Update on Antiseizure Drugs:
Case Studies

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I. INTRODUCTION

Antiseizure drugs (ASDs) are mainstays of therapy for most of the approximately 2 million patients with epilepsy in the United States. As with treatments for other neurologic conditions, ASDs must be taken on a daily basis, typically for years. Short- and long-term adverse drug effects are therefore of critical importance: A drug that causes drowsiness or dullness on a daily basis is not helpful, even if the agent is completely effective in preventing seizures.

During the past 8 years, 8 new ASDs have been approved by the U.S. Food and Drug Administration (FDA). Also available are 2 new intravenous preparations of existing ASDs. These important advances have expanded treatment options for patients with epilepsy; however, the sheer number of such agents often makes distinguishing between them difficult for many neurologists, particularly members of practices who do not focus solely on treating epilepsy. New ASDs differ considerably in indication, effectiveness for various seizure types, adverse effects, and pharmacology. Furthermore, new ASDs generally differ from older ASDs because of a broader spectrum of action, more diverse mechanisms, and fewer or no drug-drug interactions. Table 1 lists agents that have been approved since 1993. An overall listing of drugs effective in various seizure types is given in Table 2. This review highlights distinguishing characteristics among new ASDs and their differences from conventional ASDs. However, use of these agents is expanding rapidly, and FDA indications often do not describe all appropriate uses.

II. SELECTION OF AN ANTISEIZURE DRUG: GENERAL PRINCIPLES

TYPE OF AGENT

The first and most important part of choosing an ASD is checking its appropriateness for the type of seizure the patient is experiencing. Several drugs are effective only against partial seizures (simple, complex, or secondarily generalized; see Table 2). All of these ASDs are also effective against primary generalized tonic-clonic seizures. Many agents in this group block rapid firing of voltage-sensitive sodium channels (see Section V. “Characteristics of Specific Antiepileptic Drugs”). Other ASDs are “broad-spectrum” drugs that seem to be effective against many seizure types. Many broad-spectrum agents have multiple mechanisms of action, including enhancement of gamma-amino butyric acid (GABA)-ergic transmission, inhibition of excitatory transmission (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate [AMPA] or kainate receptor mediated), or blockade of sodium channels.

Despite the existence of broad-spectrum ASDs,
individual drugs may be better suited to treat specific seizures. For example, ethosuximide is unique because it is effective only against absence seizures, and clonazepam is useful chiefly in patients with myoclonic seizures. Carbamazepine, phenytoin, and phenobarbital are equally effective for partial and secondarily generalized seizures, although in an individual patient one agent may be effective when another is not. Valproate is as effective for secondarily generalized seizures but is somewhat less effective than carbamazepine (and, presumably, phenytoin) for treating simple or complex partial seizures. Few direct comparisons have been made of the effectiveness of newer ASDs; however, one meta-analysis suggested no significant difference between gabapentin, lamotrigine, tiagabine, topiramate, vigabatrin, and zonisamide.

Although antiseizure potency appears to be roughly equivalent for all ASDs, they differ substantially in their side-effect profiles, pharmacokinetic properties, and cost. Phenytoin and zonisamide, for instance, have relatively long half-lives that allow for once-daily dosing. In patients with poor compliance, these drugs may be preferable to gabapentin, which typically must be administered 3 or 4 times daily. Carbamazepine, despite its short half-life, may be given twice daily if an extended-release formulation (Tegretol-XR or Carbatrol) is used. Concern about phenytoin’s occasional undesirable cosmetic effects (gingival hypertrophy, hirsutism, coarsening of facial features) makes carbamazepine, gabapentin, or lamotrigine preferable as initial therapy for partial seizures in some patients, particularly young women. Currently, phenobarbital and primidone are rarely used as initial therapy because of a high incidence of sedation and cognitive side effects.

As a group, generalized-onset seizures respond well to valproate, which is usually first-line treatment for...
these seizure types. In most patients, valproate can be used effectively as monotherapy even when several types of generalized-onset seizure coexist. Lamotrigine, topiramate, and zonisamide are now considered reasonable alternatives when valproate fails. Phenytoin and carbamazepine are also effective against primary generalized tonic-clonic seizures; however, when absence or myoclonic seizures coexist with generalized tonic-clonic seizures, another agent (eg, ethosuximide, clonazepam) must be used. Infrequently, phenytoin, carbamazepine, and phenobarbital may actually aggravate nonconvulsive generalized-onset seizures.  

Table 2. Drugs Used to Treat Different Seizure Types

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Effective Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum (all seizure types, including partial, absence, myoclonic, tonic, and generalized tonic-clonic)</td>
<td>Valproic acid, lamotrigine, topiramate, felbamate, zonisamide, levetiracetam (®)</td>
</tr>
<tr>
<td>Partial seizures only (including primary and secondarily generalized)</td>
<td>Carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine, phenobarbital, primidone, levetiracetam</td>
</tr>
<tr>
<td>Absence only</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Infantile spasms</td>
<td>Valproic acid, vigabatrin, levetiracetam, zonisamide</td>
</tr>
</tbody>
</table>

† = preliminary information suggests broad-spectrum efficacy.  
*Not available in the United States.

In clinical practice, treatment with 1 drug rather than 2 or more drugs is almost always preferable. Many patients with partial seizures (about 60%) usually achieve satisfactory control with the first agent tried. When the first drug was ineffective, about 50% responded to another drug used alone. Of the remaining patients, only 50% had better control of seizures with 2 drugs. Treatment with 2 or more ASDs typically results in increased side effects, often because of drug interactions, which are not necessarily reflected in “toxic” blood concentrations of either drug. For patients who cannot be completely controlled using one drug, combinations should be chosen to minimize potential complications.

