Antiepileptic Drug Treatment: New Drugs and New Strategies

Jacqueline A. French, MD, FAAN; Deana M. Gazzola, MD

ABSTRACT

Purpose of Review: Selection of the ideal antiepileptic drug (AED) for an individual patient can be a daunting process. Choice of treatment should be based on several factors, including but not limited to epilepsy classification, AED mechanism of action, AED side-effect profile, and drug interactions. Special consideration must be given to populations such as women, older adults, patients with other medical comorbidities, and patients who are newly diagnosed.

Recent Findings: Head-to-head trials between AEDs in newly diagnosed patients rarely demonstrate that one AED is more or less effective. The second-generation drugs, lamotrigine, topiramate, oxcarbazepine, zonisamide, and levetiracetam, have undergone head-to-head trials confirming similar efficacy and equal or better tolerability than standard drugs in focal epilepsy.

Summary: A thoughtful approach to the AED selection process must factor in data from clinical AED trials as well as a variety of patient characteristics and confounding factors. When neurologists apply an individualized approach to AED drug selection for their patients, they can find an effective and well-tolerated drug for most patients.

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Address correspondence to Dr Jacqueline A. French, 223 East 34th St, New York, New York 10016, *Jacqueline.french@nyumc.org*.

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INTRODUCTION

Neurologists now have many more antiepileptic drug (AED) options for the care of patients with epilepsy than ever before; however, choosing among the various AEDs and navigating their side-effect profiles and drug interactions can be challenging. It is beyond the scope of this article to review individual AEDs. Readers are encouraged to review each drug's indication of use, metabolism, side effects and toxicities, and drug-drug interactions in the available literature. The primary focus of this article is to discuss a basic approach to drug selection and manipulation that can be broadly applied. Additional information is provided in table format: **Table 4-1**[1] delineates AED mechanism of action and metabolism, and **Table 4-2**[1] reviews AED side effects.

ANTIEPILEPTIC DRUG SELECTION

Each AED has unique characteristics, including spectrum of activity, cost, pharmacokinetic and pharmacodynamic properties, likelihood for dose-related side effects, and risk of serious health problems, such as idiosyncratic reactions. Unfortunately, a clear first choice for specific treatment situations, such as initiation in the newly diagnosed patient, selection of the first add-on drug, or use in a woman anticipating pregnancy, does not exist. For each of these scenarios, some choices may be more or less optimal, but the final selection will depend on a combination of variables and patient

TABLE 4-1 Antiepileptic Drug Mechanism of Action and Metabolism[a]

