The New Antiepileptic Drugs
Clinical Applications

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Epilepsy affects nearly 2 million people in the United States.\(^1\) Despite many recent surgical advances, medications remain the mainstay of treatment. Approximately 70% of patients with epilepsy will become seizure-free using a single antiepileptic drug.\(^2\) For the remaining 30%, recurrent seizures as well as intolerable adverse effects can have significant impact on quality of life. In the last decade, 8 new antiepileptic drugs have been approved for therapy, broadening treatment options and providing hope for improved seizure control and tolerability.

The initial diagnostic evaluation and treatment of patients with new-onset seizures are complex and should be undertaken by a neurologist or epilepsy specialist. The first diagnostic goal is to confirm that the events in question are epileptic seizures and if so, whether partial or generalized in onset (FIGURE). A detailed history and description of the events in question given by the patient as well as a witness is crucial. Electroencephalography (EEG) and magnetic resonance imaging (MRI) aid in the classification of the seizure type and help assess for any underlying structural lesions that could be contributing to the onset of seizures. Finally, patient history, neurological examination findings, and results of diagnostic tests are also taken into account to classify the patient as having a particular epilepsy syndrome, which has implications for treatment as well as prognosis.

See also p 605 and Patient Page.

In the past decade, 8 new antiepileptic drugs have been approved for use in the United States, offering many new treatment options to patients with epilepsy. With expanding use of these newer agents, primary care clinicians are challenged with understanding the roles that each new agent plays in the treatment of patients with epilepsy as well as possible interactions with other pharmacological therapies. Each new medication provides a unique profile of pharmacokinetics, adverse effects, and mechanisms of action, making an appreciation of how these agents are best utilized even more difficult. Despite well-performed trials evaluating the safety and efficacy of specific antiepileptic drugs, the lack of head-to-head comparisons among them makes it difficult to endorse a single therapeutic regimen. Limited studies have compared the new antiepileptic drugs with more traditional medications and found similar efficacy but improved tolerability of the newer agents. There remains no well-established guidelines for choosing a particular antiepileptic drug or for choosing a newer agent over a traditional one. However, careful consideration of seizure type, patient comorbidities, and specific medication toxicities aids in prescribing the most appropriate medication. This article aims to familiarize the general practitioner with the appropriate roles and effective uses of the new antiepileptic drugs in specific clinical scenarios.

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CLINICAL CASES

Case 1

A 22-year-old woman, otherwise healthy, presents with a 6-month history of episodes of unresponsiveness accompanied by lip smacking lasting 1 to 2 minutes and occurring 2 to 3 times per month. She takes no medications. She is in a monogamous relationship with a male sexual partner and only occasionally uses contraception. A routine EEG shows left temporal epileptiform activity and MRI of the brain shows left mesial temporal sclerosis.

One of the most challenging populations of epilepsy patients is women of childbearing age. Many issues must be considered, including contraception, pregnancy, and bone health. Most of the traditional anticonvulsant medications enhance the metabolism of oral contraceptives, resulting in an increased risk of unexpected pregnancy, although the use of formulations with higher estrogen content may help reduce this risk. On the contrary, many of the new antiepileptic drugs have not been shown to have any effect on the metabolism of oral contraceptives, with the exception of felbamate, topiramate, and oxcarbazepine.

The treatment of epilepsy during pregnancy has always presented a unique challenge that should be managed by a specialist. Congenital malformations occur in 4% to 6% of infants born to women with epilepsy, twice that of the general population, with even higher rates in women taking more than 1 antiepileptic drug. Evidence supports the use of antiepileptic drugs as the cause for these teratogenic effects.

Recent studies have shown the incidence of congenital malformations to be increased in the offspring of women taking phenobarbital, phenytoin, carbamazepine, and valproate monotherapy and therefore each is classified as pregnancy category D. Further data are being collected from the North American Antiepileptic Drug Pregnancy Registry, which is designed to measure the teratogenic effects of all antiepileptic drugs (Box). Early data released from the registry demonstrate the strongest evidence of a link between congenital malformations and antiepileptic drug exposure. Infants exposed to valproate monotherapy had an 8.8% incidence of major birth defects (n=123; 95% confidence interval [CI], 3.0%-9.5%), and those exposed to phenobarbital monotherapy experienced a 6.3% incidence (n=79; 95% CI, 2.1%-14.2%) compared with 1.6% of controls.