Plasma drug levels have been commonly used to confirm that doses of ASDs are appropriate, and levels are now available to monitor most of the newer drugs if necessary. Phenytoin, carbamazepine, and phenobarbital all have a narrow, well-defined therapeutic range, although in individual patients effective drug levels (versus those that produce toxic symptoms) may vary. Most patients do not require plasma level measurements “routinely,” particularly when newer ASDs are used. Situations in which determining plasma levels may be helpful include suspected noncompliance; lack or loss of therapeutic effect; suspected toxicity; suspected alteration of metabolism by secondary disease, changing physiologic state, or drug–drug interaction; need for medicolegal verification of treatment; or need for verification of increased absorption when it is dose dependent (eg, gabapentin).

Drug interactions and the effects of systemic disease on antiepileptic drug disposition are complicated, particularly when older agents are involved. Most interactions result from hepatic induction or inhibition, with consequent alteration of drug half-life. Other interactions include increased free fraction of drug when highly plasma-bound agents (phenytoin, valproate, tiagabine) are coadministered. Table 3 summarizes some important pharmacokinetic drug interactions involving ASDs. Pharmacodynamic interactions may also occur, which will affect drug action and adverse effects but not plasma levels. Such interactions are less well understood and more difficult to characterize.

Although history is critical in determining whether a patient has had a seizure and in distinguishing partial from generalized seizure types, the electroencephalogram (EEG) adds important information. Focal epileptiform discharges support a diagnosis of partial epilepsy. Classic 3/second generalized spike-wave discharges suggest a primary generalized epilepsy. Patients with myoclonic seizures, including juvenile myoclonic epilepsy, classically have generalized polyspike-wave discharges on EEG.

In clinical practice, ASDs are frequently started in the acute setting, and workup (including EEG) is obtained later; however, ASDs can affect the EEG. Benzo diazepines are known to decrease epileptiform discharges but are not usually used except for acute seizure control. In general, anticonvulsant drugs for chronic therapy have little or no effect on EEG readings. Sodium valproate and phenobarbital can reduce both focal and generalized epileptiform discharges, making an epilepsy diagnosis more difficult if the drug is present; however, phenytoin and carbamazepine have no such effects. Toxic doses of anticonvulsant drugs can cause diffuse background slowing on EEG. The effects of newer agents are not well known; however, all are less likely to produce clinical toxicity because of broader therapeutic range and therefore are less likely to affect the EEG. Lamotrigine may decrease interictal discharges and the photoconvulsive response.
OTHER FACTORS

ASDs represent a diverse group of compounds with various actions on the central nervous system (CNS), and some have efficacy in CNS diseases other than epilepsy. For example, sodium valproate is FDA approved for use in migraine and bipolar disorder. Carbamazepine is frequently used for neuropathic pain, particularly trigeminal neuralgia. This principle holds true for newer ASDs as well, although none of these agents are FDA approved for other uses. Gabapentin, lamotrigine, and topiramate have all been used for migraine prophylaxis. Gabapentin and lamotrigine have been used to treat neuropathic pain and various psychiatric disturbances, including bipolar disorder and social phobia. Because of its similarity to carbamazepine, oxcarbazepine has been used as therapy for trigeminal neuralgia. The newest ASDs will no doubt be tried for many of these indications. For this reason, some clinicians refer to ASDs as “neuromodulators” because of their potential for diverse CNS actions. Still, most of these reports (except for FDA-approved indications and perhaps the use of gabapentin and lamotrigine for pain) are anecdotal, and further studies are needed to confirm efficacy.

III. PREGNANCY AND ANTI EPILEPTIC DRUGS

Considerations related to ASD use in women of child-bearing age include risks to both mother and developing fetus. Risk to the mother chiefly concerns shifts in anticonvulsant levels during pregnancy and consequently the potential for increases in seizure frequency. Risks to the developing fetus include seizures in the mother, with potential for anoxia and trauma, and teratogenic effects of anticonvulsant drugs. These risks are well known for older anticonvulsants but are uncertain for newer agents.

The overall risk of delivering an infant with a major malformation is about 2% to 3% in healthy populations. Major malformations most often encountered are cardiac and “midline” defects (eg, cleft lip/palate), but others (including those of the brain and spine) may occur. Minor malformations are more common and include unusual facial features as well as finger and nail hypoplasia; these conditions in particular may reflect a genetic, nondrug factor. For women with epilepsy taking a single antiepileptic drug, risk of major neonatal malformation increases to 5% to 6% but may be

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Table 3. Effects of Antiseizure Drugs (ASDs) on Serum Concentrations of Other ASDs*

<table>
<thead>
<tr>
<th>ASD</th>
<th>Inducers (PB, PHT, CBZ)†</th>
<th>Inhibitors (VA)†</th>
<th>FBM</th>
<th>GBP, LTG, TPM, TGB, LVT, OXC, ZSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
<td>NC (↑ TPM, OXC)</td>
</tr>
<tr>
<td>CBZ</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>NC</td>
</tr>
<tr>
<td>PB</td>
<td>↓</td>
<td>↑↑</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>VA</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>NC (↓ TPM, TGB, LTG)</td>
</tr>
<tr>
<td>FBM</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td>UNK (NC?)</td>
</tr>
<tr>
<td>GBP</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>LTG</td>
<td>↓</td>
<td>↑</td>
<td>UNK</td>
<td>NC</td>
</tr>
<tr>
<td>TPM</td>
<td>↓</td>
<td>↑</td>
<td>UNK</td>
<td>NC</td>
</tr>
<tr>
<td>TGB</td>
<td>↓</td>
<td>↑</td>
<td>UNK</td>
<td>NC</td>
</tr>
<tr>
<td>LVT</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>OXC</td>
<td>↓</td>
<td>↓</td>
<td>UNK</td>
<td>NC</td>
</tr>
<tr>
<td>ZSM</td>
<td>↓</td>
<td></td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

CBZ = carbamazepine; FBM = felbamate; GBP = gabapentin; LTG = lamotrigine; LVT = levetiracetam; NC = no change; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; TGB = tiagabine; TPM = topiramate; UNK = unknown; VA = valproic acid; ZSM = zonisamide; ↓ = decrease; ↑ = increase; ↑↓ = either increases or decreases.

