

The Role of New Antiepileptic Drugs

Based on a presentation by Jacqueline A. French, MD

Presentation Summary

For many years, epileptologists had few choices for treating seizures. Within the past 20 years several "new generation" antiepileptic drugs (AEDs) were introduced. The most recent additions include oxcarbazepine, levetiracetam, and zonisamide. New agents have been shown in clinical trials to offer similar efficacy compared with older, more established AEDs, but the new agents offer important improvements in safety. Although clinical trials to specifically measure the efficacy of the new AEDs in treating idiopathic generalized epilepsy are rare, the new agents have demonstrated efficacy in treating generalized tonic-clonic convulsions. Data for treatment of Lennox-Gastaut syndrome indicate a clear effect with lamotrigine or topiramate and possibly some effect with zonisamide and levetiracetam. Studies of juvenile myoclonic epilepsy and absence seizures suggest that zonisamide, lamotrigine, topiramate, and levetiracetam may be effective. Each of the new AEDs is effective in controlling partial seizures. These agents may also be appropriate choices for newly diagnosed patients or those whose conditions are refractory to treatment. In clinical trials, patients who are refractory to treatment are often given escalated doses to gain effect, but higher doses also result in more adverse events and higher withdrawal rates. Generally, the higher the dose, the greater the odds of withdrawal, with the exception of levetiracetam, which is not associated with increased withdrawal rates at high doses. Newly diagnosed patients are likely to be controlled with the first therapy given to them. It is therefore important to select an agent with the best safety, efficacy, and tolerability profile possible.

Within the past 2 decades there has been an explosion of new drugs available to treat epilepsy, as shown in **Table 1**. With so many options, it can be confusing to know when to use a new generation antiepileptic drug (AED) rather than an older drug. It is also necessary to differentiate between new generation AEDs to know which is most effective in a particular situation.

Older AEDs are often associated with serious side effects including aplastic anemia, thrombocytopenia, reduced white blood cell counts, and other hematological problems. This history of serious side effects has made blood and hepatic monitoring necessary. Additional concerns about older AEDs include their effect on hormonal patterns in women, teratogenicity, and potentially serious drug interactions. In contrast, new generation AEDs offer significant advantages over the older drugs, including better safety profiles and success in treating a broad spectrum of seizure types. Most new AEDs are also safer for women, and drug interactions are less likely, depending on the metabolic profile of the agent.

Role of New AEDs

Several seizure patient groups are underserved and may benefit from treatment with new generation AEDs. Patients with idiopathic generalized epilepsy syndromes, including absence, generalized tonic-clonic, and juvenile myoclonic epilepsy, usually have more

than one seizure type. Some patients experience absence and myoclonic seizures, and generalized tonic-clonic convulsions. AEDs are selected according to seizure type, thus patients with generalized seizures may take combination therapy to ensure that each type of seizure is treated. Ideally, epileptologists would have a new, broad-spectrum AED to treat patients with generalized epilepsy, obviating the need for combination therapy.

Among older AEDs, only valproic acid is effective in treating the many seizure types associated with idiopathic generalized epilepsy. Valproate is associated with serious adverse effects, however, including weight gain, tremor, pancreatitis, hepatic disease, and thrombocytopenia, among others. Unfortunately, because adult idiopathic generalized epilepsy has not been studied in clinical trials as often as other types of epilepsy syndromes, little study information is available about the efficacy of new generation AEDs for this indication. Labeling for treatment of generalized seizure types is unlikely to be pursued, thus off-label use is necessary to provide treatment

options for these patients. Some information about specific agents is available.

Effectiveness of several AEDs used to treat generalized seizures is illustrated in **Table 2**. All of these agents have demonstrated efficacy in treating generalized tonic-clonic convulsions. Data for treatment of Lennox-Gastaut syndrome indicate a clear effect with lamotrigine or topiramate and possibly some effect with zonisamide and levetiracetam. Studies of juvenile myoclonic epilepsy and absence seizures suggest that zonisamide, lamotrigine, topiramate, and levetiracetam may be effective.¹⁻⁵

In partial epilepsy syndromes, all seizure types begin in a single focus. The degree of spread from that focus determines whether the seizure is simple partial with no loss of awareness, complex partial with loss of awareness, or a generalized tonic-clonic convulsion. Any treatment that prevents the spread from the focal point will prevent seizures. Each of the new AEDs is effective in controlling partial seizures regardless of the location of the focus.