Antiepileptic Drug Name	Primary Mechanism(s) of Action	Metabolism
Bromides	Unknown; potentially stabilize neuronal membranes via hyperpolarization	Slow renal excretion, unchanged
Phenobarbital	Enhance γ-aminobutyric acid (GABA) inhibition	Hepatic; cytochrome P450 enzyme (CYP) inducer
Primidone	May act synergistically with potassium bromide to reduce high-frequency repetitive neuronal firing	Hepatic; CYP inducer
Phenytoin	Use-dependent inhibition of sodium channels, thus blocking repetitive firing of action potentials	Hepatic; CYP inducer
Ethosuximide	Reduction of low-threshold T-type calcium currents in thalamic neurons	Hepatic; CYP substrate but no effects
Carbamazepine	Use-dependent inhibition of sodium channels, thus blocking repetitive firing of action potentials	Hepatic; CYP inducer
Valproate	Precise mechanism unknown; multiple GABA-related actions, *N*-methyl-D-aspartate (NMDA) receptor antagonist, and histone deacetylase inhibitor	Hepatic; CYP inhibitor
Vigabatrin	Specifically and irreversibly inhibits GABA transaminase; may also stimulate GABA release	Minimal hepatic metabolism, excreted renally largely unchanged; CYP inducer
Felbamate	Binds to open channels of the NMDA subtype glutamate receptor, thus blocking sodium and calcium conduction; also possesses other properties, such as inhibition of voltage-gated sodium channels	Partial hepatic metabolism (excreted in urine 40–50% unchanged); variable CYP effects
Gabapentin and pregabalin	Precise mechanism unknown; bind to the $\alpha_2\delta$ modulatory subunit of voltage-sensitive calcium channels	None; excreted in the urine unchanged; no effects on CYP
Lamotrigine	Blocks sodium channels; inhibits high voltage-activated calcium currents	Hepatic via UDP-glucuronosyltransferase (UGT) metabolism; no effects on CYP
Tiagabine	Enhances GABA-mediated inhibition by blocking GABA reuptake	Hepatic; CYP substrate but no effects
Topiramate	Multiple mechanisms: blocks the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid glutamate receptor subtype; blocks voltage-activated sodium channels; enhances GABA-mediated chloride flux at $GABA_A$ receptors; reduces amplitude of high voltage-activated calcium currents; and activates potassium conduction	Liver minimally, excreted renally largely unchanged; weak CYP inducer
Levetiracetam	Precise mechanism unknown; binds synaptic vesicle protein 2A, a presynaptic protein, on synaptic vesicles	Hydrolytic metabolism, excreted renally; no effects on CYP
Oxcarbazepine	Blocks voltage-dependent ionic membrane conduction (particularly sodium, potassium, and calcium) thereby stabilizing membranes and reducing synaptic impulse propagation; acts on N-type calcium channels	Hepatic; CYP inhibitor
Zonisamide	Blocks T-type calcium channels, inhibits slow sodium channels, and inhibits glutamate release	Hepatic; CYP substrate, but no effects

Continued on next page

TABLE 4-1 Antiepileptic Drug Mechanism of Action and Metabolism[a] *(continued)*

Antiepileptic Drug Name	Primary Mechanism(s) of Action	Metabolism
Rufinamide	Exact mechanism of action unknown; prolongs inactivation of voltage-dependent sodium channels	Hydrolytic metabolism, excreted renally; modestly induces CYP
Lacosamide	Selectively enhances the slow inactivation of voltage-gated sodium channels; inhibits the collapsin response mediator protein 2 thereby possibly inhibiting neuronal growth that may occur in chronic epilepsy	Variably metabolized, excreted renally; no known CYP induction; inhibits CYP-19 at 30 times higher than therapeutic concentrations
Ezogabine[b]	Potassium channel opener, particularly KCNQ2-5 channels	Hepatic; not a CYP P450 substrate
Perampanel	Noncompetitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)-type glutamate receptors on postsynaptic neurons	Extensively metabolized via CYP3A4 via primary oxidation and sequential glucuronidation

[a] Modified from French JA, Gazzola DM. Therap Adv Drug Saf.[1] © 2011 by SAGE. Reprinted with permission of SAGE. *taw.sagepub.com/content/2/4/141.abstract*.
[b] United States Adopted Name; known in rest of world as retigabine.

characteristics. What follows is a rational sequence of issues that should be considered to optimize drug choices.

Epilepsy Syndrome

Epilepsy syndrome must be the first issue considered, since seizure control is the primary goal of therapy and many AEDs treat only certain syndromes and not others. AEDs that are considered narrow spectrum are much more effective at controlling seizures associated with select syndromes or within a specific category (partial versus generalized). Other AEDs are broad-spectrum agents able to treat both partial and generalized epilepsy.

