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# How About the New Antiepileptic Drugs?

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**Abstract:** No new antiepileptic drugs (AEDs) were licensed in the United States from 1978 to 1992. In late 1992, felbamate and gabapentin were recommended for approval, and in early 1993, lamotrigine. In July 1993, felbamate was licensed, and gabapentin and lamotrigine may soon follow. Lamotrigine, vigabatrin and clobazam are in use outside the US. Tiagabine, oxcarbazepine, fosphenytoin, topiramate, vigabatrin and zonisamide are in Phase II clinical testing in the US. All of the new AEDs are effective against partial and tonic-clonic seizures. Few controlled clinical trials have been done in patients with absence and myoclonic seizures. Mechanisms of action of the new drugs have not been clearly defined. The new AEDs will provide an opportunity to improve the care of epileptic patients. Even with optimal management with currently available drugs, some 30% of patients remain refractory to medical management.

**Résumé: Qu'en est-il des nouveaux médicaments antiépileptiques?** Aucun nouveau médicament antiépileptique (MAE) n'a été autorisé aux Etats-Unis entre 1978 et 1992. À la fin de 1992, on a recommandé l'approbation du felbamate et de la gabapentine et, au début de 1993, celle de la lamotrigine. En juillet 1993, le felbamate a été autorisé, suivi probablement bientôt de la gabapentine et de la lamotrigine. La lamotrigine, la vigabatrine et le clobazam sont utilisés ailleurs qu'aux Etats-Unis. La tiagabine, l'oxcarbazépine, la fosphénytoïne, le topiramate, la vigabatrine et le zonisamide sont en phase II des essais cliniques aux Etats-Unis. Tous les nouveaux MAEs sont efficaces contre les crises partielles et les crises toniques-cloniques. Peu d'essais cliniques contrôlés ont été faits chez les patients qui ont des absences et des crises myocloniques. Les mécanismes d'action des nouveaux médicaments n'ont pas été clairement définis. Les nouveaux MAEs offrent la possibilité d'améliorer le traitement des patients épileptiques. Même avec un traitement optimal avec les médicaments présentement disponibles, environ 30% des patients demeurent réfractaires au traitement médical.

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Optimally, 60% of patients who have epilepsy (recurrent unprovoked seizures) achieve continued freedom from seizures without worrisome adverse effects on currently available antiepileptic drugs (AEDs). In North America, phenytoin, carbamazepine, valproate and ethosuximide are accepted to be overall the most efficacious and least toxic AEDs. Primary generalized epilepsies (particularly simple absence, juvenile myoclonic epilepsy and Rolandic epilepsy) respond better to appropriate treatment than do the symptomatic or secondary epilepsies (simple, complex partial and secondarily generalized seizures). Other symptomatic or secondary epilepsies characterized by drop attacks, tonic seizures, atypical absence and infantile spasms, Lennox-Gastaut and West syndromes and others associated with psychomotor retardation respond poorly to AED therapy.

There is clearly a need for new AEDs and, after 15 years, three anticonvulsants are poised to enter the market. The United States Food and Drug Administration released felbamate in July 1993, and gabapentin and lamotrigine may be released in late 1993. These drugs have undergone double-blind, controlled clinical trials for efficacy and safety in predominantly simple,

complex partial and generalized tonic-clonic seizures, and all have demonstrated efficacy in double-blind dose-ranging studies.

Additional drugs in various stages of clinical testing – vigabatrin, tiagabine, topiramate and zonisamide – are in advanced stages of testing in the US. Vigabatrin is available in Europe and zonisamide in Japan. Clobazam, a benzodiazepine drug, is available in Canada and Europe but is not being tested in the US. Two new drugs are in advanced testing: oxcarbazepine, a modification of carbamazepine, in Europe; and fosphenytoin, a parenteral prodrug for phenytoin, in the US. Many other drugs are in early stages of testing; however, their potential entry into the AED market will be several years in the future.

