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ALASTAIR J.J. WOOD, M.D., *Editor*

NEW ANTIEPILEPTIC DRUGS

MARC A. DICHTER, M.D., PH.D., AND MARTIN J. BRODIE, M.D.

IN the past two years, three new antiepileptic drugs — gabapentin, lamotrigine, and felbamate — have been approved for use in the United States. They are the first such drugs to be approved since valproic acid, in 1978. These three drugs and others now in use in Europe, Canada, or Japan or being tested in trials in the United States reflect the resurgence of interest in developing new drugs for the treatment of epilepsy. This article reviews the pharmacologic characteristics of these new drugs, indications for their use, side effects, and appropriate regimens.

In many patients with epilepsy, seizures can be controlled with the established antiepileptic drugs,[1] but 25 to 30 percent of patients continue to have seizures despite optimal therapy, and others have unacceptable side effects. Thus, there is clearly a need for additional drugs, as well as for new strategies for preventing epilepsy.

In the United States, antiepileptic drugs are approved by the Food and Drug Administration (FDA) for the treatment of specific types of seizures in adults or children, after both the efficacy and the safety of the drugs have been established. Once an antiepileptic drug is on the market and physicians have become familiar with its use and safety, however, it is often used for other indications, either in younger patients or in patients with types of seizures other than those for which the drug was approved. Each of the three new drugs in the United States has been approved for use in adults who have partial seizures either alone or with secondarily generalized (grand mal) seizures. Felbamate has also been approved for use in children with seizures associated with the Lennox–Gastaut syndrome, which is a severe form of epilepsy characterized by multiple types of seizures, extreme electroencephalographic abnormalities, and some degree of psychomotor retardation.

The initial evaluation process for a new antiepileptic drug involves a determination of its efficacy in reducing the frequency of seizures in patients who continue to have them despite adequate therapy with established drugs. Demonstrating efficacy in such patients is a rather stringent requirement, and in all the studies supporting the use of new antiepileptic drugs, very few patients have become free of seizures. Usually, 25 to 50 percent of patients have a 50 percent or greater reduction in the frequency of seizures, and some patients have a reduction in their severity. Once a drug has been approved, however, it can be given to patients with much less severe epilepsy, including those who are being treated for the first time. How effective the new antiepileptic drugs will be when used in this way is difficult to predict, but it is assumed that if they can ameliorate seizures in patients with intractable epilepsy, they should be even more effective in those with less severe epilepsy. The choice of a drug may then depend on the ease of its use, the range of seizures for which it is effective, side effects, interactions with other drugs, and cost.

Studies evaluating the efficacy of new antiepileptic drugs vary widely in the number of patients enrolled, the types of seizures, and even the end points. In this review, we shall give most weight to double-blind, placebo-controlled studies. However, we shall also review other clinical data on efficacy and safety, in order to present as complete a picture of each drug as possible.

ANTIEPILEPTIC DRUGS RECENTLY APPROVED IN THE UNITED STATES

Gabapentin

Gabapentin was approved for use in the United States in 1994 as an add-on drug in adults who have partial seizures either alone or with secondarily generalized seizures. The drug's mechanism of action is unknown, although it binds to a specific receptor in the brain,[2] inhibits voltage-dependent sodium currents,[3] and may enhance the release or actions of γ-aminobutyric acid.[4,5]

Three double-blind, placebo-controlled trials have demonstrated the efficacy of gabapentin in adults with intractable partial seizures.[6-8] In one study of incremental doses of 600, 1200, and 1800 mg per day, there was a dose-dependent decrease in the frequency of seizures, with at least a 50 percent decrease in 27 percent of the patients receiving the highest dose, as compared with a 9 percent decrease in those receiving placebo.[7] In the three trials combined, there were 792 patients; among those receiving 1800 mg of gabapentin per day, 26 percent had a 50 percent or greater reduction in partial seizures, and 54 percent had a 50 percent or greater reduction in secondarily generalized seizures.