Narrow-spectrum agents that treat focal epilepsy include carbamazepine, oxcarbazepine, gabapentin, pregabalin, tiagabine, and vigabatrin. Some of these drugs (particularly carbamazepine, oxcarbazepine, gabapentin, pregabalin, and tiagabine) may in fact exacerbate some generalized seizures, such as myoclonus and absence.[2] Vigabatrin, while considered a narrow-spectrum drug, is exceptionally useful in the treatment of infantile spasms (often considered a generalized seizure type) due to tuberous sclerosis.[3]

Narrow-spectrum agents that treat generalized epilepsy syndromes include rufinamide (especially for atonic seizures in Lennox-Gastaut syndrome) and ethosuximide (specifically for absence seizures). These drugs are not typically used in the setting of partial epilepsy. Broad-spectrum agents (suitable for treatment of both focal and generalized epilepsy) include levetiracetam, lamotrigine, phenytoin, topiramate, felbamate, zonisamide, valproic acid, and phenobarbital. Although phenobarbital is considered a broad-spectrum agent, it has been associated with triggering absence seizures. In addition, a worsening of Lennox-Gastaut syndrome and myoclonic epilepsies has been seen with phenobarbital use; however, this effect may be related to drug sedation.[2]

Levetiracetam tends to be very effective for myoclonic seizures. Lamotrigine can sometimes exacerbate myoclonus but can be effective in treating tonic-clonic seizures (**Case 4-1**). Lamotrigine

KEY POINT

- Antiepileptic drugs that are narrow spectrum are much more effective at controlling seizures associated with select syndromes or within a specific category (partial versus generalized). Other antiepileptic drugs are broad-spectrum agents able to treat both partial and generalized epilepsy.

TABLE 4-2 Antiepileptic Drug Adverse Effects[a]

Antiepileptic Drug	Potential Adverse Effects (Not Fully Inclusive)
Bromides	Drowsiness; restlessness; headache; delirium; acneiform rashes; granulomatous skin lesions; loss of appetite; psychosis
Phenobarbital and other barbiturates	Sedation, depression, and paradoxical hyperactivity in children; neurologic toxicity (such as dysarthria, ataxia, and nystagmus) with increasing doses; rare hematologic toxicity
Phenytoin	Nystagmus; ataxia; diplopia; drowsiness; impaired concentration; gingival hyperplasia; hirsutism; acne; hepatotoxicity and idiosyncratic reactions including lupuslike reactions and aplastic anemia
Ethosuximide	Nausea; abdominal discomfort; anorexia; drowsiness; dizziness; numerous idiosyncratic reactions; rarely, hematologic toxicity
Carbamazepine	Nausea; dizziness; drowsiness; diplopia; weight gain; rash; Stevens-Johnson syndrome; toxic epidermal necrolysis; hyponatremia; leukopenia; rare cases of hepatotoxicity; other idiosyncratic reactions
Valproate	Dose-related tremor (less with controlled-release formulations); hair loss; weight gain; nausea; vomiting; hepatotoxicity; acute hemorrhagic pancreatitis; thrombocytopenia; hyperammonemia; less commonly, lethargy
Vigabatrin	Headache; fatigue; dizziness; drowsiness; depression; permanent visual field deficits
Felbamate	Headache; nausea; dizziness; weight loss; fulminant hepatic failure; aplastic anemia
Gabapentin	Somnolence; dizziness; fatigue; weight gain
Lamotrigine	Hypersensitivity reactions; Stevens-Johnson syndrome (increased occurrence with rapid titration); dizziness; nausea; insomnia; headache
Tiagabine	Dizziness; tremor; abnormal thinking; nervousness; abdominal pain; rare psychosis; rare nonconvulsive status epilepticus
Topiramate	Drowsiness; paresthesias; metabolic acidosis; oligohidrosis; renal calculi (most commonly reported idiosyncratic reaction); rare hepatic failure; impaired language fluency and cognition; weight loss; rarely acute glaucoma
Levetiracetam	Dizziness; somnolence; asthenia; headache; irritability; behavioral problems; depression; psychosis
Oxcarbazepine	Fatigue; headache; dizziness; ataxia; diplopia; nausea; vomiting; rash; hyponatremia; Stevens-Johnson syndrome
Zonisamide	Fatigue; dizziness; somnolence; anorexia; abnormal thinking; rash; Stevens-Johnson syndrome; renal calculi; aplastic anemia; oligohidrosis
Pregabalin	Dizziness; somnolence; weight gain
Rufinamide	Fatigue; vomiting; loss of appetite; somnolence; headache; aggravated seizures; status epilepticus
Lacosamide	Dizziness; headache; nausea; diplopia
Ezogabine[b]	Urinary retention; dizziness; somnolence; fatigue; confusion; vertigo; tremor; abnormal coordination
Perampanel	Dizziness; somnolence; irritability; falls; ataxia; risk of severe changes in mood and behavior, including aggression, hostility, anger, and homicidal ideation and threats

