

those who received placebo (489 vs 453 L/minute) and used less concomitant medications. However, in the second year, these differences were not significant. There was no difference in symptom scores between the groups in either year. The authors concluded

that the clinical effects were limited and many were not sustained for 2 years.

The NIH guidelines recommend consideration of allergen immunotherapy only for select patients in whom asthma cannot be controlled by other means. ■

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# New treatment options for epilepsy

Most patients with epilepsy face a lifetime of drug therapy. Approximately 70% of patients with epilepsy have satisfactory seizure control with standard anticonvulsants. Of the remaining patients, 15% may be helped by epilepsy surgery, but treatment options for patients with uncontrolled seizures and who are not surgical candidates have been limited. Four new anticonvulsant drugs have gained approval by the Food and Drug Administration in the past 3 years, and more are on the horizon.

A "perfect" drug for treating epilepsy has not yet been found, but with the approval of these new drugs and with others in development, we are drawing closer. Some patients

resistant to other anticonvulsants will experience greater seizure control with these new compounds. Further, these newer drugs (particularly gabapentin and lamotrigine) have side-effect and drug-interaction profiles that compare favorably with those of older drugs.

Despite these advantages, clinicians must take into account the higher cost of the newer treatments and bear in mind that little is known about possible adverse effects of long-term use.

## NEW ANTICONVULSANTS

The four newest approved anticonvulsant drugs—gabapentin (Neurontin), lamotrigine



(Lamictal), felbamate (Felbatol), and topiramate (Topamax)—offer some advantages over previously available agents. In clinical trials, these drugs produced similar response rates, each reducing seizure frequency by 50% or more in 20% to 30% of patients.

### Gabapentin

Gabapentin was specifically designed to mimic the neurotransmitter gamma-aminobutyric acid (GABA), believed to inhibit epileptogenic activity in the brain. Although the drug's structure is similar to that of GABA, it does not reproduce GABA's activity of binding to GABA receptors. Ironically, it acts as an anti-convulsant anyway.

Gabapentin was approved only as adjunctive therapy in patients with partial and secondarily generalized seizures. Studies have shown, however, that it is effective when used as monotherapy. It has an extremely favorable side-effect profile (mild sedation, dizziness, and slight ataxia at higher doses) and does not interact with other drugs.

Because it is excreted almost entirely by the kidneys and is not protein-bound, gabapentin is an excellent choice for patients with liver insufficiency and those receiving drugs for multiple medical problems, provided their kidneys are functioning adequately.

The dosages of gabapentin given during clinical trials (1200 to 1800 mg/day) were inadequate; therefore, dosages should be titrated up to 3600 to 4800 mg per day to determine its effectiveness in a given patient. One disadvantage is gabapentin's short half-life, necessitating dosing three or four times a day.

### Lamotrigine

Lamotrigine, an inhibitor of voltage-gated sodium channels, acts similarly to the older drugs phenytoin and carbamazepine. This drug offers the advantages of having a broad spectrum of anticonvulsant activity, a long half-life when used as monotherapy, and predictable behavior because of its linear kinetics. It is moderately protein-bound and conjugated in the liver, so it is associated with very few drug interactions. Its half-life and clearance, how-

ever, are altered when it is given with drugs that induce or inhibit hepatic metabolism.

Lamotrigine is approved only for use as add-on therapy for partial seizures, but European studies have shown it to be effective for generalized tonic-clonic, partial, and absence seizures, and for Lennox-Gastaut syndrome. In other European studies it was as effective as carbamazepine for patients with newly diagnosed partial seizures, but it caused fewer side effects.

One problem with lamotrigine is that patients must be started on a low dose that can only be increased gradually, because of the potential for developing a rash (occurring in 3% to 5% of patients) that is directly related to how rapidly the drug is introduced. The rash is sometimes severe and in rare cases fatal. In patients also receiving valproic acid, which inhibits hepatic metabolism and in effect triples the lamotrigine dose, this potential becomes even more significant.

### Felbamate

Felbamate is effective for multiple seizure types. It has significant disadvantages, however. Besides causing insomnia in many patients, it has a poor drug-interaction profile and is associated with serious treatment complications: aplastic anemia and acute liver failure. This drug is recommended only as second-line therapy in patients for whom the risks of intractable seizures outweigh the risks of therapy.

### Topiramate

Topiramate (Topamax) is the most recent anticonvulsant to receive FDA approval (December 1996). The agent is a monosaccharide derivative that modulates sodium channels and enhances the effect of GABA at the GABA receptor; it may also have an effect at the N-methyl-D-aspartate (NMDA) receptor.

Topiramate was approved for adjunctive therapy in adults with partial and secondarily generalized seizures. Studies have demonstrated that it has a broad spectrum of activity and may prove to be effective for generalized seizures as well. In US trials, approximately 44% of patients with intractable partial

Valproic acid  
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lamotrigine  
dose

seizures experienced a reduction in seizures frequency of at least 50% when topiramate was used as adjunctive treatment.

In monotherapy, topiramate's half-life is approximately 24 hours, but when taken with enzyme-inducing drugs the half-life may be shortened to 12 hours. Topiramate does not alter the kinetics of carbamazepine or valproic acid but may produce a slight elevation of phenytoin level in some patients. Topiramate may reduce the effectiveness of oral contraceptives because of increased metabolism of the hormones.

Side effects of this drug tend to be mild and dose-related, with dizziness, drowsiness,

and ataxia being most common. Cognitive problems are seen in some patients and may be more likely to occur with rapid dose escalation. About 1.5% of patients receiving this drug developed kidney stones, the same frequency as with acetazolamide. ■

#### ■ SUGGESTED READING

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# Beyond statistics: What is really important in medicine?

Misuse of statistics in the medical literature and unjustified faith in statistical significance have often made physicians disregard their own clinical judgment and experience. To counteract this tendency, clinicians should apply critical reasoning when interpreting the results of trials, and researchers should find better ways of measuring clinical outcomes that are considered "soft" (such as patient symptoms and quality of life), although often of paramount importance.

#### ■ WHEN IS STATISTICAL SIGNIFICANCE CLINICALLY SIGNIFICANT?

Given a large enough sample size, even a trivial difference can achieve statistical significance. For example, if a hypothetical trial enrolled thousands of patients and found that 1% fewer patients died if they received an experimental treatment, such a difference might well be statistically significant. How-

ever, clinicians might question whether the difference was important.

Further, results can be expressed in ways that exaggerate their importance. Of the following statements, which sounds most impressive?

- *Treatment decreased the mortality rate by 38% compared with placebo.*
- *The mortality rates were 5% with treatment and 8% with placebo.*
- *Treatment improved the survival rate by 3% compared with placebo.*

The three statements describe the same data, but a 38% decrease in mortality sounds much more impressive.

For another example, consider three statements about the effect of exposure to an agent on the incidence of a disease:

- *The risk ratio for the disease is increased to 5 in persons exposed to the agent.*
- *The incremental risk of the disease is increased by only 4 per 10 000 in persons exposed to the agent.*