

## Which Antiepileptic Drugs Work Best?

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### Which Antiepileptic Drugs Are Best for Seizures?

A wide range of antiepileptic drugs (AEDs) is available for the treatment of epilepsy (Table). Since 1993, the US Food and Drug Administration (FDA) has approved 13 new AEDs, with more in the pipeline. As the number of therapeutic options has increased, choosing the best AED for a particular patient has become more challenging.

**Table. Currently Available Antiepileptic Drugs**

Old Drugs (since 1912)	New Drugs (since 1993)
Carbamazepine (Tegretol®)	Ezogabine (Potiga®)
Divalproex sodium (Depakote®)	Felbamate (Felbatol®)
Ethosuximide (Zarontin®)	Gabapentin (Neurontin®)
Phenobarbital (Luminal®)	Lacosamide (Vimpat®)
Phenytoin (Dilantin®)	Lamotrigine (Lamictal®)
Primidone (Mysoline®)	Levetiracetam (Keppra®)
Valproic acid (Depakene®)	Oxcarbazepine (Trileptal®)
	Pregabalin (Lyrica®)
	Rufinamide (Banzel®)
	Tiagabine (Gabitril®)
	Topiramate (Topamax®)
	Vigabatrin (Sabril®)
	Zonisamide (Zonegran®)

With the exception of rufinamide, which is indicated uniquely for seizures associated with Lennox Gastaut syndrome, all of the new drugs are approved for the treatment of partial seizures.

### Choosing an Antiepileptic Drug

Many factors must be considered when prescribing an AED for a particular patient including the patient's seizure type, epilepsy syndrome, history of allergies, medical and psychiatric comorbidities, potential drug-drug interactions, renal function, hepatic function, protein binding, possibility of pregnancy, dosing schedule, availability of liquid, parenteral and extended release formulations, pharmacogenetics, and cost. When AEDs are similar in efficacy, differences in tolerability often guide medication selection.

The growing science of pharmacogenetics has not yet provided new tools to predict drug efficacy in an individual patient.<sup>[1]</sup> However, pharmacogenetics does enable identification of Asian patients more likely to suffer carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.<sup>[2]</sup> These adverse reactions may be avoided by prospectively testing patients for the human leukocyte antigen-B\*1502 allele.

Overall, only about 50% of patients with newly diagnosed seizures become seizure free with their first AED.<sup>[3]</sup> This sobering statistic emphasizes the importance of trying the drug most likely to succeed the first time around to prevent further seizures and their related medical and psychosocial morbidity.

## Head-to-Head Trials

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Additional information that would help physicians select the best AED for a given patient are data from head-to-head trials. This new study that compares pregabalin with lamotrigine is one of a growing list of valuable such trials.<sup>[4]</sup> A landmark head-to-head study that has strongly influenced epilepsy care is the Veterans Administration (VA) multicenter, monotherapy trial that compared the most widely used AEDs at the time; carbamazepine, phenobarbital, phenytoin, and primidone.<sup>[5]</sup> The VA study revealed that carbamazepine and phenytoin offer better total control of partial seizures, but that all 4 drugs had similar efficacy for secondarily generalized tonic clonic seizures.

A subsequent VA study concluded that carbamazepine had greater efficacy and fewer persistent side effects when treating complex partial seizures than valproate, but both were comparable for the treatment of secondarily generalized tonic clonic seizures.<sup>[6]</sup>

A prospective, multicenter, double-blind, parallel group trial compared an older drug (controlled release carbamazepine) with a newer drug (levetiracetam) in patients with newly diagnosed epilepsy and determined "noninferiority" of levetiracetam.<sup>[7]</sup> Both drugs produced similar seizure free rates and incidence of adverse reactions. Side effect profiles differed, with more back pain in patients treated with controlled-release carbamazepine and more depression and insomnia in patients taking levetiracetam.

Examples of other head-to-head trials include an open label comparison of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy, which concluded that both were equally effective, but lamotrigine was better tolerated.<sup>[8]</sup> A study of elderly patients revealed that carbamazepine had the highest seizure-free rates, but patients treated with gabapentin or lamotrigine were more likely to remain in the study at 12 months.<sup>[9]</sup>

None of the newer drugs has been shown to control seizures better than any of the older drugs in a head-to-head trial.<sup>[3]</sup> However, new drugs offer different side effect profiles that affect tolerability. Comparative trials yield important information, but not necessarily the last word on drug choice. Factors such as dose selection, dose escalation schedules, use of immediate or controlled release preparations, and other variables in trial design may bias the results toward 1 drug or the other.<sup>[4]</sup>

### Pregabalin vs. Lamotrigine

The authors of the aforementioned study comparing pregabalin with lamotrigine randomly assigned patients with newly diagnosed partial seizures to pregabalin (N = 330) or lamotrigine (N = 330) in a phase 3, double-blind, multicenter study.<sup>[4]</sup> Patients began dosing with pregabalin 150 mg/day, which could be increased to 300 mg/day, 450 mg/day, or 600 mg/day. Lamotrigine was started at 100 mg/day, which could be increased to 200 mg/day, 400 mg/day, or 500 mg/day. More patients receiving lamotrigine (68%) reached the primary endpoint of seizure freedom for 6 or more months than patients on pregabalin (52%). The 5 most common adverse events were headache, dizziness, somnolence, fatigue, and weight increase, and were all more common in subjects on pregabalin than lamotrigine, although these differences were not statistically significant.

### Pharmaceutical Sponsorship

Parenthetically, this Pfizer-sponsored study disproves the cynical notion professed by some that all comparative studies sponsored by pharmaceutical companies can be summarily dismissed because they always conclude that their drug is superior. Pfizer manufactures pregabalin.

## Conclusions

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Choosing an AED for a patient with epilepsy is a complex decision that must be individualized for each patient based on numerous factors including seizure type, epilepsy syndrome, comorbidities, and many other variables. An increasing number of head-to-head trials, although imperfect, offer guidance for the practitioner. The most recent study comparing pregabalin and lamotrigine in patients with newly diagnosed partial seizures suggests that while both AEDs have similar tolerability, lamotrigine provides better seizure control.

## References

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