[a] Modified from French JA, Gazzola DM. Therap Adv Drug Saf.[1] © 2011 by SAGE. Reprinted with permission of SAGE. *taw.sagepub.com/content/2/4/141.abstract*.
[b] United States Adopted Name; known in rest of world as retigabine.

Case 4-1

A high school student on the soccer team was slowly transitioned from valproate to lamotrigine for juvenile myoclonic epilepsy. She experienced generalized tonic-clonic seizure breakthroughs, but with gradual dose increase she eventually stabilized, and no generalized tonic-clonic seizures occurred for 6 months. Her lamotrigine level was obtained and found to be 6 μg/mL. She then returned to clinic and reported experiencing insomnia and twitches in her upper body involving her hands and head. When asked about her dosing, she reported taking her lamotrigine before going to bed at 10:00 PM. Levetiracetam was added for control of her myoclonus. She reported sleeping better after starting levetiracetam, and the myoclonus had largely resolved. She now took a low dose of levetiracetam at bedtime and lamotrigine in the morning before school. She remained seizure free at a follow-up appointment 6 months later.

Comment. Because of the potentially stimulating properties of lamotrigine, it should be taken in the morning (after breakfast, if possible). By shifting doses to the morning, insomnia can be avoided in many patients. In addition, this patient is now experiencing myoclonic jerks for the first time. These may have been controlled on her prior valproate regimen but now appear to be exacerbated by lamotrigine.
The myoclonus impedes her handwriting in school and affects her performance on the soccer field, thus justifying initiation of levetiracetam. Consideration could be given to discontinuing lamotrigine, but, by doing this, there is a possibility of destabilization in a patient who is currently seizure free with no complaints.

KEY POINTS

- Studies indicate that, at the time of diagnosis, classification of partial or generalized seizures can only be made about half of the time. If a clear diagnosis cannot be made, it is wise to choose a broad-spectrum antiepileptic drug.
- The choice of initial therapy can be crucial because many patients will remain on the initial therapy long term.
- The first antiepileptic drug should be one that is expected to be well tolerated and reasonably safe.

was inferior to valproate and ethosuximide in controlling absence seizures and inferior to valproate in all generalized seizures in randomized controlled trials.[4,5] A table delineating narrow- and broad-spectrum agents is provided (**Table 4-3**).

In one controlled study, valproic acid was inferior to carbamazepine for control of complex partial seizures but equal to carbamazepine in its ability to control partial seizures evolving to generalized tonic-clonic convulsions.[6]

Several newer AEDs (ie, lacosamide, ezogabine [United States Adopted Name; known in rest of world as retigabine], perampanel) have only been tested against focal seizures, and therefore the spectrum of activity is currently unknown.

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Drugs for Initial Therapy

The choice of initial therapy can be crucial because many patients will remain on the initial therapy long term. Recent studies have indicated that 37% of patients with newly diagnosed epilepsy will become seizure free on the initial therapy.[7] A seizure-free patient may be unwilling to attempt a change in therapy, even when side effects are present. A clinician is also less likely to risk medication conversion in seizure-free patients because they may become destabilized. This is a particularly relevant concern if the patient has resumed activities such as driving. Only one chance may therefore exist to select the optimal therapy. The first AED should be one that is