*Some of these interactions have not been directly studied; however, probable effects can be inferred from known drug properties. The effects shown in the table represent the effects that each drug class in the top row has on serum concentrations of each of the drugs listed on the left.

†Inducers and inhibitors refer to agents that induce or inhibit hepatic microsomal enzymes.
considerably higher in women taking multiple drugs. This increased risk does not entirely result from ASDs because women who experience seizures have a slightly increased risk in the absence of medication (possibly due to genetics and/or seizures during pregnancy). Despite these potential complications, women with epilepsy have a nearly 95% chance of delivering a healthy baby.

Risks to pregnant women associated with newer ASDs are unknown, although many are less likely to be teratogenic. Gabapentin, lamotrigine, and oxcarbazepine do not increase arachidonic acid metabolites (which may be related to teratogenesis), and topiramate use increases them insignificantly. Although several animal models have demonstrated teratogenesis with use of older drugs, few or no trials have shown these effects with use of newer agents. Furthermore, most newer ASDs do not alter hepatic metabolism, and all except tiagabine have no significant protein binding and thus make drug levels more stable during pregnancy. Although supportive evidence is indirect, newer ASDs are no more likely to cause birth defects than the older drugs. Only further experience will determine which generation of drugs (newer versus older) is actually safer. Given that seizures constitute a risk to mother and developing fetus that is probably greater than risks associated with ASDs, the best treatment for pregnant women with epilepsy is optimal treatment of seizures using monotherapy whenever possible.

IV. CASE PATIENT 1

PRESENTATION

Patient 1 is a 25-year-old right-handed woman who has been well until 1 year ago, when she had a sudden onset of severe bifrontal headache while running. Her headache was not associated with nausea, vomiting, visual changes, or any other symptoms. The headache subsided within hours but was followed immediately by severe neck pain. Patient 1 was evaluated in an emergency department, where results of a computed tomography (CT) scan were normal but those from a lumbar puncture (LP) suggested subarachnoid hemorrhage. Further workup, including magnetic resonance imaging (MRI) and angiography, revealed a right parieto-occipital arteriovenous malformation. Patient 1 subsequently underwent 4 embolizations followed by resective surgery. During this time, she took carbamazepine (Tegretol) 200 mg twice daily for seizure prophylaxis. Four months ago, she became confused in her sleep and wandered into her parents’ room. She has no memory of this event and suddenly awoke without knowledge of how she got there.

Patient 1’s first definite seizure occurred about 1 month ago. For the previous 4 days, she had not been taking carbamazepine and was feeling less tired with an overall improved sense of well-being. When the seizure began, she was alone; she reports feeling a “current” running through her body and saw a yellow-white light beginning in her left visual hemifield. She then saw faces and heard music, none of which she recognized. She called for her mother, who reports that patient 1 was able to speak coherently but was quite frightened. The patient herself does not recall this episode. She returned to baseline within minutes and experienced no symptoms apart from fatigue. No incontinence or tongue biting occurred during the seizure. Patient 1 resumed taking carbamazepine at 200 mg twice daily. A few days later, she feels a similar “current,” and her dose is increased to 3 times a day. Her side effects subsequently worsen, particularly dizziness, confusion, and grayness in her vision.

• Given patient 1’s history, where did her seizure most likely begin?
  A) In the dominant occipital region
  B) In the nondominant occipital region
  C) In the dominant frontal region
  D) In the nondominant frontal region

DISCUSSION

The correct answer is B. Patient 1’s first definitive symptom was visual, consisting of colored light. This symptom is most consistent with seizures arising in the primary visual cortex. Afterward, she reported seeing faces and music, suggesting spread to visual association areas and her temporal lobe, respectively. The fact that she was able to speak during the episode strongly indicates a nondominant origin for the seizure. The presence of music supports this conclusion, as does the patient’s known right occipital lesion. Therefore, the history and workup are consistent with partial seizures arising in the nondominant occipital region.

• What alternative antiseizure medications for use as monotherapy would be appropriate for patient 1?
  A) Phenytoin (Dilantin)
  B) Gabapentin (Neurontin)
  C) Lamotrigine (Lamictal)
  D) Oxcarbazepine (Trileptal)
  E) All of the above

DISCUSSION

The correct answer is E. This question is more difficult. All of these agents are FDA approved for use as add-on therapy in partial seizures. Only phenytoin...
and oxcarbazepine are approved as initial monotherapy, although lamotrigine and gabapentin are also widely used alone and would be appropriate. The following section highlights differences between these drugs, with an emphasis on those approved within the past 10 years.

V. CHARACTERISTICS OF SPECIFIC ANTI EPILEPTIC DRUGS

In this section, properties of the most commonly used antiseizure agents will be described. Felbamate will not be discussed because this drug is rarely prescribed owing to a higher incidence of serious adverse effects (although the drug may occasionally be useful in patients with very refractory seizures). Phenobarbital is included in summary tables but also will not be discussed because the agent is rarely used in adults with new-onset seizures. Table 4 contains information on usual dose, effective plasma concentrations, half-life, and common side effects. Drug interactions are listed in Table 3, and a summary of each drug’s important characteristics is provided in Table 5.

This section is divided into 2 main categories: broad-spectrum agents and agents that are effective only against partial seizures. Levetiracetam is included in the latter group because the evidence for the drug’s broad-spectrum efficacy is preliminary. Agents are described chronologically in order of FDA approval.