Because effectiveness does not seem to be specific to seizure type or location in partial epilepsy, determining which drug to use can be confusing. Data currently available for new AEDs usually are from add-on studies, rather than trials of these drugs used as monotherapy. Add-on studies generally include a sample of patients whose conditions have been refractory to treatment. The entire sample is often given the same dose or a few fixed doses. The effect of background AEDs used by patients in the trial may skew efficacy and adverse event data. It is therefore important to distinguish between *efficacy* and *effectiveness*. Efficacy is defined as seizure reduction in the setting of a controlled clinical trial, whereas effectiveness is the ability of a drug to control seizures in the setting of use. In nontrial use, epileptologists can tweak drug effects by increasing or decreasing both the new and the old AEDs used by a patient to find the dose that provides the maximal effect and tolerability for that individual. This

Table 1. Old and New Antiepileptic Drugs

Older Generation
■ Phenytoin
■ Carbamazepine
■ Sodium valproate
■ Phenobarbital
■ Primidone
New Generation
■ Felbamate
■ Gabapentin
■ Lamotrigine
■ Topiramate
■ Tiagabine
Newer Generation
■ Oxcarbazepine
■ Levetiracetam
■ Zonisamide

dose adjustment may possibly increase effectiveness beyond the efficacy reported in clinical trials.

AED Use in Refractory and Newly Diagnosed Patients

New AEDs also have many characteristics that make them useful for patients whose conditions are refractory to older agents. Ideal characteristics of an agent for refractory conditions include a high response rate, good seizure control, tolerability when used as adjunctive therapy, ability to be used as monotherapy, and no development of tolerance. Trial data reporting only a reduction in the number of seizures for patients with refractory conditions may be misleading. In these patients, doses are often escalated before significant effects occur. High doses are likely to increase adverse effects and, subsequently, withdrawal rates. Even when patients drop out of studies, however, their last measurement of efficacy is commonly carried forward and reported. A more balanced view of effectiveness includes response and withdrawal from a study. **Figure 1** illustrates the relationship between efficacy in clinical trials and withdrawal rates. In general, higher efficacy is associated with higher withdrawal rates. Levetiracetam is an exception; the efficacy of this agent is relatively high but there is a low withdrawal rate. (In **Figure 1**, a higher odds ratio on the x-axis translates to higher efficacy in a meta-analysis of clinical trial results, and a higher odds ratio on the y-axis corresponds to higher withdrawal rates).^{6,7}

Ideally, an AED selected for newly diagnosed patients should be effective as monotherapy and should cover a broad spectrum of seizure types, because the diagnosis may not be definitive when the epileptologist first sees the patient. Rapid titration is also important to reduce the likelihood of another seizure. A recently published study by Kwan and Brodie⁸ reported that 47% of newly diagnosed patients remained free of seizures during treatment with their first AED. An additional 14% became seizure free during treatment with a second or third drug.⁸

This study suggests that most patients will remain on the first drug prescribed, thus it is important for a clinician to select an agent with the best safety, efficacy, tolerability, and quality-of-life profile. Patients who become seizure free will be reluctant to change medication later.

Monotherapy

Despite the increased number of AEDs available, only 3 have been approved for monotherapy: felbamate, lamotrigine, and oxcarbazepine. Felbamate was approved for treatment in newly diagnosed patients and those with refractory conditions, but it is associated with fatal aplastic anemia, ruling it out as an option for newly diagnosed patients.⁹ Lamotrigine was approved for withdrawal to monotherapy for refractory patients. Oxcarbazepine was approved as monotherapy for newly diagnosed and refractory patients. Yet, having only old AEDs and oxcarbazepine labeled for use as monotherapy does not provide epileptologists with enough safe, effective choices to offer newly diagnosed patients. To complicate matters for physicians, important clinical data about the effectiveness of new AEDs used as monotherapy in newly diagnosed patients have not been accepted for labeling purposes in