TABLE 4-3 Narrow- and Broad-Spectrum Agents

Seizure Type	Antiepileptic Drug	Narrow- or Broad-Spectrum Efficacy	Comments
Focal seizures with or without secondarily generalized tonic-clonic seizures	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Eslicarbazepine Vigabatrin	Narrow	Carbamazepine, gabapentin, oxcarbazepine, pregabalin, and tiagabine may aggravate myoclonic and absence seizures. The full spectrum of activity of eslicarbazepine is not yet identified. Vigabatrin is also useful for infantile spasms.
Generalized seizures	Ethosuximide Rufinamide	Narrow	Rufinamide is minimally effective for focal seizures.
Focal and generalized seizures	Valproate Benzodiazepine Phenobarbital Primidone Lamotrigine Levetiracetam Topiramate Zonisamide Felbamate	Broad	Phenobarbital is not useful for absence seizures. Lamotrigine may aggravate myoclonic and absence seizures.
Other	Phenytoin Lacosamide Ezogabine[a] Perampanel	Spectrum not yet fully identified, or mixed	Phenytoin may be useful for generalized tonic-clonic convulsions even when not of focal origin. The full spectrum of activity of lacosamide, ezogabine, and perampanel is not yet identified.

[a] United States Adopted Name; known in the rest of the world as retigabine.

KEY POINT

- When using drugs in polytherapy, pharmacokinetic interactions must be considered and doses should be altered as appropriate.

expected to be well tolerated and reasonably safe. Head-to-head trials between both new and old AEDs in newly diagnosed patients rarely demonstrate that one AED is more or less effective.[8] Drugs of the second generation that have undergone head-to-head trials that confirm similar efficacy and equal or better tolerability than first-generation drugs in focal epilepsy include lamotrigine, oxcarbazepine, zonisamide, and levetiracetam.[9–12] Vigabatrin and tiagabine were inferior to carbamazepine in head-to-head trials[13]; gabapentin was inferior to carbamazepine for efficacy in one large, unblinded randomized trial that was designed to mimic clinical practice[11]; pregabalin was inferior to lamotrigine in controlling newly diagnosed focal seizures in a blinded, randomized trial.[14] Topiramate was less well tolerated than valproate or lamotrigine for generalized seizures in one pragmatic trial.[5]

Use of Add-On Drugs

When drugs are combined, a risk of both pharmacokinetic and pharmacodynamic interactions exists. In the

past, sequential monotherapy was highly recommended by experts because AEDs were likely to cause side effects when combined. Presently, it is very common to add AEDs to each other, and many treatment-resistant patients are maintained on two, three, or even four AEDs. This is likely because the newer AEDs do not cause as many side effects when combined as first-generation AEDs did. When using drugs in polytherapy, pharmacokinetic interactions must be considered, and doses should be altered as appropriate. Also, certain combinations that tend to produce more side effects should be avoided as primary choices. Some examples of such challenging drug combinations include the following:

1. Phenobarbital and valproate: Sedation and weight gain can be difficult to combat.
2. Phenytoin and carbamazepine: Dizziness and diplopia are common, and maintaining therapeutic levels can be difficult because of a bidirectional induction of metabolism.
3. Valproate and lamotrigine: Requires adjustment of lamotrigine dose because of increased levels of lamotrigine that can cause dizziness and increase the risk of Stevens-Johnson syndrome; however, this combination has been noted to be very efficacious in some patients.[15]
4. Topiramate, lamotrigine, or zonisamide and enzyme-inducing AEDs (eg, carbamazepine, phenytoin): When adding drugs to enzyme inducers, doses of the additive drugs will need to be substantially higher because of increased clearance.[16]

A summary of the above is provided in **Table 4-4**.

Avoiding combinations of AEDs with similar side-effect profiles can be helpful, but it is often impossible. For example, multiple AEDs can cause dizziness, imbalance, and diplopia. The following combinations, which are commonly employed, are notorious for exacerbating these symptoms: (1) carbamazepine and lamotrigine, (2) carbamazepine and lacosamide, (3) oxcarbazepine and lacosamide, (4) lamotrigine and lacosamide.

