The current developments in the availability of new antiepileptic drugs (AEDs) are unprecedented. After a period of many years during which no new AED became available, 5 new AEDs were introduced in the United States between 1993 and 1997, and 2 more are expected to be approved soon. These new drugs are a most welcome addition to the therapeutic options in the treatment of epilepsy, but they also create a dilemma for the clinician because their individual places and their optimal use in the treatment of various forms of epilepsy are yet to be determined. This review serves to summarize the main characteristics of the newer AEDs.

Some of the new antiepileptic drugs (AEDs) are quite different from those previously established in terms of their mechanisms of action,1 their pharmacokinetic properties,2 and/or their spectrum of efficacy and adverse effects.3,4 As a group, the newer AEDs tend to have fewer adverse effects and less pharmacokinetic interactions. For most of the newer AEDs, the role of serum level monitoring is unclear, and a therapeutic range has not been established for any of these drugs. Herein I discuss the newest AEDs in the chronological order of their release or anticipated release.

**FELBAMATE**

Felbamate (Felbatol, Wallace Laboratories, Cranbury, NJ) was introduced in the United States in 1993. It underwent innovative clinical trials: felbamate was the first AED to undergo double-blind testing in patients withdrawn from AED regimens for presurgical monitoring, it was the first drug to be tested in a placebo-controlled trial in children with Lennox-Gastaut syndrome, and it was the first AED to be tested in double-blind monotherapy trials. Uncontrolled observations have suggested that felbamate also may be effective in the treatment of absence seizures, juvenile myoclonic epilepsy, Landau-Kleffner syndrome, and infantile spasms. The main common adverse effects of felbamate have been anorexia, weight loss, and insomnia. Within a year, however, it became evident that felbamate was associated with a relatively high incidence of 2 life-threatening adverse effects: aplastic anemia and liver failure. In August 1994, 1 year after its release, the drug came close to being withdrawn from the market. Aplastic anemia presented, on the average, 154 days after the initiation of felbamate therapy.5 The risk is estimated to be 1:4000 to 5000. The risk of fatal hepatotoxic effects has been estimated to be 1:26 000 to 34 000, which does not seem to exceed the risk associated with valproate. A warning was included in the felbamate package insert, requiring frequent laboratory monitoring. The overall experience with felbamate has shown that it is clearly an effective AED and it remains indicated for patients with refractory seizures, particularly for those with Lennox-Gastaut syndrome.

**GABAPENTIN**

Gabapentin (Neurontin, Parke-Davis, Morris Plains, NJ) was marketed in the United States in early 1994. There is still uncertainty about its mechanism of action. Since bromide, gabapentin is the first AED that is eliminated entirely by the kidneys, a property shared by vigabatrin. Neither gaba-
topiramate nor vigabatrin is the object or the cause of any significant pharmacokinetic interactions. This is a distinct clinical advantage. Also, because they do not induce hepatic oxidation, gabapentin and vigabatrin may be the AEDs of choice in patients with seizures and acute intermittent porphyria. Because of a short half-life as well as saturable bioavailability, the total daily dosage of gabapentin should be divided into at least 3 doses. Gabapentin is effective against partial and secondarily generalized seizures. A placebo-controlled study of gabapentin in the treatment of benign epilepsy of childhood with centrotemporal spikes (rolandic epilepsy) is still being conducted. There is no evidence that gabapentin is effective against primarily generalized seizures, including absence seizures. The optimal dosage range of gabapentin has not been established. It has become increasingly evident that adult doses of 3600 to 4800 mg/d are often well tolerated and may be more effective. Corresponding doses in children may be close to 100 mg/kg per day. Adverse effects of gabapentin include somnolence, dizziness, ataxia, behavioral problems, weight gain, and movement disorders. Serious adverse events have been exceedingly rare.

**LAMOTRIGINE**

Lamotrigine (Lamictal, Glaxo Wellcome Inc, Research Triangle Park, NC) was released in the United States in early 1995. Its mechanism of action is most likely considered to be sodium channel blockade, resulting in inhibition of glutamate release. Lamotrigine is eliminated largely by the liver. The metabolism of lamotrigine is markedly accelerated by inducing drugs and markedly inhibited by valproate. This may result in 5-fold dosage differences for the same lamotrigine blood level. Lamotrigine itself does not significantly affect the metabolism of other drugs. Although it was approved for add-on therapy of partial and secondarily generalized seizures, it appears that this AED has a relatively broad spectrum of efficacy. There is increasing evidence that lamotrigine is quite effective against generalized seizures, particularly absence seizures, and its efficacy in the treatment of Lennox-Gastaut syndrome has been demonstrated in a double-blind study. The most common dose-related adverse effects of lamotrigine are dizziness, sedation, headache, diplopia, and ataxia. The most bothersome adverse effect of lamotrigine is a rash (about 10% overall incidence), which can evolve into potentially lethal Stevens-Johnson syndrome. This association between lamotrigine and rash, which is more frequent in children, has prompted the recent inclusion of a warning in the package insert. There is good evidence that the likelihood of a rash increases with faster titration rates, especially in the presence of valproate, an inhibitor of the elimination of lamotrigine. This observation has led to the current recommendation for very slow titration. In children taking valproate concurrently, the lamotrigine dosage during the first week should be less than 0.5 mg/kg per day, and preferably closer to 0.2 mg/kg per day.