BROAD-SPECTRUM AGENTS

Valproate

Anticonvulsant properties of valproate (available as valproic acid [Depakene] or divalproex sodium [Depakote]) were discovered accidentally when it was used as a solvent in other compounds being tested for anticonvulsant activity. As a broad-spectrum ASD, valproate is the drug of choice for all forms of primary generalized epilepsy and is also effective for partial seizures, migraine, and bipolar disorder. The mechanism of this agent’s antiepileptic effect is unknown. Early evidence suggested an action-enhancing GABA-mediated inhibition. However, although valproate increases brain GABA levels, this explanation does not correlate well with anticonvulsant effect. More recent evidence suggests that, like phenytoin, valproate blocks voltage-dependent sodium channels. Modulation of brain GABA levels may also play a long-term role. Like ethosuximide, valproate reduces T-type calcium currents. Multiple mechanisms of action are consistent with the drug’s known wide spectrum of action.

Valproate is available as tablets (Depakote and Depakene), sprinkles (Depakote), and as an intravenous solution (Depacon). An extended-release preparation, Depakote ER, was recently introduced. A maximum rate of 20 mg/min is recommended for the intravenous solution; however, much faster rates have been used safely. The most common adverse effects of oral valproate are nausea, vomiting, and gastrointestinal distress, which are reduced if the drug is taken with food. Other common side effects include weight gain, hair loss (usually thinning and not complete alopecia), menstrual irregularity, and an essential-like tremor. Hyperammonemia is relatively common with valproate; although usually asymptomatic, this may produce encephalopathy even in the absence of other indications of hepatic dysfunction. In addition, mild-to-moderate alterations in liver enzymes and hepatic function are common (40%), usually dose related, and reversible. Fatal hepatitis can occur as an idiosyncratic reaction that is not predictable by routine laboratory screening tests or by preexisting hepatic dysfunction. The greatest risk of fatal hepatic disease is to children younger than 2 years who receive valproate as polytherapy (1/500). Acute pancreatitis can be caused by valproate, more often in children than adults.

Lamotrigine

Lamotrigine (Lamictal) was originally developed because of an observation that some anticonvulsants have antifolate properties. Although lamotrigine weakly inhibits dihydrofolate reductase, there is no correlation between this activity and the agent’s anticonvulsant action, which involves prolonging inactivation of voltage-sensitive Na+ channels. Use-dependent inhibition of Na+ channels has also been shown, and lamotrigine may act specifically on the slow, inactivated site. These actions resemble those of the older ASDs phenytoin and carbamazepine. Unlike these agents, however, lamotrigine inhibits glutamate release. In 1995, lamotrigine was approved in the United States for use as add-on therapy in partial seizures (with or without secondary generalization); in 1999, lamotrigine was approved for conversion to monotherapy and for generalized seizures associated with the Lennox-Gastaut syndrome. Its known efficacy against many seizure types—including absence, atonic, and partial seizures—is consistent with its multiple mechanisms of action.

Although lamotrigine does not appreciably affect the metabolism of other drugs, its elimination rate is profoundly influenced by agents that enhance (phenytoin, carbamazepine, phenobarbital) or inhibit (valproic acid) hepatic enzymes. When used as monotherapy, lamotrigine has an elimination half-life of about...
25 hours. When used with an enzyme inducer, the half-life is reduced to 15 hours; with an inhibitor, the half-life substantially increases to about 60 hours. Dose and titration rates must therefore be adjusted when lamotrigine is used in combination with any of these drugs.

Lamotrigine is generally well tolerated. In add-on trials, the most commonly observed adverse effects were blurred vision, ataxia, diplopia, and dizziness. For poorly understood reasons, lamotrigine can exacerbate symptoms of carbamazepine toxicity. The most troublesome side effect of lamotrigine seen in initial trials was rash, which occasionally was serious and required hospitalization. Rash occurred in up to 10% of patients in add-on trials and seems to be more problematic and severe in the pediatric population. Subsequent analysis suggests that rapid titration may increase risk of rash, particularly when valproic acid is administered concomitantly; therefore, the recommendation is to slowly titrate the drug over 4 to 6 weeks. In a monotherapy trial of lamotrigine compared with carbamazepine, rates of rash were approximately equal.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dose, mg/day</th>
<th>Half-life, hr</th>
<th>Metabolism</th>
<th>Usual Effective Plasma Concentration, µg/mL</th>
<th>Time to Peak Concentration, hr</th>
<th>Bound Fraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol, Carbatrol)</td>
<td>800–1600</td>
<td>8–22</td>
<td>&gt; 90% hepatic with induction</td>
<td>8–12</td>
<td>4–8</td>
<td>75</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)</td>
<td>750–1500</td>
<td>60</td>
<td>65% hepatic, no induction</td>
<td>40–100</td>
<td>3–7</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Felbamate (Felbatol)</td>
<td>2400–3600</td>
<td>14–23</td>
<td>60% hepatic</td>
<td>20–140*</td>
<td>2–6</td>
<td>25</td>
</tr>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>1800–3600</td>
<td>5–7</td>
<td>&gt; 95% renal</td>
<td>4–16*</td>
<td>2–3</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>100–500</td>
<td>12–60†</td>
<td>&gt; 90% hepatic, no induction</td>
<td>2–16*</td>
<td>2–5</td>
<td>55</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>1000–3000</td>
<td>6–8</td>
<td>&gt; 65% renal excretion</td>
<td>5–45*</td>
<td>1</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal)</td>
<td>600–1800</td>
<td>8–10‡</td>
<td>&gt; 90% hepatic, mild induction</td>
<td>10–35‡</td>
<td>3–13</td>
<td>40‡</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>90–180</td>
<td>100</td>
<td>&gt; 90% hepatic with induction</td>
<td>15–40</td>
<td>2–8</td>
<td>45</td>
</tr>
<tr>
<td>Phenytoin (Dilantin)</td>
<td>300–400</td>
<td>22</td>
<td>&gt; 90% hepatic with induction</td>
<td>10–20</td>
<td>3–8</td>
<td>90–95</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>32–56</td>
<td>5–13</td>
<td>&gt; 90% hepatic, no induction</td>
<td>NE</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>200–400</td>
<td>19–25</td>
<td>30% hepatic, no induction</td>
<td>4–10</td>
<td>2–4</td>
<td>9–17</td>
</tr>
<tr>
<td>Valproate (Depakote, Depaken)</td>
<td>1000–3000</td>
<td>15–20</td>
<td>&gt; 95% hepatic with inhibition</td>
<td>50–120</td>
<td>3–8</td>
<td>80–90</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
<td>100–400</td>
<td>63</td>
<td>70% hepatic, no induction</td>
<td>10–40*</td>
<td>2–6</td>
<td>40</td>
</tr>
</tbody>
</table>

ASD = antiseizure drug; NE = not established.