Reducing the original dose of one of the AEDs is often necessary to accommodate the addition of a second AED with a similar side-effect profile. This can improve tolerability and allow

TABLE 4-4 Challenging Drug Combinations

Antiepileptic Drug Combination	Side Effects and Challenges
Phenobarbital and valproate	Sedation and weight gain
Phenytoin and carbamazepine	Dizziness and diplopia; maintaining therapeutic levels can be difficult
Valproate and lamotrigine	Requires adjustment of lamotrigine dose because of increased levels of lamotrigine
Topiramate, lamotrigine, or zonisamide and enzyme-inducing antiepileptic drugs (eg, carbamazepine, phenytoin)	Doses of the additive drugs to enzyme-inducers will need to be substantially higher because of increased clearance

KEY POINTS

- Avoiding combinations of antiepileptic drugs with similar side-effect profiles can be helpful but is often impossible. For example, multiple antiepileptic drugs can cause dizziness, imbalance, and diplopia. The following combinations, which are commonly employed, are notorious for exacerbating these symptoms: (1) carbamazepine and lamotrigine, (2) carbamazepine and lacosamide, (3) oxcarbazepine and lacosamide, (4) lamotrigine and lacosamide.
- Elimination of drugs that have been deemed ineffective is optimal.
- The reduction of any medication, even those deemed ineffective, can trigger a withdrawal response and seizure clusters or status epilepticus.

KEY POINTS

- Complex polypharmacy is one of the most challenging aspects of managing patients with epilepsy, as both physicians and patients continue to search for the ''Goldilocks'' combination of antiepileptic drugs that is ''just right.''
- Drugs such as levetiracetam, gabapentin, pregabalin, and valproate have a low risk of hypersensitivity and may be good choices in patients with a history of rash or hypersensitivity to antiepileptic drugs or other agents.

for higher doses of a new drug leading to increased efficacy.

Determining the Adequate Number of Drugs

In cases of severe refractory epilepsy, patients for whom the first two drugs fail will often have a third and fourth added to their regimen in an attempt to increase seizure control. As a result patients may be on five or more medications at once. Elimination of drugs that have been deemed ineffective is optimal and done for many reasons, including to reduce side effects, to allow increased doses of newer drugs to be added to the regimen, to avoid complex drug-drug interactions that can further impede the ability to achieve therapeutic levels, and to reduce the overall drug burden on a patient's body.

The reduction of any medication, even those deemed ineffective, can trigger a withdrawal response and seizure clusters or status epilepticus. AED removal should therefore be performed gradually over many weeks when taking place in the outpatient setting. Although some propose that rapid weaning of one drug and simultaneous rapid induction of a new drug can be performed, the authors urge a more gradual approach. As a matter of patient safety and out of a desire to avoid status epilepticus in the home, it is preferable to first introduce the desired new agent, build the dose gradually based on patient tolerability and seizure frequency, and then slowly reduce the ineffective drug that is intended to be removed. Depending on the combination of AEDs being manipulated, reduction of the ineffective drug might need to begin before a therapeutic level of the new agent is reached, for tolerability purposes. If toxic side effects, serious drug reactions, or worsened seizure control necessitate a more rapid AED withdrawal, admission to a monitored setting in the hospital is highly recommended. Occasionally, removal of an ineffective drug will trigger withdrawal seizures, even when it is done slowly. Some patients seem particularly prone to this, and it is these patients who may end up on multiple AEDs, as withdrawal of background AEDs is difficult. These patients may need hospital admission for AED adjustment or removal (**Case 4-2**).

SPECIFIC HEALTH ISSUES

Patients with a history of rash or hypersensitivity to AEDs or other agents should have a drug selected that is not likely to produce such a reaction; lamotrigine is not an optimal choice. In addition, cross-sensitivity exists between phenobarbital, carbamazepine, and phenytoin. Drugs such as levetiracetam, gabapentin, pregabalin, and valproate have a low risk of hypersensitivity and may be good choices. Drugs that produce weight gain (eg, valproic acid, gabapentin, pregabalin, carbamazepine, and the new AED ezogabine) may not be optimal choices in patients who are obese; topiramate and zonisamide, which can cause weight loss, might be preferable in this patient population. Topiramate and zonisamide might not, however, be first-line agents in patients with renal calculi, because both drugs predispose patients to stone development.