The elimination half-life of gabapentin is approximately six hours, suggesting that multiple daily doses are necessary. Starting doses and typical dose ranges are shown in Table 1. Gabapentin is well absorbed, is not metabolized or bound to plasma proteins, but is excreted unchanged by the kidneys, and the dose should therefore be reduced in patients with renal impairment. The drug is effectively cleared by dialysis. So far, there

From the Department of Neurology, University of Pennsylvania, Philadelphia (M.A.D.), and the Epilepsy Research Unit, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland (M.J.B.). Address reprint requests to Dr. Dichter at the Department of Neurology, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

are no published target ranges for serum concentrations of gabapentin, but concentrations as low as 2 μg per milliliter may be effective, and concentrations as high as 20 μg per milliliter are not toxic.

Gabapentin has few side effects but can cause somnolence, fatigue, ataxia, dizziness, and gastrointestinal upset (Table 2). No pharmacokinetic interactions with other antiepileptic drugs have been reported, although there may be pharmacodynamic interactions (e.g., additive side effects). Thus, gabapentin may be very useful in patients who are taking other medications, especially the elderly.

Lamotrigine

Lamotrigine is approved in the United States as an add-on drug for use in adults who have partial seizures alone or with secondarily generalized seizures. In animal studies, lamotrigine has antiseizure activity similar to that of phenytoin and carbamazepine,[9] and although the structure of lamotrigine is different, it also inhibits sodium currents in a voltage- and use-dependent manner.[10] Since lamotrigine was approved in Europe for use in both adults and children several years ago, there is clinical experience with this drug beyond that from the controlled clinical trials.

In placebo-controlled, double-blind, crossover or parallel studies in the United States and Europe,[11-19] a dose of 200 to 500 mg of lamotrigine per day was more effective than placebo in patients with intractable partial seizures; 70 percent of the patients had fewer seizures, and 27 percent had at least 50 percent fewer seizures. In the European studies, the drug was effective in patients with either partial or generalized seizures. There is one report of the successful intravenous use of lamotrigine to treat status epilepticus.[20] The drug has been shown to be continuously effective for up to three years.[21]

Lamotrigine is also effective as monotherapy.[22,23] In a recently completed double-blind comparison of lamotrigine and carbamazepine in 260 patients with newly diagnosed partial or generalized tonic–clonic seizures, the efficacy of the two drugs was similar, but lamotrigine was better tolerated.[24] A few single-blind and open studies suggest similar efficacy in children with multiple types of seizures,[21,23] including those with the Lennox–Gastaut syndrome.[23]

When administered orally, lamotrigine is well absorbed, and its plasma elimination half-life is about 25 hours. Drugs that induce the production of drug-metabolizing enzymes in the liver (phenobarbital, phenytoin, and carbamazepine) decrease the half-life of lamotrigine by 50 percent, necessitating a higher dose, whereas valproic acid slows the metabolism of lamotrigine and extends its half-life to 60 hours, necessitating a reduced dose (Tables 1 and 3). Some patients have headache or nausea with a low dose of lamotrigine, whereas others tolerate doses above 800 mg daily (with serum concentrations >10 μg per milliliter).[25]

The most common side effects of lamotrigine are headache, nausea and vomiting, dizziness, diplopia, and ataxia (Table 2).[26] Tremor can be troublesome at high dosages. In approximately 5 percent of adults, a rash develops, which subsequently disappears in some patients, despite continued therapy. In a few patients, however, the rash is more serious and fever, arthralgias, and eosinophilia occur; in rare cases (<1 percent), the Stevens–Johnson syndrome develops. The concomitant administration of valproic acid with lamotrigine may increase the likelihood of a serious rash, whereas the gradual introduction of lamotrigine may lower the likelihood.

Felbamate

Felbamate was approved in 1993 for use as an add-on drug or as monotherapy in adults who have partial seizures alone or with secondarily generalized seizures and in children with partial or generalized seizures associated with the Lennox–Gastaut syndrome. The drug is effective against multiple types of seizures in animals, and effective doses are considerably lower than

Table 1. Antiepileptic Drugs Recently Approved for Use in the United States.