*NE; represents usual concentration in patients receiving therapeutic dose.

†Varies with concomitant ASD (lower with enzyme inducers, higher with enzyme inhibitors).

‡Of 10-monohydroxyl metabolite, which is the active metabolite.
Topiramate

Chemically, topiramate (Topamax) is a weak carbonic anhydrase inhibitor, a characteristic that is probably not responsible for its anticonvulsant action. Topiramate prolongs inactivation of voltage-sensitive Na+ channels and in this way resembles the action of the older ASDs (eg, phenytoin and carbamazepine). Also, topiramate acts as an agonist at (inhibitory) GABA<sub>A</sub> receptors and an antagonist at the (excitatory) non–N-methyl-D-aspartate glutamate receptor.<sup>25</sup> These mechanisms are consistent with the agent’s broad spectrum of action, given that topiramate has additional efficacy against absence and atonic seizures. In 1996, topiramate was approved in the United States for use as add-on therapy in partial seizures and was later approved for use in children 2 years and older and for primary generalized seizures.

Topiramate is generally well tolerated. In add-on trials, the most commonly observed adverse effects were fatigue, somnolence, and dizziness. Cognitive impairment and word-finding difficulties may occur; these typically worsen with rapid titration and improve with dose reduction. About 1% of patients may develop renal stones;<sup>25</sup> possibly because of topiramate’s action as a carbonic anhydrase inhibitor. When taking the drug, patients should be instructed to remain well hydrated, and the drug should be used with caution when combined with zonisamide, acetazolamide, or with a ketogenic diet. Mild weight loss can occur, which is also dose related.<sup>27</sup>

Zonisamide

In 2000, zonisamide (Zonegran) was approved as adjunctive treatment for partial seizures in adults. Despite this limited indication, there is broad experience worldwide with this compound in children and for adults with generalized seizures.<sup>26</sup> Chemically, zonisamide is a sulfonamide that acts to block voltage-dependent sodium channels<sup>25</sup> (like phenytoin, carbamazepine, and several other ASDs) but also reduces voltage-dependent T-type calcium currents, binds to the GABA<sub>A</sub> receptor,<sup>30</sup> and facilitates dopaminergic and serotonergic neurotransmission.<sup>31</sup> These multiple mechanisms are consistent with clinical observations of zonisamide as a broad-spectrum anticonvulsant. Also, zonisamide is a weak carbonic anhydrase inhibitor; this is probably responsible

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**Table 5. Summary of Antiseizure Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Inexpensive, bid dosing (extended release)</td>
<td>Drug interactions (including OC), hypersensitivity, rare sedation, hyponatremia, rare aplastic anemia</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No drug interactions, rapid titration, useful in other conditions</td>
<td>tid/qid dosing, dose-dependent absorption</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Broad spectrum, few drug interactions, once-daily/bid dosing</td>
<td>Hypersensitivity, slow titration</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>No drug interactions, rapid titration, bid dosing</td>
<td>Limited experience, spectrum of action unknown</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Few drug interactions, rapid titration</td>
<td>Interferes with OC, hypersensitivity, hyponatremia</td>
</tr>
<tr>
<td>Phenytoin&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Inexpensive, once-daily dosing, IV available</td>
<td>Sedation, withdrawal, drug interactions (including OC)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Few drug interactions</td>
<td>Highly protein bound; slow titration; cognitive, GI effects</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Broad spectrum, few drug interactions, bid dosing</td>
<td>Slow titration, cognitive effects, interferes with OC, renal stones (rare)</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Broad spectrum, useful in other conditions, IV available</td>
<td>Drug interactions, highly protein bound, tremor, weight gain, rare sedation, hepatic toxicity (especially in pediatrics)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Broad spectrum, few drug interactions, once-daily/bid dosing</td>
<td>Hypersensitivity, renal stones (rare)</td>
</tr>
</tbody>
</table>

ASD = antiseizure drug; bid = twice daily; GI = gastrointestinal; IV = intravenous; OC = oral contraceptives; qid = 4 times daily; tid = 3 times daily.

<sup>*</sup>Rarely used in adults with new-onset seizures.

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**Update on Antiseizure Drugs: Case Studies**

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for an increased incidence of symptomatic renal stones, although in clinical trials the rate was similar to placebo.\textsuperscript{32} Zonisamide has a long half-life and may be administered either once or twice daily. Adverse effects, usually transient and self-limited, include CNS symptoms (eg, somnolence, dizziness), gastrointestinal problems (anorexia, nausea, diarrhea), and rash.\textsuperscript{33} Slow titration may decrease the incidence of adverse effects.

