigine for seizure control and tolerability in patients with partial seizures. Double-blind studies comparing vigabatrin and tiagabine with carbamazepine suggested slightly lower efficacy for vigabatrin. Hence, most available trials have failed to demonstrate superior ef- fects of lamotrigine and tiagabine with carbamazepine—remains valid. Drugs effective for partial and secondarily gener- alized seizures are carbamazepine, phenytoin, gabapen- tin, tiagabine, and oxcarbazepine. Drugs effective for both partial-onset and generalized-onset seizures include val- proate, lamotrigine, topiramate, and zonisamide. Etho- suximide is effective for absence seizures. Phenobarbital, primidone, felbamate, and benzodiazepines are used in selected circumstances. Kwan and Brodie showed that the first AED will lead to freedom from seizures in 47% of patients with newly diagnosed (idiopathic, symptomatic, or cryptogenic) epilepsy. Thirteen percent were free of seizures with the second AED, and only 1% with the third monotherapy choice. In 60% the condition will be controlled with monotherapy.

PHARMACORESISTANT EPILEPSIES

In patients refractory to 2 or 3 AEDs at maximally tol- erated dosages given as monotherapy, combination therapy may be tried.

Primary Generalized Epilepsies

Usually, idiopathic generalized epilepsy is pharmacores- pondive. Randomized studies are mainly available for symptomatic or cryptogenic generalized epilepsies. In Len-nox-Gastaut syndrome, felbamate was significantly more effective than placebo for 4 of 5 efficacy variables, including a 34% decrease in the frequency of atonic seizures (vs 9% in the placebo group) and a 19% decrease in total sei- zure frequency (vs 4%). In 2 double-blind, placebo- controlled crossover studies, lamotrigine was effective and well tolerated when used as an add-on treatment in pharmaco- resistant generalized epilepsy. In a randomized, double-blind, placebo-controlled study, topiramate was ef-
effective as adjunctive treatment of primary generalized tonic-clonic seizures and Lennox-Gastaut syndrome. In infantile spasms (West syndrome), randomized placebo-controlled trials found that corticoretin and vigabatrin were effective. Despite the problem of concentric visual field constriction, vigabatrin is considered the drug of choice for West syndrome in many countries. Some small open-label studies and case reports suggest that zonisamide might be useful.

Partial Seizures

All the new AEDs are efficacious for refractory partial seizures, as they were initially tested in these patients. Although many trials studied the efficacy of each new AED as add-on treatment compared with placebo, no studies compared the new AEDs with one another. Marson et al performed a meta-analysis of topiramate, lamotrigine, zonisamide, gabapentin, and tiagabine and failed to show a significant difference in efficacy and tolerability. A second meta-analysis of levetiracetam, oxcarbazepine, and zonisamide found that levetiracetam and oxcarbazepine had the best estimates for a 50% response, zonisamide had a modest response rate, and remacemide hydrochloride had the poorest response rate.

Levetiracetam had the more favorable “responder-withdrawal ratio,” followed by zonisamide and oxcarbazepine. Cramer et al also compared newer AEDs by analyzing success rates (placebo response rate subtracted from AED response rate) and complaint rates (placebo events subtracted from AED events) reported in controlled add-on trials for 7 new AEDs. Overall success rates fell into 2 general groups, with ranges of 12% to 20% for gabapentin, lamotrigine, tiagabine, and zonisamide and 27% to 29% for levetiracetam, oxcarbazepine, and topiramate. Summary complaint scores also fell into 2 general groups, with ranges of −27 to −82 for gabapentin, levetiracetam, tiagabine, and zonisamide and −113 to −205 for lamotrigine, oxcarbazepine, and topiramate. These results suggest that, in general, drugs with the highest success rates are also the ones with the most adverse effects, except for levetiracetam.

INDIVIDUAL MEDICAL OPTIONS FOR PHARMACORESISTANT SEIZURES

Felbamate

Felbamate is approved in the United States and in a limited number of countries worldwide for monotherapy and adjunctive treatment of partial seizures with or without generalization in adults 14 years and older, and as adjunctive therapy for partial and generalized seizures associated with Lennox-Gastaut syndrome in children 2 to 14 years of age. After its approval by the Food and Drug Administration in the United States, cases of aplastic anemia and hepatic failure were reported in significant numbers (34 cases of aplastic anemia and 18 cases of hepatic failure), hence its use is now restricted to patients with refractory epilepsy for whom benefits of treatment outweigh its risks. The manufacturer requires completion of an informed consent form and inscription into a registry.