Drug	Indications	Starting Dose	Maintenance Dose	Plasma Half-Life (hr)	Plasma Binding (%)
Gabapentin (Neurontin)	Partial seizures and secondarily generalized seizures in adults	300 mg/day, with the dose increased by 300 mg/day every 1–3 days	1200–2400 mg/day*	6	0
Lamotrigine (Lamictal)	Partial seizures and secondarily generalized seizures in adults	25 to 50 mg daily, with the dose increased by 50 mg/day every 1–2 weeks (25 mg every other day with valproic acid, with the dose increased by 25 mg/day every 1–2 weeks)	Up to 700 mg/day (100–150 mg/day with valproic acid)	25 (12–14 with enzyme-inducing drugs, 60 with valproic acid)	54
Felbamate (Felbatol)†	Partial seizures and secondarily generalized seizures in adults	400 mg 2 or 3 times/day‡ (reduce concomitant phenytoin, carbamazepine, or valproic acid by 20 to 33 percent), with the dose increased by 400 to 600 mg/day every 2 weeks	1800–4800 mg/day	20 to 23	22 to 25
	Seizures in children with the Lennox–Gastaut syndrome	15 mg/kg/day in 3 or 4 doses‡ (reduce concomitant phenytoin, carbamazepine, or valproic acid by 20 to 33 percent), with the dose increased by 15 mg/kg/day every 1–2 weeks‡	Up to 45 mg/kg/day		

*The dose required to achieve control of seizures may be much higher.

†Felbamate should be used only in patients with seizures that are refractory to all other medications.

‡These doses are smaller than those recommended in the package insert and are suggested as a way of possibly minimizing side effects.

Table 2. Side Effects of New Antiepileptic Drugs.

Drug	Principal Side Effects	Serious but Rare Side Effects
Gabapentin	Somnolence, fatigue, ataxia, dizziness, gastrointestinal upset	
Lamotrigine	Rash, dizziness, tremor, ataxia, diplopia, headache, gastrointestinal upset	Stevens–Johnson syndrome
Felbamate	Irritability, insomnia, anorexia, nausea, headache	Aplastic anemia, hepatic failure
Clobazam	Sedation, dizziness, irritability, depression, disinhibition	
Vigabatrin	Behavioral changes, depression, sedation, fatigue, weight gain, gastrointestinal upset	Psychosis
Oxcarbazepine	Dizziness, diplopia, ataxia, headache, weakness, rash, hyponatremia	
Zonisamide	Somnolence, headache, dizziness, ataxia, renal calculi	
Tiagabine	Confusion, dizziness, gastrointestinal upset, anorexia, fatigue	
Topiramate	Cognitive difficulties, tremor, dizziness, ataxia, headache, fatigue, gastrointestinal upset, renal calculi	

toxic doses.[27] The mechanisms of action are not completely understood, but felbamate reduces sodium currents (as do phenytoin and carbamazepine), enhances the inhibitory actions of γ-aminobutyric acid, and blocks *N*-methyl-D-aspartate receptors.[28]

In two double-blind, placebo-controlled, add-on studies, felbamate was superior to placebo in reducing focal seizures in adults.[29,30] In two other studies, felbamate used alone was better than placebo or a low dose of an alternative antiepileptic drug in preventing the recurrence of seizures after the withdrawal of other antiepileptic medications during evaluation for surgery.[31-33] In children with the Lennox–Gastaut syndrome, felbamate (45 mg per kilogram of body weight or 3600 mg per day) was superior to placebo in reducing the frequency of seizures; it was particularly effective in patients with atonic seizures. No change, however, was noted in seizures recorded by video electroencephalographic monitoring.[34]

Starting and maintenance doses of felbamate are shown in Table 1. The drug is well absorbed when administered orally. Its elimination half-life is approximately 20 to 23 hours, suggesting that it can be given twice daily, although three to four divided doses are recommended by the manufacturer. Felbamate is minimally metabolized, and most of it is excreted in the urine.

Felbamate was well tolerated in clinical trials. After it had been approved, however, side effects appeared to be more prominent (Table 2).[35-37] After approximately 100,000 patients had been treated, two very serious toxic effects occurred that had not previously been noted. Aplastic anemia developed in 32 patients, 10 of whom died (incidence, 1 in 3600 to 1 in 5000), and serious hepatotoxic effects occurred in 19 patients, 5 of whom died (incidence, 1 in 24,000 to 1 in 34,000). The FDA currently recommends that felbamate be given only to patients who have seizures that are refractory to treatment with all other medications and in whom risk–benefit considerations warrant its use. Weekly or biweekly complete blood counts and liver-function tests are also recommended, although it is not known whether early detection of either reaction will prevent the most serious outcomes.