There have been insufficient data collected on the teratogenic effects of the new antiepileptic drugs; therefore, each is classified as pregnancy category C. However, the Lamotrigine Pregnancy Registry has been collecting data from women with exposure to lamotrigine during the first trimester and preliminary results have recently been published. A total of 168 women taking lamotrigine monotherapy were followed up, with a resultant 1.8% incidence of major birth defects compared to rates in the general population. Further data are being collected to more conclusively evaluate the safety of lamotrigine as well as the other new antiepileptic drugs in pregnancy.

Although the exact mechanism of teratogenesis is unknown, folate deficiency is thought to be a major contributing factor. Serum and red blood cell folate levels have been found to be decreased in women taking phenobarbital as well as phenytoin, particularly in combination. Various mechanisms have been proposed to explain the antifolate effects of antiepileptic drugs, including decreased intestinal ab-

Figure. Algorithm for Diagnosis and Treatment of Recurrent Seizures
sorption, induction of hepatic enzymes, and inhibition of folate synthesis, although the exact mechanism is unknown.\textsuperscript{15} The effects of the newer antiepileptic drugs on folate metabolism have not been evaluated; however, the lack of induction of hepatic enzymes by most of the new medications may suggest minimal interference. Nevertheless, folate supplementation is recommended for all women of childbearing age taking any antiepileptic drug.

Finally, phenobarbital, phenytoin, and carbamazepine have been associated with decreased bone mineral density.\textsuperscript{16-18} Although many theories have been proposed, the principal mechanism is thought to be induction of hepatic enzymes leading to increased catabolism of vitamin D.\textsuperscript{16,19} However, a recent study demonstrated a link between valproate, a hepatic enzyme inhibitor, and bone loss, suggesting that other mechanisms may be involved.\textsuperscript{20} No studies have been performed evaluating the effect of any of the new antiepileptic drugs on bone density, although lack of induction of hepatic enzymes suggests a possible benefit over the conventional antiepileptic drugs.

Table 1. Comparison of Traditional and Newer Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Protein Binding, %</th>
<th>Metabolism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>80</td>
<td>Hepatic</td>
<td>Extensive patient exposure</td>
<td>Drug interactions, hyponatremia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>50</td>
<td>Hepatic</td>
<td>Inexpensive, once-daily dosing</td>
<td>Sedation, cognitive effects</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>90</td>
<td>Hepatic</td>
<td>Inexpensive, once-daily dosing</td>
<td>Nonlinear kinetics, drug interactions</td>
</tr>
<tr>
<td>Valproate</td>
<td>95</td>
<td>Hepatic</td>
<td>Broad spectrum</td>
<td>Weight gain, tremor, hair loss</td>
</tr>
<tr>
<td>Newer agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felbamate</td>
<td>25</td>
<td>Hepatic</td>
<td>Broad spectrum</td>
<td>Risk of aplastic anemia, hepatotoxicity</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>&lt;10</td>
<td>Renal</td>
<td>No drug interactions, rapid titration</td>
<td>Sedation, weight gain</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>55</td>
<td>Hepatic</td>
<td>Broad spectrum, favorable adverse effect profile</td>
<td>Slow titration, rash</td>
</tr>
<tr>
<td>Topiramate</td>
<td>15</td>
<td>Hepatic/renal</td>
<td>Broad spectrum</td>
<td>Slow titration, cognitive effects, kidney stones</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>95</td>
<td>Hepatic</td>
<td>Novel mechanism of action</td>
<td>Multiple doses per day, tremor</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>&lt;10</td>
<td>Renal</td>
<td>No drug interactions, rapid titration</td>
<td>Rare behavioral changes</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>50</td>
<td>Hepatic</td>
<td>Less neurotoxic adverse effects than carbamazepine</td>
<td>Hyponatremia risk</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>40</td>
<td>Hepatic</td>
<td>Broad spectrum, once-daily dosing</td>
<td>Slow titration, anorexia</td>
</tr>
</tbody>
</table>