**PARTIAL SEIZURES ONLY**

**Phenytoin**

Phenytoin (Dilantin) acts by inhibiting high-frequency repetitive firing of neurons through a use-dependent blockade of the voltage-dependent sodium channel.\textsuperscript{34} **Phenytoin is used to treat complex partial and generalized tonic-clonic (primary and secondary) seizures.** This agent is the only chronically administered ASD that may be given orally, intravenously, or intramuscularly as fosphenytoin (which has been approved by the FDA). Fosphenytoin (Cerebyx), a phosphate ester produg of phenytoin, was developed to avoid adverse effects associated with the parenteral phenytoin vehicle (40% propylene glycol, 10% ethanol, pH 12). Because it is highly water soluble, fosphenytoin may be administered in aqueous solutions; this improves its side-effect profile compared with parenteral phenytoin. Administration is also more rapid (up to 150 mg phenytoin equivalents (PE)/min), with a conversion half-life of 8 to 15 minutes. When administration time and conversion are considered, the 2 preparations produce bioequivalent plasma-free phenytoin concentrations at about the same rate.\textsuperscript{32}

Phenytoin use is complicated by its zero-order kinetics at therapeutic doses,\textsuperscript{18} which further exaggerates differences in bioavailability between brand and generic preparations. Neurotoxicity is dose related.\textsuperscript{18} Cerebellar atrophy and peripheral neuropathy can occur with chronic phenytoin use, but their clinical importance remains controversial. Limiting side effects, apart from rare idiosyncratic reactions including Stevens-Johnson syndrome,\textsuperscript{35} are cosmetic: gingival hyperplasia, hirsutism, and coarsening of facial features. These conditions seem to occur most often in children, adolescents, and young adults. Hypocalcemia and osteomalacia may result from phenytoin-induced alterations in vitamin D metabolism.

**Carbamazepine**

Carbamazepine (Tegretol, Carbatrol) is a dibenzepine derivative (which is chemically and pharmacologically related to tricyclic antidepressants) that has a clinical spectrum and mechanism of action very similar to that of phenytoin. **Carbamazepine is used to treat complex partial and generalized tonic-clonic (primary and secondary) seizures but can worsen other generalized seizure types, particularly myoclonic.**\textsuperscript{4} Additionally, carbamazepine can be used for trigeminal neuralgia and mood stabilization. This agent is available for oral administration only, as immediate or sustained-release tablets, and as an oral suspension (100 mg/5 mL).

The clinical pharmacokinetics of carbamazepine are complicated by autoinduction of its own metabolism by hepatic microsomal enzymes. Dose-related, reversible neurotoxicity includes blurred or double-vision, nystagmus, dizziness, headache, and incoordination. Skin rashes occur in about 10% of patients.\textsuperscript{34} Life-threatening idiosyncratic reactions (eg, Stevens-Johnson syndrome) are very rare.\textsuperscript{35} Mild elevations in hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) occur in 5% to 10% of patients and are of no clinical significance. Mild leukopenia is common\textsuperscript{36} but has no clinical significance and does not correlate with rare cases of aplastic anemia. Carbamazepine has antidiuretic effects that result in hyponatremia and water retention, which are usually clinically unimportant\textsuperscript{36} but may relate to symptoms of dizziness, headache, and nausea. Severe hyponatremia (< 122 mEq/L) and water retention can exacerbate seizures or contribute to congestive heart failure in patients with compromised cardiac function.

**Gabapentin**

Gabapentin (Neurontin) is an amino acid consisting of a cyclohexyl group added to the chemical backbone of GABA, a major inhibitory neurotransmitter. This agent increases extraneuronal GABA but does not directly interact with GABA receptors or GABA transport mechanisms. In addition, the drug binds to a specific site in neuronal membranes that acts as an l-amino acid transporter.\textsuperscript{28} Although the FDA approved it in 1994 for adjunctive treatment of partial complex seizures (with or without secondary generalization), gabapentin is widely used in monotherapy and is commonly used for neuropathic pain, migraine, mood stabilization, and social phobia. Notably, this agent is not useful for generalized seizures and can worsen certain types (particularly myoclonic).\textsuperscript{26} Gabapentin is unique among ASDs in exhibiting dose-dependent absorption, probably because of uptake by a saturable amino acid transport mechanism in the gut. Bioavailability therefore decreases from 52% of a 400-mg dose to 31% of a 1600-mg dose when administered 3 times daily.\textsuperscript{37} Bioavailability is not affected by food. Because of this dose-dependent bioavailability, plasma concentrations of gabapentin are not proportional to dose.

Gabapentin has no significant drug–drug interactions, making it an ideal agent in complicated medical
patients taking numerous medications. It is typically well tolerated. In add-on trials, the most common side effects observed were headache, ataxia, fatigue, nausea, and somnolence. These conditions are generally mild and self-limited, rarely requiring withdrawal of medication. No serious or idiosyncratic adverse effects have been seen to date.

Tiagabine

Tiagabine (Gabitril) was designed specifically as a GABA-reuptake inhibitor. Administration of the drug results in increased levels of synaptic GABA in the brain, which is probably responsible for the agent’s effectiveness against seizures. In 1997, tiagabine was approved in the United States for use as add-on therapy in partial seizures. At present, little evidence exists to support a broader spectrum of action in epilepsy treatment. In fact, tiagabine can occasionally induce new seizure types in patients with partial seizures. Tiagabine is generally well tolerated. In add-on trials, the most commonly observed adverse effects were somnolence, dizziness, confusion, and gastrointestinal upset. Gastrointestinal side effects that may occur can improve if the drug is taken with meals and if it is titrated slowly (usually over several weeks).

Levetiracetam

Levetiracetam (Keppra) was approved in 1999 as adjunctive therapy for partial seizures in adults, although the agent’s efficacy against photoparoxysmal response suggests that it may have a broader spectrum of action. Chemically, levetiracetam is a single enantiomer, (-)-(S)-α-ethyl–2-oxo-1-pyrrolidine acetamide, and is an analogue of piracetam. The precise mechanism of action in seizure control is unknown; however, levetiracetam binds to a stereoselective site on ion synaptic membranes in the CNS and may inhibit bursts of neuronal firing without affecting normal neuronal excitability. The major advantage of levetiracetam over most other ASDs is ease of administration and lack of drug–drug interactions. Levetiracetam may be started at a full dose (500 mg twice daily) on the first day of therapy, whereas most antiseizure agents must be slowly titrated to avoid adverse effects.

As with most ASDs, predominant adverse effects of levetiracetam involve the CNS. The most common are dizziness, somnolence, and “asthenia” (lack or loss of strength), although rates of discontinuation in clinical trials were not different from placebo. No serious or life-threatening adverse effects have thus far been attributed to levetiracetam. Mild decreases in hematocrit and leukocyte cell count have been seen rarely, which in clinical trials did not require discontinuation of the drug.