Felbamate interacts with other antiepileptic drugs (Table 3). Thus, if a patient receiving phenytoin, carbamazepine, or valproic acid is given felbamate, the dose of the former drugs should be reduced by 20 to 33 percent to prevent toxic effects. Phenytoin and carba-

Table 3. Interactions between New Antiepileptic Drugs and Conventional Drugs.

New Drug	Effect of Conventional Drugs on New Drug	Effect of New Drug on Conventional Drugs
Gabapentin	None known	None known
Lamotrigine	Phenobarbital, phenytoin, and carbamazepine increase metabolism by 50 percent Valproic acid decreases metabolism by 50 percent	Does not induce cytochrome P-450 When added to carbamazepine, may induce neurotoxicity because of pharmacodynamic interactions
Felbamate	Valproic acid decreases clearance Phenytoin and carbamazepine increase clearance	Decreases metabolism of phenytoin and valproic acid (increases serum phenytoin levels by approximately 20 percent and increases serum valproic acid levels by 18–31 percent) Decreases serum carbamazepine levels but increases serum carbamazepine epoxide levels
Clobazam	Target for enzyme inducers or inhibitors	May precipitate toxic effects of phenytoin and increase serum carbamazepine epoxide levels
Oxcarbazepine	Not affected by enzyme inducers	Induces cytochrome P-450, 3A isoform family (but less so than carbamazepine) May increase serum phenytoin and valproic acid levels by 20–30 percent if oxcarbazepine is substituted for carbamazepine Increases metabolism of oral contraceptives
Tiagabine	Phenobarbital, phenytoin, and carbamazepine increase clearance	Does not induce cytochrome P-450 Does not affect serum phenytoin, carbamazepine, or valproic acid levels
Topiramate	Phenytoin and carbamazepine increase clearance Valproic acid has no marked effect	Weak inducer of cytochrome P-450 May increase serum phenytoin levels in some patients (mechanism unknown)
Vigabatrin	None known	May decrease serum phenytoin levels by 20 percent (mechanism unknown)
Zonisamide	Phenobarbital increases clearance	May increase serum phenytoin and carbamazepine levels (not in all studies)

Table 4. Antiepileptic Drugs Currently Approved for Use in Europe, Canada, or Japan.

Drug	Indications	Starting Dose	Maintenance Dose	Plasma Half-Life (hr)	Plasma Binding (%)
Clobazam	Partial and generalized seizures	10 mg at bedtime or 10 mg twice daily	20–30 mg/day Up to 60 mg/day	30–46	85
Oxcarbazepine	Partial and tonic–clonic seizures	300 mg twice daily	1200–2400 mg/day	8–24 (for active metabolite)	40
Tiagabine	Partial and secondarily generalized seizures	Not available	32–56 mg/day	6–8	96
Topiramate	Partial and secondarily generalized seizures	100 mg/day, with the dose increased by 100 mg/day at weekly intervals	400–1000 mg/day	20–24	10–20
Vigabatrin	Partial and secondarily generalized seizures and possibly infantile spasms	500 mg twice daily	Up to 3 g/day	4–8 (effect lasts ≥3 days)	Minimal
Zonisamide	Partial and secondarily generalized seizures	100–200 mg/day	400–600 mg/day	50–68 (27–38 with enzyme-inducing drugs)	38–40

mazepine (but not valproic acid) can increase the clearance of felbamate.

Antiepileptic Drugs Available in Europe, Canada, or Japan or Being Tested in the United States

Clobazam

Clobazam was introduced as an anxiolytic drug in 1975, and its antiseizure activity was recognized soon thereafter. It is currently available as an adjuvant antiepileptic drug in more than 50 countries, including the United Kingdom and Canada; a notable exception is the United States. Clobazam, a 1,5-benzodiazepine, has a slightly different chemical structure from that of clonazepam and diazepam, which are 1,4-benzodiazepines, and is less likely to cause psychomotor impairment and sedation.[38,39] Clobazam probably exerts its antiseizure activity by potentiating the inhibitory actions of γ-aminobutyric acid.[40]

Several double-blind, placebo-controlled trials have shown that clobazam is effective in patients with refractory epilepsy.[41-45] Several open studies have been performed to identify the types of seizures most likely to be controlled.[46-52] The most consistent results have been in patients with partial seizures,[43-45,47,51,52] but the drug is also active in patients with typical or atypical absence seizures, in those with myoclonic and secondarily generalized tonic–clonic and atonic seizures, and those with the Lennox–Gastaut syndrome.[49-53] Clobazam has been used as monotherapy in one trial, in which 11 of 24 children became free of seizures.[54]