Table 2. Effectiveness of New AEDs

	GTCC	Lennox-Gastaut	JME	Absence
Zonisamide	+	?	?+	?
Gabapentin	+	-	-	-
Lamotrigine	+	+	?	?+
Oxcarbazepine	+	-	-	-
Topiramate	+	+	?+	?
Levetiracetam	+	?	?+	?+
Tiagabine	+	-	-	-

+ = effective; - = not effective; ? = possibly effective; ?+ = probably effective. AEDs = antiepileptic drugs; GTCC = generalized tonic-clonic convulsions; JME = juvenile myoclonic epilepsy.

the United States. A study by Brodie et al¹⁰ demonstrated that newly diagnosed patients taking lamotrigine or carbamazepine as monotherapy in a double-blind, randomized, parallel study over 48 weeks reported no difference in efficacy

between the 2 drugs but fewer withdrawals were found in the lamotrigine cohort (15% versus 27%), as shown in **Figure 2**. Withdrawals were the result of a lack of seizure control or lack of tolerability.

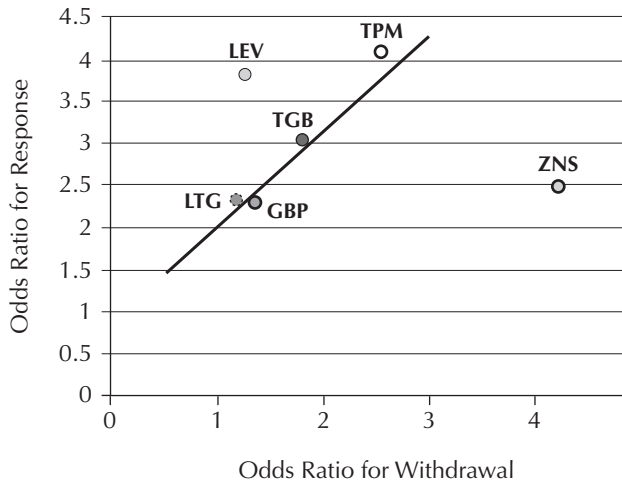
Despite the efficacy and safety of new generation AEDs, older agents continue to be used for various reasons. Phenytoin is commonly used in emergency departments because the drug can be administered at high doses for maximum control without the need for titration. Levetiracetam and gabapentin are new drugs that also do not need to be titrated, making them potentially good candidates for use in emergency department situations, once effectiveness in monotherapy is established (**Table 3**).

Other Factors in Selecting AEDs

Determining which drug will effectively control a patient's seizures takes time. For reasons that are not yet clear, a drug may be effective for some patients with partial epilepsy but not for others. Epileptologists do not always know why a patient's condition is refractory to therapy, so access must be made to every drug available to allow the specialist to find the one agent that works as monotherapy or the agents that will be effective as combination therapy. Access to a wide array of AEDs, including the more expensive new generation therapies, allows physicians to provide patients with the best chance for optimal seizure control.

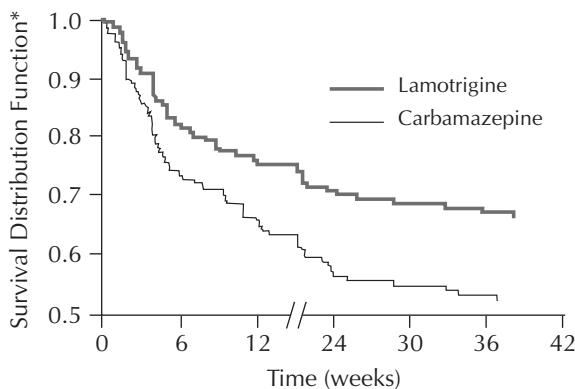
Factors in selecting an AED include spectrum of activity, titration rate, short- and long-term side effects, dosing schedule, and the potential for teratogenicity. Dosing schedule is an important consideration for patients who have difficulty adhering to treatment regimens. Teratogenicity is relevant primarily in female patients. The potential for side effects in the new AEDs will vary depending on dose, pharmacodynamic profile, and coadministration with other medications. Polypharmacy can significantly increase the incidence of side effects, as shown in **Table 4**. In a study by Gilliam et al,¹¹ for example, lamotrigine was added to existing regimens of carba-

Figure 1. Odds Ratios of Response Versus Withdrawal



GBP = gabapentin; LGT = lamotrigine; TGB = tiagabine; TPM = topiramate; ZNS = zonisamide; LEV = levetiracetam.
Source: Reference 6.