Gabapentin

Gabapentin was formed by the addition of a cyclohexyl group to γ-aminobutyric acid, allowing this form of γ-aminobutyric acid to cross the blood-brain barrier. Three double-blind, placebo-controlled, parallel-group studies in patients with refractory disease and 2 smaller studies, totaling 792 patients, demonstrated its efficacy. It is approved for adjunctive use in 34 countries for treatment of partial seizures with or without secondary generalization in patients older than 12 years. Two randomized studies evaluated gabapentin as adjunctive therapy in a pediatric population, the first in patients aged 3 to 12 years, where it was effective, and the second in patients aged 1 to 36 months, where only a trend was demonstrated.

Lamotrigine

Lamotrigine is approved for adjunctive therapy in adults with partial epilepsy, for conversion to monotherapy in patients receiving a single AED inducer, and in children and adults as add-on treatment of generalized seizures in Lennox-Gastaut syndrome. Three randomized, placebo-controlled, parallel add-on studies and 8 crossover studies proved its efficacy in pharmacoresistant partial epilepsy. More recently, lamotrigine has been shown to be useful in a variety of subgroups: (1) Frank et al showed its efficacy in typical absence by means of a “responder-enriched” study design; (2) Gilliam et al showed that patients with partial seizures receiving lamotrigine (target dosage, 250 mg twice daily) continued taking monotherapy longer and met the exit criteria later (ie, longer time to doubling of average monthly seizure rate; doubling of the highest consecutive 2-day seizure rate; emergence of a new, more severe seizure type; or clinically significant prolongation of generalized tonic-clonic seizures) than patients receiving valproate sodium (target dosage, 500 mg twice daily) in a double-blind, double-dummy, active control study; (3) Brodie et al showed that more lamotrigine-treated patients were free of seizures during the last 16 weeks of treatment compared with carbamazepine-treated patients in a multicenter double-blind monotherapy trial; and (4) Crawford et al showed that lamotrigine was as efficacious and well tolerated as gabapentin in patients with learning disabilities and refractory partial epilepsy in an open-label, randomized, parallel-group, multicenter add-on study.

Topiramate

Topiramate is approved for adjunctive therapy for partial and generalized seizures in adult and pediatric (2 years and older) patients. Three randomized, double-blind, placebo-controlled, parallel-group trials demonstrated efficacy for add-on treatment in refractory partial epilepsy with or without generalization. Topiramate is also efficacious as adjunctive therapy for Lennox-Gastaut syndrome and infantile spasms. More recently, a double-blind study with 252 adults and children with newly or recently diagnosed epilepsy randomized to a low dosage (25 or 50 mg/d) or a high dosage (200 or 500 mg/d) demonstrated efficacy for partial-onset seizures with a longer time to first seizure and second seizure in the high-dosage group.
Tiagabine

Tiagabine is approved as adjunctive therapy for partial seizures in adults and adolescents. Five placebo-controlled, add-on studies demonstrated its efficacy in refractory partial epilepsy. Efficacy and tolerability in children have been similar. Tiagabine should be used with caution in patients with generalized seizures, as they may be exacerbated.

Vigabatrin

Vigabatrin is indicated as add-on treatment of patients with refractory partial epilepsy. Its efficacy was shown by numerous randomized controlled add-on studies. Vigabatrin has been approved in more than 65 countries but not the United States. With the report of irreversible visual field defects, its use has been limited to patients with refractory partial epilepsy when other appropriate drugs have failed, and to patients with infantile spasms. Many regard vigabatrin as the drug of choice for infantile spasms. In a randomized multicenter study, 11 of 11 patients taking vigabatrin became free of spasms compared with 5 of 11 hydrocortisone-treated patients. Seven hydrocortisone-treated patients were crossed over to receive vigabatrin (6 because of inefficacy and 1 because of adverse effects) and also became free of spasms. This dramatic benefit was confirmed in a randomized, placebo-controlled trial in 40 children with infantile spasms. Vigabatrin may exacerbate absence and myoclonic seizures.