Clobazam can be given intermittently. For example, as prophylaxis against catamenial epilepsy, the drug can be given in a dose of 30 mg daily before the start of menstruation and for five to seven days afterward. A daily dose of 30 to 60 mg can also be effective in patients prone to have clusters of seizures in a single day. Clobazam is an inexpensive, safe, well-established adjuvant antiepileptic drug with relatively few side effects. Interest in the drug has been stimulated by reports that it controls seizures in 10 to 30 percent of patients with refractory epilepsy.[44,45,47,49,50,53,55]

Starting and maintenance doses of clobazam are shown in Table 4. The drug is readily absorbed after oral administration, with 85 percent bound to plasma proteins. It is metabolized mainly by dealkylation and hydroxylation to *N*-desmethyl-clobazam, which is pharmacologically active, and 4-hydroxy-clobazam.[56] The elimination half-lives of clobazam and its active desmethyl metabolite are 30 and 46 hours, respectively,[57] and are slightly prolonged in the elderly.[58]

As with other benzodiazepines, tolerance to clobazam's antiepileptic action may develop, often within three months. Sometimes this problem can be overcome by increasing the dose,[55] and it may be prevented by administering the drug intermittently.[59] Sedation and dizziness are the most common side effects (Table 2).[53] Other problems can include mood changes, with occasional irritability, depression, aggression, and disinhibition.

Vigabatrin

The first antiepileptic drug to be developed on the basis of a targeted mechanism of action, vigabatrin (γ-vinyl γ-aminobutyric acid) is an irreversible inhibitor of the enzyme γ-aminobutyric acid transaminase. Inhibition of this enzyme increases the amount of γ-aminobutyric acid available in the brain for inhibitory action.[60]

In nine placebo-controlled European studies[61] and in a large cooperative, multicenter study in the United States,[62] vigabatrin was effective in patients who had partial seizures alone or with secondarily generalized seizures. In several of these studies, the frequency of seizures was reduced by at least 50 percent in more than half the patients. Vigabatrin is used relatively widely in Europe for the treatment of partial seizures in adults and has been effective in children with infantile spasms and other forms of catastrophic epilepsy (characterized by uncontrollable seizures in the context of severe underlying neurologic dysfunction).[63,64] Vigabatrin was also effective as monotherapy in small, randomized, controlled studies involving patients with newly diagnosed epilepsy.[65]

Because vigabatrin irreversibly inactivates γ-aminobutyric acid, its plasma half-life (four to eight hours) is less critically related to its duration of action than is

usual with other drugs. Vigabatrin's action appears to be maximal at a dose of approximately 3 g per day in most patients.[66] It takes approximately three days or more for the γ-aminobutyric acid transaminase to regenerate after vigabatrin treatment has been stopped.

Vigabatrin is usually well tolerated but can cause sedation or depression (Table 2), and a few patients have serious psychiatric symptoms (7 percent in one series).[67] In the U.S. trial, 5 of 92 patients dropped out because of psychiatric symptoms and 1 because of cognitive symptoms.[62] U.S. trials were temporarily halted when rats and dogs receiving relatively high doses of vigabatrin were found to have intramyelinic edema in various white-matter tracts,[68,69] which resolved shortly after the drug was discontinued. Such changes have not been found in primates, or in patients evaluated with extensive evoked-potential studies,[70-73] magnetic resonance imaging,[74] or pathological examination of surgically removed brain tissue.[75-78]

Oxcarbazepine

Oxcarbazepine is the 10-keto analogue of carbamazepine. It is functionally a pro-drug, which is rapidly and completely reduced in the liver to the active 10,11-dihydro-10-hydroxycarbamazepine.[79] In clinical trials in which oxcarbazepine was substituted for or compared with carbamazepine, the efficacy of the two drugs was similar.[79-81] Like carbamazepine, oxcarbazepine is not effective against absence seizures or myoclonic jerks. Open studies suggest that the drug's efficacy in children is similar to that in adults.[82]