**TOPIRAMATE**

Topiramate (Topamax, McNeil Pharmaceutical, Raritan, NJ) has been available in the United States since early 1997. At least 3 mechanisms of action of topiramate have been identified, including state-dependent blockade of sodium channels, potentiation of γ-aminobutyric acid–mediated neuroinhibition, and blockade of glutamate-mediated neuroexcitation. Topiramate also is a weak carbonic anhydrase inhibitor. Its elimination is accelerated by inducing drugs, but pharmacokinetic interactions with topiramate are otherwise limited. Topiramate is clearly an effective and promising drug, and its place among AEDs will be determined by its adverse effect profile. Controlled studies have demonstrated its effectiveness not only against refractory partial seizures in adults, but more recently also against partial seizures in children, generalized tonic-clonic seizures in children and adults, and drop attacks in patients with Lennox-Gastaut syndrome. The most common adverse effects of topiramate include sedation, problems with concentration and word finding, decreased appetite, and weight loss. Nephrolithiasis has occurred in 1.5% of patients, mostly adults. Adverse effects on the central nervous system appear to be accentuated by rapid titration. Accordingly, a slow titration schedule is recommended with an initial dosage of 25 to 50 mg/d in adults and weekly increases by the same amount, up to an initial goal of 200 to 400 mg/d. The corresponding initial dosage in children is 1 mg/kg per day or less.

**TIAGABINE**

Tiagabine hydrochloride (Gabitril, Abbott Laboratories, North Chicago, Ill) was approved in the United States in October 1997. Tiagabine increases synaptic γ-aminobutyric acid by inhibiting its uptake. The elimination half-life of tiagabine is only 5 to 8 hours, and it is shortened to about 3 hours by inducing drugs. Tiagabine does not seem to affect the kinetics of other drugs. The efficacy of tiagabine has been demonstrated in placebo-controlled studies in patients with partial and secondarily generalized seizures. So far, the recognized adverse effects of this AED are mostly dose-related effects on the central nervous system, such as dizziness, asthenia, and tremor. There have been no significant laboratory abnormalities or dangerous idiosyncratic reactions. The average effective dosage is 32 to 64 mg/d in adults taking inducing drugs, mostly 2 or 3 times per day. The recommended initial dosage is 4 to 8 mg/d, with weekly increases of 4 to 12 mg/d.

**VIGABATRIN**

Vigabatrin (Sabril, Hoechst Marion Roussel, Kansas City, Mo) has not yet been released in the United States at the time of this writing. It has been available in England since 1990 and in several other countries since then, including Canada. Vigabatrin binds irreversibly to γ-aminobutyric acid transaminase, thus decreasing the breakdown of γ-aminobutyric acid. The pharmacokinetic properties of vigabatrin are similar to those of gabapentin, including the lack of pharmacokinetic interactions. Although the elimination half-life of vigabatrin is quite short, its pharmacodynamic action after a single dose can be detected for several days. Studies of vigabatrin in...
adults have clearly demonstrated its efficacy against partial seizures, with little or no efficacy against other seizure types. In children, the efficacy of this AED does not seem to be limited to partial seizures. In fact, vigabatrin has emerged as a potential first-choice AED against infantile spasms.\textsuperscript{10} The most common adverse effects of vigabatrin include drowsiness, dizziness, ataxia, tremor, amnesia, depression, weight gain, and hyperactivity in children. A recent concern has been the occurrence of several cases of visual field constriction, bilateral optic disc pallor, and subtle peripheral retinal atrophy. These cases have prompted the recommendation of initial and periodic (approximately every 3 months) ophthalmologic examinations in patients treated with vigabatrin. The recommended initial dosage of vigabatrin is 1 g/d in adults and 40 mg/kg per day in children, with subsequent titration to 2 to 4 g/d in adults and 80 to 100 mg/kg per day in children (up to 150 mg/kg daily for the treatment of infantile spasms).

**OXCARBAZEPINE**

Oxcarbazepine (Trileptal, Novartis, East Hanover, NJ) has not yet been released in the United States at the time of this writing. Oxcarbazepine is closely related to carbamazepine. It is a prodrug, the active compound being the metabolite mono-hydroxy-carbamazepine. There is no other active metabolite. Efficacy and adverse effects of oxcarbazepine do not differ much from those of carbamazepine. Pharmacokinetic differences between the 2 drugs include the absence of autoinduction of the metabolism of oxcarbazepine and mono-hydroxy-carbamazepine, and the fact that oxcarbazepine is a weaker enzymatic inducer than carbamazepine. In terms of skin rashes, it appears that less than 50% of patients experience a rash when carbamazepine is replaced by oxcarbazepine because of a rash.

Accepted for publication January 22, 1998.

Reprints: Blaise F. D. Bourgeois, MD, Harvard Medical School, Boston Children’s Hospital, Hunnewell 2, 300 Longwood Ave, Boston, MA 02115.

**REFERENCES**