Patients with renal insufficiency or who require dialysis often require lower doses of renally excreted AEDs; extra doses may be administered after dialysis treatments. AEDs that are almost exclusively renally cleared include levetiracetam, gabapentin, and pregabalin. Information about renal dosing is usually found on the package insert. Similarly, it is preferable to avoid potentially hepatotoxic agents, such as valproate and felbamate, in patients with known hepatic disease; similar to

Case 4-2

A 78-year-old man presented with refractory focal epilepsy resulting from a traumatic brain injury sustained in a car accident 30 years before. He experienced three to four secondarily generalized tonic-clonic seizures a month and had two to three complex partial seizures per week. He had a right temporal lobectomy 15 years ago that was extended 10 years ago, and a vagus nerve stimulator that helped to control his seizures but did not eliminate them. He was currently taking phenytoin, which he had been on for 20 years; carbamazepine, which he had been on for 15 years; and lamotrigine, levetiracetam, and topiramate, which were added over the past 10 years. He had chronic renal insufficiency and diabetes and had received multiple bone fractures due to osteoporosis. He was sedated and depressed and was on warfarin for a deep vein thrombosis.

The patient's serum levels and routine blood work were obtained. His carbamazepine and topiramate levels were high therapeutic, but his phenytoin, lamotrigine, and levetiracetam levels were subtherapeutic. The patient's phenytoin (300 mg at bedtime), which was likely driving down his lamotrigine level, was reduced by 100 mg. This led to a cluster of convulsions, and the patient was brought to the emergency department, where he was given IV fosphenytoin and admitted to an epilepsy monitoring unit for further medication adjustment.

While in the epilepsy monitoring unit, a reduction of the patient's dose of phenytoin was attempted again; simultaneously, his lamotrigine and levetiracetam doses were increased. He was eventually tapered off of phenytoin and topiramate. As a result, his lamotrigine level became therapeutic. At a follow-up appointment 3 months later, he was taking levetiracetam, lamotrigine, and carbamazepine and reported having more energy. His seizure frequency had been reduced to one to two generalized tonic-clonic convulsions a month and one to two complex partial seizures per week. He noted occasional nosebleeds as well as increased bleeding from his gums when he brushed his teeth. His international normalized ratio (INR) was 4 (high). Reduction of his warfarin dose corrected the problem.

Comment. This medically complex patient had severe treatment-resistant epilepsy and multiple medical issues and was receiving multiple drugs with associated side effects. The treatment approach in such a case should be twofold: (1) attempt better seizure control and (2) reduce medication burden and side effects. Of the agents this patient was taking at the time he presented, phenytoin and carbamazepine present the greatest challenge to his quality of life because they are responsible for major drug-drug interactions and side effects. Both also affect bone health and can lower warfarin levels, thus making it difficult to achieve therapeutic international normalized ratios (INRs).

Tapering any medication—even if the medication is subtherapeutic and the tapering is gradual—can have unexpected consequences. If time is of the essence, more rapid changes can be made in the hospital setting while increasing other antiepileptic drugs (AEDs).

Further changes could be made to this patient's regimen over time. Ideally, his regimen would result in freedom from seizures; however, avoidance of side effects is also crucial. Discontinuation of carbamazepine, which is a hepatic enzyme inducer that could make warfarin adjustment more difficult, would be ideal. A future exchange of carbamazepine with a different agent, such as lacosamide, could be considered, although the combination of lacosamide and lamotrigine in such a patient could cause dizziness. Addition of a small dose of valproate could also be considered as this has been seen to improve seizures in some treatment-resistant cases.[15] Addition of valproate would likely require a reduction in lamotrigine dose because valproate is an inhibitor of lamotrigine metabolism. Ezogabine remains a possibility, although bladder function should be monitored in a patient in this age group, since bladder issues were a rare side effect in clinical trials of this agent. Further increases in levetiracetam could be performed while monitoring for sedation or exacerbation of depression. Any adjustments (particularly of carbamazepine) could cause fluctuations in the patient's warfarin metabolism; therefore, more frequent INR checks are recommended, as is communication with the patient's primary care physician.