Approximately 40 percent of the active metabolite is bound to plasma proteins; its elimination half-life ranges from 8 to 24 hours (Table 4).[83] As compared with its parent drug, carbamazepine, oxcarbazepine is metabolized through a different pathway and may have milder side effects, cause fewer idiosyncratic reactions, and have fewer interactions with other drugs (Table 2).[79-82] Hyponatremia, probably due to the release of antidiuretic hormone, is at least as common with oxcarbazepine as with carbamazepine.[84] This effect is occasionally apparent clinically[85] but is usually mild and asymptomatic.[82] Treatment with oxcarbazepine has not resulted in autoinduction of metabolism.[83]

Zonisamide

Zonisamide is currently approved for use in Japan. Its spectrum of activity appears to be similar to that of phenytoin and carbamazepine. The exact mechanism of action of zonisamide is unknown, but it can block sodium and calcium channels.[86-88] Several open studies in Japan have shown that the drug is effective in patients who have partial seizures alone or with secondarily generalized seizures.[89] In one double-blind, placebo-controlled, multicenter study in Europe, seizures were reduced by more than 50 percent in 30 percent of patients receiving zonisamide but in only 19 percent of those receiving placebo.[90] In a second multicenter study, 41 percent of patients with intractable partial seizures had over a 50 percent reduction in the frequency of seizures.[91] Zonisamide is currently being evaluated in patients with partial seizures in the United States and Europe.

Zonisamide is well absorbed orally and has a relatively long elimination half-life, approximately 50 to 68 hours, which is shortened to 27 to 38 hours in patients receiving enzyme-inducing antiepileptic drugs (Tables 3 and 4). Two important differences have emerged between the trials in Japan and those in the United States and Europe. In Japan, serum concentrations increased linearly with increasing doses of the drug,[92] whereas in the United States, the relation between the dose and the serum concentration was nonlinear.[93] In addition, renal calculi developed in 13 of 700 U.S. and European patients (1.9 percent),[91] whereas in Japan the incidence was 0.2 percent. The U.S. trials were initially suspended because of the renal effects but have since resumed, with an increased emphasis on screening eligible patients for preexisting conditions that might predispose them to renal calculi and monitoring enrolled patients for renal calculi.

Tiagabine

Tiagabine was designed to act specifically on the inhibitory action of γ-aminobutyric acid by blocking its uptake, thereby prolonging its action after synaptic release.[94,95] The consequences of this action are unexpectedly complex. Tiagabine may enhance certain forms of inhibition,[96] but presynaptic effects on γ-aminobutyric acid receptors have variable consequences, depending on which neurotransmitter's release is being inhibited.[97]

Clinical trials are currently investigating the use of tiagabine as an add-on drug in adults with intractable focal seizures. In one small, phase 2, double-blind, crossover study, patients who had a response to the drug in an open screening phase were randomly assigned to receive maximally tolerated doses of tiagabine or placebo. Twenty-six percent of the patients receiving tiagabine had a 50 percent or greater reduction in focal seizures and 60 percent had a 50 percent or greater reduction in generalized tonic–clonic seizures,[98] as compared with the frequency of seizures during the placebo period. Side effects included tiredness, dizziness, confusion, and gastrointestinal upset.

Topiramate

Topiramate has a spectrum of antiseizure activity resembling that of phenytoin and carbamazepine but also appears to have additive effects when combined with these antiepileptic drugs.[99] The mechanism of action of topiramate is not entirely known, although it can block sodium channels, attenuate kainate-induced responses, and enhance the inhibitory action of γ-aminobutyric acid[100] by acting at a unique modulatory site.

Topiramate has been shown to be effective in two placebo-controlled, add-on studies in the United States and one in Europe. In these studies, 40 to 50 percent of patients had a 50 percent or greater reduction in partial seizures with topiramate. At doses of 400 to 600 mg per day, secondarily generalized tonic–clonic seizures were reduced by 89 to 100 percent.[101] Most side effects are mild to moderate in severity and do not require discon-

tinuation of the drug (Table 2). The risk of renal-calculus formation is increased (1 to 2 percent, which is similar to the risk associated with acetazolamide) and is especially high in patients with a predisposition to nephrolithiasis. In 1995, topiramate was approved for use in the United Kingdom as add-on therapy for refractory partial seizures; it is currently under review for approval in the United States.