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**NEW DRUGS****Felbamate**

Structurally related to meprobamate, this AED is not similar to current AEDs. Unlike meprobamate, it is not sedating and may be mildly stimulating. In animal models, it blocks maximal electroshock (MES)- and pentylenetetrazol (PTZ)-induced seizures. This activity predicts action against partial, generalized tonic-clonic and other seizure types such as absence. Acute and chronic administration in animals demonstrated low toxicity and lethality.<sup>1</sup>

Felbamate has been tested in double-blind, placebo-controlled monotherapy and add-on trials in refractory patients with simple and complex partial seizures with or without generalized tonic clonic seizures. In these trials, felbamate demonstrated statistically significant efficacy without serious adverse effects.<sup>2-4</sup>

Felbamate is administered in a tablet formulation. Maximum serum concentrations are achieved after 2-4 hours.<sup>4</sup> Protein binding is slight at 25-35%. The volume of distribution is 0.8 L/kg. The half-life ranges from 18 to 24 hours in adults on monotherapy. The maximum daily dose of 3600 mg should be given in three or four divided doses because of gastrointestinal adverse effects associated with single large doses.<sup>4</sup> Fifty percent of felbamate is metabolized to inactive metabolites and 50% is excreted unchanged in the urine.

Significant drug interactions occur when felbamate is co-administered with other AEDs. For instance, felbamate decreases carbamazepine plasma levels and increases carbamazepine epoxide levels. Felbamate increases the levels of phenytoin and valproic acid.<sup>5</sup> Phenytoin, carbamazepine and phenobarbital decrease felbamate levels, and valproic acid significantly increases felbamate levels. When felbamate is used as add-on therapy, levels of concomitantly administered AEDs should be carefully monitored.<sup>5</sup>

Felbamate shows promise in helping manage some of the AED-refractory syndromes. In a controlled clinical trial of patients with Lennox-Gastaut syndrome, felbamate reduced the number of seizures and improved the ease of management rendered by parents and care givers.

Adverse effects have been reported by a number of investigators. Nausea, headache, anorexia, somnolence, insomnia, constipation, taste perversion, vomiting, dizziness, abdominal pain, diarrhea and fatigue were reported by Sachdeo et al., in 1992.<sup>2</sup> Tolerance developed to many of the above adverse effects; however, anorexia did not abate. Insomnia, taste perversion and fatigue continued in many of the patients reporting these adverse effects. In the author's study,<sup>6</sup> abdominal distress, insomnia, and anorexia were bothersome, and weight loss persisted.

Felbamate is recommended for monotherapy and add-on therapy.

**Gabapentin**

Gabapentin is a synthetic amino acid that was specifically designed to transport gamma-aminobutyric acid (GABA, a naturally occurring amino acid inhibitory neurotransmitter) across the blood-brain barrier. Gabapentin, however, does not alter whole brain levels of GABA or have any effect on GABA transaminase or GABA uptake by presynaptic terminals or glia.

It also does not appear to act as a GABA agonist or antagonist and has no demonstrable effect on chloride channels. Gabapentin blocks MES-induced convulsions in experimental animals and, to a lesser extent, PTZ-induced convulsions. Therefore gabapentin can be expected to modify partial and tonic-clonic seizures as well as other generalized seizure types.

Controlled clinical trials including double-blind, placebo-controlled and dose-ranging studies have demonstrated efficacy in simple, complex partial and generalized tonic-clonic seizures. Efficacy has been shown to be dose related, increasing from 300 mg/day to 1800 mg/day. Currently, monotherapy trials and doses higher than 1800 mg/day are being conducted.<sup>7,8</sup>

Gabapentin is absorbed from the gastrointestinal tract by a mucosal L-amino acid transport mechanism, which is saturable. Three times a day dosing is recommended to achieve maximal absorption. The half-life of gabapentin is 5-8 hours. The drug is not metabolized. It does not bind to plasma proteins, and it is excreted unchanged in the urine and feces. It is readily transported across the blood-brain barrier and is transported into the cytosol of neurons. It is bound to receptors in the neuronal membrane. The significance of these neuronal membrane binding sites is unknown. Gabapentin blocks repetitive neuronal firing in a way that is similar to the action of phenytoin and carbamazepine but only after a delay, as demonstrated by *in vitro* studies. Gabapentin does not interact with other drugs.