Table 2. Dosing and Cost Comparison

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Starting Daily Dose, mg*</th>
<th>Daily Dosing Interval</th>
<th>Average Daily Maintenance Dose, mg</th>
<th>Titration Schedule†</th>
<th>Monthly Cost, $‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>400</td>
<td>3 Times</td>
<td>1200</td>
<td>Slow</td>
<td>91.80</td>
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<tr>
<td>Phenobarbital</td>
<td>60</td>
<td>Once</td>
<td>150</td>
<td>Slow</td>
<td>2.70</td>
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<tr>
<td>Phenytoin</td>
<td>300</td>
<td>Once</td>
<td>300</td>
<td>Rapid</td>
<td>21.60</td>
</tr>
<tr>
<td>Valproate</td>
<td>750-1000</td>
<td>3 Times</td>
<td>2000</td>
<td>Rapid</td>
<td>217.20</td>
</tr>
<tr>
<td>Newer agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900</td>
<td>3 Times</td>
<td>2400</td>
<td>Rapid</td>
<td>235.80</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>50</td>
<td>Twice</td>
<td>400</td>
<td>Slow</td>
<td>176.71</td>
</tr>
<tr>
<td>Added to valproate</td>
<td>25 (Every other day)</td>
<td>Twice</td>
<td>100-200</td>
<td>Slow</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>25-50</td>
<td>Twice</td>
<td>400</td>
<td>Slow</td>
<td>228.28</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>4</td>
<td>2-4 Times</td>
<td>48</td>
<td>Slow</td>
<td>206.40</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000</td>
<td>Twice</td>
<td>1500</td>
<td>Rapid</td>
<td>164.58</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>600</td>
<td>Twice</td>
<td>1200</td>
<td>Slow</td>
<td>193.20</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>1000</td>
<td>Once</td>
<td>200</td>
<td>Slow</td>
<td>113.40</td>
</tr>
</tbody>
</table>

*As recommended by each manufacturer’s package insert.
†Rapid titration indicates maintenance dose achieved in less than 2 weeks; slow titration, an average of 2 to 12 weeks required to achieve maintenance dose.
‡Brand name prices from the 2002 Drug Topics Red Book. Retail prices may be higher or lower depending on the pharmacy and patient’s insurance coverage.
also start daily folate supplementation.

Case 2
A 65-year-old man with a history of hypertension, atrial fibrillation, hypercholesterolemia, and a right middle cerebral artery stroke 6 months previous reports 3 separate episodes of head deviation to the left with rhythmic jerking of the left arm and left side of his face lasting approximately 1 minute. He is taking warfarin, atenolol, and atorvastatin.

Elderly individuals have the highest incidence of epilepsy across age groups, approaching nearly twice that of childhood. Common underlying causes of epilepsy in this population include stroke, neurodegenerative disease, and brain neoplasm. Therefore, neuroimaging is critical in the evaluation of these patients. However, up to half of these patients have no specific identifiable underlying cause. Physiological changes associated with aging as well as concurrent illnesses and resultant polypharmacy pose particular challenges in the treatment of epilepsy in the elderly population. In addition, elderly individuals have been shown to be more susceptible to the neurotoxic effects of antiepileptic drugs, including gait disturbance, sedation, and tremor. Fortunately, seizures in elderly persons are usually easily treated with a single agent at low therapeutic doses.

There are limited studies on the effects of the new antiepileptic drugs in the elderly population. Two studies compared gabapentin and lamotrigine with carbamazepine in elderly patients and found equal efficacy but better tolerability in the patients taking gabapentin or lamotrigine. The lack of significant drug interactions in addition to low protein binding seen in the majority of the new antiepileptic drugs, particularly gabapentin and levetiracetam, suggest a benefit of these medications in the elderly population.

Stroke is the most common identifiable cause for the development of partial-onset seizures in elderly individuals, as is demonstrated in this particular case. The onset of seizures can occur immediately following the stroke or months to years later with the risk of recurrence as high as 50%. In this patient, minimizing drug interactions is of utmost importance, especially in the setting of warfarin therapy. Lamotrigine has been shown to have a favorable adverse effect profile in this population, with minimal drug interactions, and would therefore be a good consideration as initial therapy. Gabapentin has not been definitively shown to be efficacious as monotherapy in younger, refractory study populations and therefore is currently approved only for adjunctive use. However, minimal central nervous system adverse effects and the lack of drug interactions coupled with the fact that seizures in the elderly population are typically more responsive to medication than are traditional study populations make gabapentin an attractive option for elderly patients with seizures. In fact, a recent survey of experts in the field of epilepsy showed that gabapentin is often prescribed as monotherapy in the elderly population. Like wise, levetiracetam, which has not been evaluated in randomized controlled trials as monotherapy, is often used in the elderly population by the same field of epilepsy experts because of a similar, very favorable pharmacokinetic profile and lack of toxicity.

Case 3
A 21-year-old obese man who is otherwise healthy reports a 5-year history of generalized tonic-clonic seizures that occur approximately 2 to 3 times per year. A routine EEG shows occasional generalized spike and slow-wave discharges. Findings on MRI of the brain are normal. He has been taking valproate since the onset of the seizures but is noncompliant and complains of lethargy as well as a tremor in both hands when taking the medication as prescribed.