Levetiracetam

Levetiracetam was recently approved for adjunctive therapy in children aged 4 years or older, with partial seizures with or without secondary generalization. Efficacy for adjunctive therapy was demonstrated in randomized placebo-controlled trials. Efficacy for partial seizures in monotherapy was assessed by placebo- and active-control studies.

Oxcarbazepine

Oxcarbazepine was recently approved for monotherapy or adjunctive therapy in adults, and adjunctive therapy for children aged 4 years or older, with partial seizures with or without secondary generalization. Efficacy for adjunctive therapy was demonstrated in randomized placebo-controlled trials. Efficacy for partial seizures in monotherapy was assessed by placebo- and active-control studies.

Zonisamide

Zonisamide was recently approved for adjunctive treatment of partial seizures in adults. Its development was temporarily halted in the United States when 3.5% of patients in an open-label study in 1993 developed renal calculi. A concurrent study in Europe and studies in Japan reported much lower rates and confirmed its efficacy and safety. Three multicenter, placebo-controlled, double-blind trials demonstrated efficacy in refractory partial epilepsy (also B. J. Wilder, MD, R. E. Ramsay, MD, and A. Guterman, unpublished data, 1986).

INDIVIDUAL SURGICAL OPTIONS FOR PHARMACORESISTANT SEIZURES

Although polytherapy can result in freedom from seizures in a small proportion of patients with resistant disease, in up to 30% of patients seizures still cannot be fully controlled. The new AEDs can reduce seizure frequency by 50% or more in 30% to 55% of patients with medically intractable seizures, but only 1% to 10% will become free of seizures. Vagal nerve stimulation or epilepsy surgery is then considered.

Resective Surgery

Multiple studies documented cure or significant improvement in seizure severity and frequency after resection of the epileptogenic area. Accurate definition of the location and boundaries of this area is crucial to success. Definition of the epileptogenic area involves analysis of structural (magnetic resonance imaging), electrophysiologic (ictal and interictal activity), and functional (positron emission tomography, single-photon emission computed tomography, and neuropsychological evaluation) findings, the convergent localization of which increases the likelihood of success. Invasive intracranial electroencephalographic studies may be required. Advances in magnetic resonance imaging (improved gradient echo, increased magnet strength, special surface coils, and quantitative magnetic resonance imaging) have disclosed previously undetected lesions, including subtle cortical developmental malformations and hippocampal atrophy. Until recently, there were no randomized controlled trials comparing temporal lobe epilepsy surgery with medical treatment. Because the waiting list for surgery at their institution already exceeded 1 year, Wiebe et al were able to ethically justify randomization to medical or surgical treatment during that 1 year of delay, assigning an equal number of patients to immediate surgery and to medical therapy. This randomized, parallel-group, controlled trial yielded a seizure-free rate of 58% in the surgical group compared with 8% in the medical treatment group. There are no randomized controlled trials for extratemporal lobe surgery.

Multiple Subpial Transections

When the epileptogenic zone lies in or near functional cortex, resection may lead to unacceptable deficits. Multiple subpial transections were developed for these circumstances. The procedure exploits the knowledge that functional cortical organization is primarily vertical (columnar), whereas intracortical fibers responsible for seizure spread are horizontally oriented. This technique consists of a series of small parallel cortical slices 5 mm apart made perpendicular to the long axis of the gyrus to spare function while propagation is aborted. It is used alone or in combination with resection in patients with seizures arising in or around the motor, sensory, or language cortices. The procedure has also been applied to patients with Landau-Kleffner syndrome. Evaluation of efficacy of multiple subpial transections by itself is difficult, as published series were small.
and frequently contained patients with combined resection. Recently, Spencer et al. performed a meta-analysis, grouping data on 211 patients from 6 major epilepsy centers, 53 of whom had only multiple subpial transsections. The number of patients was still not sufficient to achieve statistically significant results from a multivariable analysis of predictive factors for seizure response, but results suggested that performing multiple subpial transsections is efficacious by itself with minimal neurologic compromise.