Other New Antiepileptic Drugs

Several other new drugs, including losigamone, remacemide, and levetiracetam, are in relatively early stages of clinical investigation in several countries. Two new formulations of established antiepileptic drugs are also undergoing clinical testing and may soon be approved by the FDA. Fosphenytoin is a water-soluble phenytoin pro-drug that can be given by intramuscular or intravenous injection and appears to be less irritating than the parent drug. Tegretol-oros is a slow-release form of carbamazepine designed for oral administration twice daily.

Current Recommendations for Use

On the basis of the limited clinical experience with the new antiepileptic drugs available in the United States, it appears to be appropriate to recommend these drugs for the treatment of adults with focal seizure disorders in whom other drugs are not effective or cause intolerable side effects. Two of the new antiepileptic drugs, gabapentin and lamotrigine, may become the drugs of choice for patients with newly diagnosed epilepsy. Ease of use, the absence of metabolism or interaction with other drugs, and relatively mild side effects may eventually make gabapentin a first-line treatment. The drug may be particularly useful in older patients with focal epilepsy who have other medical conditions and are taking other medications.

Lamotrigine has been accepted relatively rapidly in Europe on the basis of its broad spectrum of activity against multiple types of seizures, its wide toxic:therapeutic ratio, absence of sedative action, and absence of serious toxicity. Pediatricians have been particularly interested in the use of lamotrigine because it is effective in children with idiopathic generalized seizures and does not impair cognition. Early post-marketing experience indicated that felbamate was effective but its tolerability varied. However, the occurrence of serious idiosyncratic toxic effects has made this drug useful only when seizures cannot be controlled with other medications and remain a serious problem.

In the United States, only felbamate has been approved for use in children, but its toxicity will prevent widespread use. Gabapentin and lamotrigine will probably be used in children as well, even if not expressly approved for such use, but only in those children in whom conventional antiepileptic drugs have failed to control seizures. In Europe, lamotrigine and vigabatrin are already widely used in children.

Oxcarbazepine is gaining popularity in Europe as a drug with a spectrum of action similar to that of carbamazepine but with better tolerability. Vigabatrin and clobazam are used commonly in Europe and Canada, mostly as secondary antiepileptic drugs. The use of vigabatrin as monotherapy is currently being examined. The future roles of zonisamide, tiagabine, and topiramate also remain to be determined.

We do not have adequate data on the possible teratogenic effects of the new antiepileptic drugs. Early anecdotal experience suggests that lamotrigine given during pregnancy is associated with a low risk of teratogenic effects. Unfortunately, it is very difficult (or impossible) to obtain such information before new drugs are marketed, and we must depend on post-marketing surveillance to determine the safety of each of these drugs for use in women of childbearing age. Most of the new antiepileptic drugs do not induce hepatic cytochrome P-450 and therefore should not interfere with the action of contraceptive hormones. (An exception is oxcarbazepine, which induces cytochrome P-450 isoform 3A and accelerates the metabolism of components of oral contraceptive pills.)

Given the limited efficacy of all the new antiepileptic drugs and the potential for serious side effects, why are they approved, why are they being marketed, and why should they be used, especially if they are more expensive than the older drugs? Epilepsy is a common disorder that has many forms and many causes. It can be complex and very difficult to control, often requiring treatment for many years just to keep seizures under control. Epilepsy is currently not satisfactorily treated in a substantial proportion of patients. All the clinical trials have shown that some patients have a better response to one drug than to another, even when they have similar types of seizures and the drugs used have similar mechanisms of action; the frequency and severity of side effects also vary substantially. Thus, until either epilepsy can be cured or a potent, safe new drug with broad activity is discovered, multiple medications with different mechanisms of action and side-effect profiles will be needed.

It will also be necessary to develop algorithms for the most efficient and effective use of various drugs, both as monotherapy and in a scheme for rational polytherapy. These algorithms should take into account continued clinical experience with the new drugs, comparisons of the new drugs with older drugs, and an evaluation of adverse effects during prolonged therapy in large numbers of patients. An improved scheme for classifying patients on the basis of the pharmacologic responsiveness of epileptic seizures and syndromes may also be needed. The more strategies available to treat epilepsy, the more likely that patients with this disorder will be able to achieve good physical and mental health, as well as social, educational, and vocational fulfillment.

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