Generalized-onset seizures are most effectively treated with broad-spectrum antiepileptic drugs. For many years, valproate was the only broad-spectrum agent available and is still considered first-line therapy by many experts for generalized-onset seizures. Unfortunately, its use has the potential for intolerable adverse effects, which include weight gain, tremor, hair loss, and lethargy. Valproate has also been associated with neural tube defects in the offspring of women who take it during pregnancy as well as rare cases of hepatoxicity and acute pancreatitis.

Lamotrigine and topiramate are both effective in the treatment of generalized-onset seizures and neither has been associated with systemic organ toxicities. Rash is the most serious potential adverse effect of lamotrigine and is seen predominantly in children, patients taking concurrent valproate, and with rapid titration. Patients starting lamotrigine therapy who develop a rash should seek medical attention. Topiramate has been associated with modest weight loss, averaging 1 to 6 kg, as well as rare cases of nephrolithiasis and recently reported angle-closure glaucoma, which occurs early in the course of therapy and reverses rapidly with discontinuation of the drug. Topiramate also has the potential for causing cognitive dysfunction, specifically language disturbances, although this complication may be related to dosage and titration schedule.

In this particular patient, the EEG finding of generalized epileptiform discharges confirms the diagnosis of generalized epilepsy. Medication noncompliance is likely contributing to breakthrough seizures; thus, switching to another antiepileptic drug may im-
prove compliance as well as seizure control. Topiramate offers the potential for weight loss in this obese patient with potentially fewer adverse effects. Although currently not approved for monotherapy, topiramate has shown efficacy as a single agent in a placebo-controlled trial enrolling 80 patients with primary generalized tonic-clonic seizures. In that study, 56% of patients experienced a 50% or greater reduction in seizures (P = .001). Because lethargy was a reason for previous noncompliance, lamotrigine could be considered an option since it has been shown to be associated with less sedation than traditional antiepileptic drugs.

Case 4
A 45-year-old woman presents with a long history of partial-onset seizures. She is currently taking carbamazepine, 800 mg/d, which has decreased her seizure frequency remarkably but she continues to have a complex partial seizure every 2 to 3 months. Higher doses of carbamazepine have resulted in dizziness, ataxia, and diplopia. It is not uncommon for a patient to experience an incomplete response to a modest dosage of an antiepileptic drug but not tolerate dose increases due to adverse effects. This patient has responded to carbamazepine but has far from complete seizure control. Because increasing the dose of her current antiepileptic drug is not possible, there are 2 options: switch to a different agent or add an additional agent as adjunctive therapy. Oxcarbazepine is an analogue of carbamazepine but with the advantage of fewer adverse effects due to its lack of formation of a toxic metabolite. Switching this patient from carbamazepine to oxcarbazepine monotherapy would potentially allow for increasing to higher doses and improve seizure control without the addition of adverse effects. Potential adverse effects include hyponatremia, although it is usually largely asymptomatic and seen mostly in elderly persons and in patients taking concomitant diuretics. Any of the new antiepileptic drugs could be used as adjunctive therapy in combination with carbamazepine; however, choosing an antiepileptic drug with a different mechanism of action would provide more comprehensive coverage. Topiramate, tiagabine, and zonisamide offer unique mechanisms of action but require a slow titration schedule of at least 4 weeks to reach target maintenance doses. Gabapentin and levetiracetam have minimal interaction with other medications including carbamazepine and can be initiated more rapidly, reaching effective doses within 1 to 2 weeks.

CONCLUSIONS
Physicians now have more pharmaceutical options for treating epilepsy than ever before. Although this has led to more complex decision making for practitioners, it has given patients greater hope for seizure control without intolerable adverse effects. Despite a lack of direct comparisons among the new antiepileptic drugs and between the new and traditional agents, informed choices can still be made. Primary care clinicians should have an understanding of the important advantages as well as adverse effects and drug interactions that accompany the new antiepileptic drugs and guide treatment choices. Initial studies show the new agents to be equally efficacious but overall better tolerated than traditional agents. In addition, most of the new agents have a more favorable pharmacokinetic profile with limited hepatic metabolism and fewer drug interactions. Finally, many of the newer agents offer a broader spectrum of activity. Ultimately, the choice of an antiepileptic drug should be tailored to the individual patient to accomplish seizure freedom without medication toxicity.

REFERENCES