Oxcarbazepine

Oxcarbazepine (Trileptal) is chemically related to carbamazepine but has fewer drug–drug interactions, mainly because of reduced hepatic induction. Moreover, carbamazepine is metabolized chiefly into carbamazepine-10,11-epoxide, an active metabolite responsible for a number of toxic adverse effects. In contrast, oxcarbazepine is rapidly reduced to the 10-monohydroxyl metabolite (MHD), which is principally responsible for the agent’s anticonvulsant effects. The mechanism of MHD (like carbamazepine) probably involves blockade of voltage-sensitive sodium channels. Oxcarbazepine, therefore, may have fewer adverse effects than carbamazepine but be similarly effective against partial seizures.

Oxcarbazepine is approved for partial seizures in adults as adjunctive and monotherapy; it is approved for partial seizures in children aged 4 years and older as adjunctive therapy. Chemical and pharmacologic similarities to carbamazepine suggest that oxcarbazepine will not be useful in other seizure types. If switching from carbamazepine (or other drugs that induce hepatic isoenzymes), de-induction of isoenzymes will occur, thereby increasing oxcarbazepine levels; therefore, in this setting, lower doses of oxcarbazepine should be used after the first 2 weeks.

Oxcarbazepine has been used in trigeminal neuralgia and affective disorders, although no large well-controlled studies on the effectiveness of this treatment have been published. Oxcarbazepine can cause CNS toxicity, predominantly somnolence and diplopia. Rash may also occur, and cross-reactivity in patients with a previous carbamazepine rash is about 30%. As with carbamazepine, hyponatremia can occur that is usually asymptomatic. Leukopenia, aplastic anemia, and hepatic failure have not been reported.

OTHER AGENTS

Ethosuximide

Ethosuximide (Zarontin) is unique among ASDs in that it seems to be effective only against absence seizures. In seizure models, ethosuximide inhibits chemically induced seizures but is ineffective against seizures induced by maximal electroshock test. This agent’s mechanism of action is probably through reduction of low-threshold T-type calcium current. Dose-related side effects include both gastrointestinal (pain, nausea, vomiting, diarrhea) and CNS (headache, irritability, drowsiness, and dizziness) symptoms. Rare, serious
idiosyncratic reactions include severe rash (Stevens-Johnson syndrome) and bone marrow toxicity.\textsuperscript{18}

\section*{VI. CASE PATIENT 1 FOLLOW-UP}

Because oxcarbazepine has a mechanism of action similar to carbamazepine but can be less toxic, patient 1’s physician decides to change her treatment from carbamazepine (200 mg twice daily) to oxcarbazepine (450 mg twice daily). Initially, patient 1 tolerates the transition well, with no seizures and no adverse effects. Two weeks after the transition is complete, however, she develops continuous dizziness and blurred vision.

- \textbf{What is the most likely reason for delayed toxicity in patient 1?}
  
  A) Accumulation of drug because of prolonged half-life
  B) De-induction of hepatic enzymes
  C) Unrecognized seizures
  D) Toxicity not related to drug

\section*{DISCUSSION}

The correct answer is B. Carbamazepine is a potent inducer of hepatic enzymes; oxcarbazepine does not induce its own metabolism, although it is metabolized by the same system. Thus, oxcarbazepine levels would be expected to increase as patient 1 discontinues carbamazepine and begins oxcarbazepine monotherapy. The half-life of oxcarbazepine is relatively short (8 to 10 hours); therefore, a steady state would be reached in a matter of days. Patient 1’s symptoms (dizziness, blurred vision) typically are not caused by seizures but would be caused by increased levels of oxcarbazepine; however, if unrecognized seizures were involved, one would expect symptoms to be episodic rather than constant.

\section*{VII. CASE PATIENT 2}

\section*{PRESENTATION}

Patient 2 is a 38-year-old man who presents with severe static encephalopathy and a history of seizure disorder since childhood. His seizures, which began at about age 8 years, consist of generalized tonic-clonic, petit mal, and simple partial seizures. He has tried multiple anticonvulsants including ethosuximide, phenobarbital, valproic acid, gabapentin, and phenytoin. Recently, he has been maintained on tiagabine (16 mg twice daily), phenytoin (200 mg twice daily), and clonazepam (1 mg 3 times daily). Three days ago, however, he developed uncontrolled episodes of generalized shaking and was taken to the emergency department.

Patient 2’s seizure episodes are characterized by virtually continuous abnormal activity interrupted by purposeful activities such as pushing, kicking, and shouting. Benzodiazepines have failed to completely resolve the episodes. On examination, patient 2 is sleepy but in no apparent distress. He is oriented to place but does not know the year. He inconsistently follows very simple commands but is unable to follow complex commands. During the examination, he has an action tremor that is greater on the right side and more prominent distally. The remainder of his neurologic examination is unremarkable.

- \textbf{Of the agents listed, which is most likely to exacerbate generalized seizure types?}
  
  A) Phenytoin
  B) Clonazepam
  C) Tiagabine
  D) Valproic acid

\section*{DISCUSSION}

The correct answer is C. Cases of exacerbation and partial status epilepticus have been noted with tiagabine. Phenytoin, carbamazepine, and gabapentin rarely exacerbate generalized seizures; these agents typically only exacerbate myoclonic seizures. Clonazepam and valproic acid can be used to treat all seizure types.

- \textbf{Given the presence of a substantial tremor in patient 2, valproic acid is thought to be a poor treatment option. Which of the following newer agents would NOT treat all of his seizure types?}
  
  A) Lamotrigine
  B) Topiramate
  C) Oxcarbazepine
  D) Zonisamide

\section*{DISCUSSION}

The correct answer is C. Oxcarbazepine is only effective for partial and generalized tonic-clonic seizures. Substantial evidence shows that the other agents listed are effective in all types of generalized seizures and would therefore be appropriate choices.