**Gamma-Knife Surgery**

Gamma-knife radiosurgery is stereotactic delivery of a focused dose of radiation to a single point within the brain, identified on magnetic resonance imaging (without causing significant radiation to adjacent tissues). There is a long delay before optimal effect is seen (12-36 months). Benefits include reduced hospitalization, no craniotomy, and lower risk of infection and bleeding. Initially used for deep brain lesions, its application was successfully extended to include tumors and arteriovenous malformations. Gamma-knife surgery is currently being evaluated for 3 situations associated with epilepsy: vascular malformations (especially in eloquent cortex), hypothalamic hamartomas associated with gelastic epilepsy, and mesial temporal lobe sclerosis associated with medial temporal lobe epilepsy.

Regis et al. conducted a retrospective multicenter analysis of 49 patients with refractory epilepsy caused by cavernous malformations treated by gamma-knife surgery. At follow-up (mean, 24 months), 53% were free of seizures (Engel class I), 20% had a significant improvement in the number of seizures (Engel class IIb), and 26% showed little or no improvement. Although the malformations were located in highly functional areas in 17 patients, complications were limited to 1 case of aphasia caused by radiation-induced edema and 1 case of bleeding.

Gamma-knife surgery was recently investigated as treatment for hypothalamic hamartomas. Regis et al. described 8 patients from 7 centers. All exhibited improvement, with 4 becoming free of seizures, 1 having persisting rare nocturnal seizures, and 1 having rare partial seizures but no more generalized attacks. Two patients became free of seizures with retreatment.

**Vagus Nerve Stimulation**

The vagus nerve stimulator is a small implantable device approved in 1997 as adjunctive therapy for adults and adolescents older than 12 years with refractory partial epilepsy. The programmable generator is implanted in the left upper part of the chest and sends a signal to the left vagus nerve through a subcutaneous lead. Its mechanism of action is uncertain, but it is known to desynchronize the electroencephalogram.

Initial favorable single-blind studies were followed by 2 multicenter randomized, active-control, parallel, 3-month add-on studies comparing high stimulation (output current, 0.25-3 mA; frequency, 20-50 Hz; pulse width, 500 microseconds; on time, 30-90 seconds; off time, 5-10 minutes) with a pseudoplacebo (low-dose stimulation; output current, 0.25-2.75 mA; frequency, 1-2 Hz; pulse width, 130 microseconds; on time, 30 seconds; off time, 60-180 minutes) in patients with refractory partial epilepsy. In one trial, mean seizure frequency fell by 24.5% on high and 6.1% on low stimulation; in the other, the reductions were 28% and 15%, respectively. Although vagus nerve stimulation significantly decreased seizure frequency, few patients become free of seizures. Some small, open-label, uncontrolled studies suggested that vagus nerve stimulation is efficacious and safe in younger children.

**Deep Brain Stimulation**

Numerous attempts have been made to reduce seizure frequency by stimulation of deep brain structures, including the anterior thalamus, the centromedian thalamic nucleus, the caudate nucleus, the posterior hypothalamus, and the hippocampus. Only 1 randomized controlled study was done, which did not confirm efficacy. Multicenter studies are in progress to assess the value of deep brain stimulation of the anterior thalamus and the subthalamic nucleus.

**CONCLUSIONS**

Although a novel treatment option for epilepsy (medical or surgical) was marketed almost every year during the past decade, many patients still experience uncontrolled seizures or have adverse effects. Several antiepileptic compounds are currently being tested; some are completely novel chemical structures, whereas others are derivatives of existing AEDs “designed” to be more efficacious or safer and better tolerated. Furthermore, recent advances in pharmacogenomics and seizure prediction hold the promise of individualized therapy. Drug trials will most likely become longer, more complex, and expensive, requiring atypical designs to allow study of targeted heterogeneous epileptic syndromes and populations, multiple end-point measurements (eg, seizure frequency, count, time to first seizure, adverse effects, and quality of life) for optimal drug evaluation, inclusion of pharmacokinetic data for polytherapy studies, and use of historical controls, when possible, to avoid borderline ethical pseudoplacebo trials. On the surgical front, novel nonablative techniques are currently being evaluated, and outcomes are being reassessed with inclusion of quality-of-life measures and in light of better presurgical localization tools. Demonstration that randomized controlled trials comparing surgical with medical therapy are feasible should stimulate more similar studies.

With the increasing number of therapeutic tools, physicians must rely on clinical judgment more than ever, tempered by scientific and evidence-supported knowledge.
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