Reported adverse effects are minor. In one study, they consisted of only drowsiness and dizziness to a greater extent than in patients receiving placebo.<sup>9</sup> Patients became tolerant to adverse effects in a short period of time. In studies by Crawford et al., 1987,<sup>10</sup> and Dodrill et al., 1992,<sup>7</sup> psychometric testing showed no changes or improvement between baseline and active treatment, and no differences were noted between low and high doses. Gabapentin appears to be a safe, effective AED with few adverse effects and no drug interactions.<sup>7,8,10</sup>

**Lamotrigine**

Lamotrigine is chemically unrelated to current AEDs. It is a mild antifolate drug that was found to be effective in preventing MES- and PTZ-induced seizures. This action suggests an anti-convulsant effect against partial and tonic-clonic seizures as well as other seizure types. *In vitro* pharmacological studies show the inhibition of release of excitatory amino acids glutamate and aspartate and use-dependent block of Na<sup>+</sup> channels, similar to the action of phenytoin and carbamazepine.<sup>11,12</sup>

Pharmacokinetic studies in humans show near complete absorption, with peak levels achieved within 1-4 hours and a 98% bioavailability. Lamotrigine is approximately 50% bound to plasma proteins. Lamotrigine is metabolized to inactive metabolites and has an elimination half-life of 24 hours in non-induced patients and 12 hours in patients on phenobarbital, carbamazepine or phenytoin. Valproic acid inhibits lamotrigine metabolism and increases lamotrigine's elimination half-life to 50-60 hours in patients receiving both drugs. Lamotrigine does not change the metabolism of other AEDs.<sup>13,14</sup>

In a number of double-blind, placebo-controlled studies using both crossover and parallel design, lamotrigine has been shown to reduce seizure frequency significantly in patients with simple and complex partial and tonic-clonic seizures. Patients with tonic and atonic seizures and Lennox-Gastaut syndrome have been shown to benefit from lamotrigine in controlled clinical trials.<sup>15</sup>

Dose-ranging blinded studies have demonstrated increasing efficacy from 300 to 500 mg/day. Monotherapy and higher daily dose trials are under way.

The safety of lamotrigine has been shown in a variety of clinical assessments. There have been no clinically significant changes in clinical, laboratory, ophthalmologic, electrocardiographic or neurological assessments. Adverse experiences consist of dizziness, headache, diplopia, ataxia, nausea, somnolence, rhinitis and rash. Many of these adverse effects were little different from placebo controls. The incidence of rash is similar to the incidence with carbamazepine and phenytoin therapy.<sup>14</sup>

Lamotrigine is marketed in the United Kingdom and Europe and favorable reports from widespread use have been received. The drug appears to have a mild adverse-effect profile.

### Fosphenytoin

Fosphenytoin is a phosphate ester prodrug for phenytoin. Unlike parenteral phenytoin, fosphenytoin is readily soluble in water at a near neutral pH. (Because of solubility, parenteral phenytoin is dissolved in 40% propylene glycol and 10% alcohol and adjusted to a pH of 12.) Fosphenytoin 150 mg yields sodium phenytoin 100mg after rapid enzymatic conversion by phosphatase in liver.