\section*{MANAGEMENT OF PATIENT 2}

Because of concern about nonepileptic events, patient 2 undergoes video EEG monitoring. This procedure confirms that his seizure episodes were generalized tonic seizures followed by confusion. He is started on
lamotrigine, discontinues gabapentin, and is slowly weaned from clonazepam. One year later, patient 2 maintains good control over his condition by taking lamotrigine (150 mg twice daily), and his seizures have resolved.

VIII. CASE PATIENT 3

PRESENTATION

Patient 3 is a 75-year-old woman who is admitted to the emergency department after a 5-minute generalized tonic-clonic convulsion. On arrival, she is lethargic and poorly responsive. She is treated with fosphenytoin 20 mg/kg; benzodiazepines are not deemed necessary. No further seizures occur. Patient 3 has had known partial seizures because of a left parietal meningioma that was resected 10 years ago. Recent seizure history is not obtainable; however, she had been treated with a combination of phenytoin (300 mg daily) and sodium valproate (1000 mg twice daily). Plasma concentrations on admission are phenytoin 8 µg/mL, valproate 35 µg/mL. Six hours after admission, patient 3 is free of overt seizures although she is lethargic. At one point, she opens her eyes with stimulation but quickly falls asleep again. Eye movements are full; the presence of nystagmus is unclear. No facial asymmetry is seen, and she responds to painful stimulation by moving all extremities. Reflexes are symmetric.

Which of the following is NOT a likely reason for persistent lethargy in patient 3?

A) Phenytoin toxicity
B) Valproate toxicity
C) Prolonged postictal state (uncomplicated)
D) Subclinical status epilepticus

DISCUSSION

The correct answer is B. Although this agent is highly protein bound, valproate toxicity is unlikely given a serum level of 35 µg/mL. However, phenytoin toxicity is possible. Patient 3 has a low total level of phenytoin, but this drug is also protein bound and a large intravenous loading dose has been given. In older patients, postictal state may be prolonged, but the possibility of subclinical seizures—even in the absence of overt clinical signs—must be considered.

Repeated serum levels taken for patient 3 are total phenytoin 18 µg/mL, with a free phenytoin level of 5.7 µg/mL. An EEG shows mild diffuse slowing with no epileptiform activity, confirming the absence of subclinical seizure activity. Phenytoin is withheld, and patient 3 returns to baseline within 48 hours. Serum levels at 48 hours show that free phenytoin has fallen to 2.8 µg/mL. Further history reveals that patient 3 had recently started sodium valproate because of continued seizures on a high therapeutic dose of phenytoin. Her postictal lethargy, it is felt, may have partly resulted from a prolonged postictal state but was exacerbated by high free phenytoin levels.

Alternate adjunctive therapies for patient 3 that would not interact appreciably with phenytoin include all of the following EXCEPT:

A) Gabapentin
B) Lamotrigine
C) Topiramate
D) Tiagabine
E) Levetiracetam

DISCUSSION

The correct answer is D. Tiagabine is also highly protein bound and would displace phenytoin with consequent increased free levels of phenytoin. Levels of lamotrigine and topiramate are decreased by phenytoin, but neither agent affects phenytoin. No interactions occur between phenytoin and gabapentin or levetiracetam.

IX. SUMMARY POINTS

Choice of antiseizure drugs (ASDs) must first be based on the patient’s seizure type. With partial seizures, virtually any agent (with the exception of ethosuximide) may be considered. With generalized seizures (other than generalized tonic-clonic), treatment options include valproic acid, lamotrigine, topiramate, and zonisamide. Although clinicians may have different opinions with regard to efficacy, currently the various agents do not seem to be substantially different from one another.

For new-onset partial seizures, carbamazepine remains the first-choice ASD because of its long track record of safety, efficacy, and tolerability. Carbamazepine may be started relatively rapidly, although patients must be followed for several weeks because of autoinduction and resulting changes in serum levels. These limitations make oxcarbazepine a viable alternative, which has similar efficacy, fewer adverse effects, and decreased drug interactions (with no autoinduction). Only continued experience with oxcarbazepine will determine if this agent will replace carbamazepine. Other reasonable first-line ASDs for new-onset patients include phenytoin.
gabapentin, and lamotrigine. Phenytoin may be dosed once daily; however, its complicated pharmacokinetics and adverse-effect profile will likely make it less popular as clinicians become increasingly comfortable with newer agents. For medically complicated patients, gabapentin and lamotrigine are particularly attractive because of a lack of drug-drug interactions associated with their use. These agents are widely used in older patients for this reason as well as for their favorable tolerability. The extremely favorable safety and tolerability of gabapentin make it a reasonable first-line choice for children.

- Second-line agents for partial seizures include valproic acid, topiramate, zonisamide, levetiracetam, and tiagabine. Less favorable adverse-effect profiles and limited experience (particularly with levetiracetam) usually relegate these drugs to use after first-line agents have failed or cannot be administered for other reasons, such as allergic reaction. Felbamate is used only in patients with highly refractory seizures.

- For absence seizures, valproic acid and ethosuximide remain first-choice ASDs. Lamotrigine, zonisamide, and topiramate are reasonable alternatives that may have fewer adverse effects than valproic acid. For other generalized seizure types, treatment options are the same with the exception of ethosuximide, which is not effective. In very refractory patients—especially those with multiple seizure types such as the Lennox-Gastaut syndrome—lamotrigine, zonisamide, topiramate, and felbamate may be particularly useful.

- Drugs may be chosen based on their efficacy in other diseases. Increasingly, antiseizure agents are being recognized as "neuromodulators," which have other beneficial effects on the nervous system. Thus, gabapentin may be preferred in patients with epilepsy who also have migraine, neuropathic pain, or social phobia; valproic acid should be considered in patients who also have migraine or bipolar disorder. Effectiveness of the newest agents in other conditions remains unclear.

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