Figure 2. Lamotrigine Versus Carbamazepine in Newly Diagnosed Patients: Withdrawals from Therapy



*Percentage of patients remaining on selected treatment.
Source: Reprinted with permission from Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet* 1995;345:476-479.

mazepine or phenytoin monotherapy. After 4 weeks, existing regimens were withdrawn, and patients remained on lamotrigine as monotherapy for the next 12 weeks. After existing therapy was withdrawn, side effects in the lamotrigine cohort diminished on monotherapy.¹¹ An interesting point about this study was that the existing therapy included enzyme inducers, which would have reduced blood levels of lamotrigine. After the existing therapy was withdrawn, blood levels of lamotrigine increased, but side effects decreased on monotherapy.

Nondose-related side effects must also be considered. Topiramate and zonisamide are associated with decreased weight, whereas gabapentin is associated with increased weight. Oxcarbazepine is associated with hyponatremia, thus patients should be monitored regularly. Topiramate and possibly zonisamide may produce hypohydrosis. No known serious side effects are associated with gabapentin or levetiracetam. Other serious side effects for new generation AEDs include¹²:

- Lamotrigine: rash, Stevens-Johnson syndrome, and hypersensitivity syndromes
- Topiramate: renal calculi or possibly hepatic failure
- Tiagabine: spike-wave stupor
- Oxcarbazepine: rash
- Zonisamide: renal calculi, rash, or possibly aplastic anemia

It is important to remember that drugs that are metabolized by the liver are associated with idiosyncratic reactions and drug interactions leading to serious adverse effects. Although no currently known adverse effects prevent long-term use of any of the new AEDs, some may yet present themselves. Long-term side effects associated with older AEDs are well known and are an important reason to consider newer agents. Phenobarbital is associated with Dupuytren's contractures, frozen shoulder, and joint pain, and phenytoin is associated with cerebellar ataxia, peripheral neuropathy, gingival hyperplasia, and hirsutism.¹³

Despite the safer profile of new generation AEDs, women who have epilepsy and want to become pregnant must be informed that no seizure medication has been proven safe in pregnant women. A prospective database of 40 women taking

Table 3. Types of Initiation of AEDs

AEDs	Initiation
Phenytoin	IV/oral load
Carbamazepine	Gradual initiation/1–2 weeks
Valproate	Immediate therapeutic dose
Topiramate	Gradual initiation/4–6 weeks
Gabapentin	Immediate therapeutic dose
Lamotrigine	Gradual initiation/4–6 weeks
Levetiracetam	Immediate therapeutic dose
Zonisamide	Gradual initiation/4–6 weeks
Oxcarbazepine	Gradual initiation/4–6 weeks

AEDs = antiepileptic drugs; IV = intravenous.

Table 4. Side Effects in Adjunctive Versus Monotherapy Administration of Lamotrigine

Side Effect	Adjunctive (n = 76)	Monotherapy (n = 43)
Dizziness	20%	7%
Nausea	16%	7%
Headache	13%	7%
Dyspepsia	0%	3%
Somnolence	8%	0%
Asthenia	12%	2%
Coordination abnormality	12%	2%

Source: Reference 11.

lamotrigine as monotherapy during their pregnancies found no teratogenic effects. More data are needed, but animal models show few teratogenic effects with new AEDs, compared with known effects in animal models exposed to the older agents.

Conclusion

New generation AEDs represent advances over old agents because of their superior pharmacokinetic characteristics and safer adverse effect profiles. Unfortunately, extensive clinical study of these new agents is lacking, making it necessary to extrapolate information about effectiveness from different seizure types. Labeling of new agents for broader use is not likely to occur in the United States.

Because efficacy differences have not been established between new and old agents, it is important to look at other characteristics when selecting an agent for treatment. Patients whose conditions are refractory to old treatment regimens need access to a wide variety of AEDs to improve the chances of finding a regimen that will control their seizures. Because patients use these medications to treat a chronic condition, it is important to select agents with the fewest adverse effects and the safest pharmacokinetic profile. Patients respond differently to AEDs for reasons that are still unclear, and it is often not possible to quickly determine which agent or regimen will work. Each new AED will be the "magic bullet" for some patients, so it is important to have as much choice as possible.

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