The safety, tolerance and pharmacokinetics of fosphenytoin have been studied in normal volunteers and epileptic patients in intravenous and intramuscular loading, intramuscular substitution for oral phenytoin and timed intravenous administration studies. Intramuscular loading (10-18 mg/kg) of fosphenytoin in single and split doses produced therapeutic levels after 30 minutes without significant adverse effects. Intramuscular substitution for oral phenytoin produced similar area-under-the-curve values for both routes of administration. Peak plasma levels occurred after approximately 2-3 hours with fosphenytoin, in contrast with a time of approximately 8-10 hours with oral phenytoin. Intravenous loading of fosphenytoin (150 mg phenytoin equivalence/min) produced no adverse effects associated with this rapid rate of administration. (Maximal parenteral phenytoin loading of 50 mg/min is recommended.) Although the conversion time of fosphenytoin to phenytoin is 17 minutes, free levels of phenytoin derived from fosphenytoin rose more rapidly than the level of phenytoin administered intravenously at 50 mg/min.

Fosphenytoin is not associated with the potentially serious adverse effects sometimes associated with intravenous phenytoin administration (serious tissue reactions with extravasated phenytoin). Because of tissue reactions, parenteral phenytoin cannot be administered by the intramuscular route.<sup>16</sup>

Fosphenytoin is a desirable replacement for parenteral phenytoin.<sup>16-20</sup>

### Vigabatrin and Tiagabine

Vigabatrin and tiagabine modify GABA concentrations in the intra- and extracellular compartment of neurons respectively. Vigabatrin blocks GABA metabolism by irreversibly blocking GABA transaminase. Tiagabine blocks the reuptake of GABA at the synaptic site. The significantly increased GABA concentrations enhance chloride channel openings at GABA receptors.

Vigabatrin is marketed in Europe and has undergone extensive clinical trials in the US. Safety and efficacy trials of tiagabine are nearing completion in the US and Europe. Both

drugs are effective in controlling simple and complex partial and tonic-clonic seizures. Both drugs are not effective in treating absence and have been reported to produce spike-wave stupor in some patients. Both drugs have been shown to be clinically safe. Similar adverse effects are seen. Somnolence, tiredness, and nervousness are reported early in treatment. Hallucinatory episodes and alteration in perception have also been reported. There is evidence that patients who have had significant episodes of depression should not be placed on these drugs. Vigabatrin lowers the serum concentration of phenytoin for unknown reasons. Phenytoin induces the metabolism of tiagabine. Other drug interactions have not been confirmed.<sup>21-26</sup>

### Topiramate

Topiramate is a novel investigational drug that has shown preclinical efficacy similar to that of phenytoin and carbamazepine. Double-blind, controlled clinical trials show efficacy against simple and complex partial and tonic-clonic seizures, and efficacy has been reported in open trials in patients with Lennox-Gastaut syndrome. In the author's experience, topiramate is a potent anticonvulsant but has a narrow therapeutic range. Significant cognitive impairment may occur at doses above the therapeutic range. Topiramate does not change traditional AED levels when used as add-on treatment; however, phenobarbital, carbamazepine and phenytoin induce the metabolism of topiramate and shorten its half-life.<sup>27-29</sup>

### Oxcarbazepine

Oxcarbazepine is undergoing clinical trials in Europe. It is a 10-substituted oxy-carbamazepine. It is rapidly metabolized to 10-hydroxy-carbamazepine, which has an activity spectrum similar to carbamazepine's. The purported advantages of oxcarbazepine and its active 10-OH metabolite is that during degradation to the inactive diol metabolite the epoxide stage is avoided. Clinical trials show an efficacy spectrum identical to that of carbamazepine, with the avoidance of some of the adverse effects associated with carbamazepine therapy.<sup>30,31</sup>

### CONCLUSIONS

Epileptologists welcome the arrival of new drugs to treat epileptic patients and hopefully increase the number of patients who are seizure free and unencumbered by adverse effects. The tailoring of drugs to affect a specific enzyme system or transmitter is indeed exciting. Action at specific receptor proteins and membrane binding sites heralds a new era of drug development. One can foresee the treatment of specific seizure types arising from particular loci in the brain with highly selective drugs for receptor proteins and enzymes that are peculiar to the loci of seizure initiation.

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