Complex polypharmacy is one of the most challenging aspects of managing patients with epilepsy, as both physicians and patients continue to search for the ''Goldilocks'' combination of AEDs that is ''just right.'' Clinicians sometimes do not attain this perfect balance of seizure control and AED tolerability, but with the increased number of AEDs in today's armamentarium from which to choose, chances of success are higher than they were in the past.

KEY POINTS

- It is preferable to avoid enzyme-inducing antiepileptic drugs (eg, phenytoin, carbamazepine, phenobarbital, and primidone) in patients with chronic medical conditions other than epilepsy since two-thirds of drugs will undergo increased clearance as a result of enzyme induction.
- Older patients tend to have lower thresholds for developing side effects.

patients with renal insufficiency, those with reduced hepatic function may require lower doses of medications that are hepatically metabolized.

It is preferable to avoid enzyme-inducing AEDs (eg, phenytoin, carbamazepine, phenobarbital, and primidone) in patients with chronic medical conditions other than epilepsy since two-thirds of drugs will undergo increased clearance as a result of enzyme induction, including the antiarrhythmic drugs, calcium channel blockers, propranolol, amiodarone, digoxin, lipid-lowering agents, warfarin, antiretroviral agents, many antifungals, chemotherapeutic agents, immunosuppressives, and psychiatric medications, including some antidepressants and antipsychotics.[17]

Lastly, some drugs are more likely to produce behavioral problems, while others with mood-stabilizing properties might be helpful in patients with concomitant psychiatric illness. Carbamazepine, lamotrigine, oxcarbazepine, and valproate in particular are known for their mood-stabilizing effects. Levetiracetam (and phenobarbital in children) can produce irritability, and topiramate, phenobarbital, mysoline, and vigabatrin can cause depressed mood. Drugs that can produce stimulation (such as lamotrigine or felbamate) may produce anxiety or insomnia (**Table 4-1**).[18]

Antiepileptic Drug Treatment in Women

Hepatic-enzyme inducers (eg, phenytoin, carbamazepine, phenobarbital, and primidone) and inhibitors (eg, valproate) alter the clearance of oral contraceptives, steroid hormones, and vitamins.[19] The hormonal milieu may be affected, leading to an altered menstrual cycle and ovulation. The effects of enzyme induction and inhibition on women in their childbearing years are not completely known, but if noninducing agents such as the newer AEDs are an option, they may be preferable in this population. Induction of vitamin D metabolism by the enzyme-inducing agents may lead to increased risk of osteopenia. Vitamin D and calcium supplementation, while advisable in all young women, is particularly important in the presence of enzyme-inducing AEDs. Valproate may also affect bone density by other mechanisms (this is also the case for men who chronically take enzyme-inducing AEDs). In cases where osteopenia or osteoporosis is already present in the setting of the use of enzyme-inducing AEDs, referral to an endocrinologist may be useful.[20]

Pregnancy must also be considered when selecting an AED. Major and minor fetal anomalies—including cardiac defects, cleft lip and palate, microcephaly, and developmental delay—may occur with AED exposure during pregnancy.[21] Neural tube defects have been reported with the use of carbamazepine (0.5% risk) and sodium valproate (1.0% risk). Several recent pregnancy registries in women with epilepsy have demonstrated an increased risk of teratogenicity associated with valproate when compared to other AEDs.[21] Lamotrigine was recently identified as having an increased risk of cleft lip or palate in a single pregnancy registry,[22] although follow-up data from separate registries have revealed a lower risk than originally presented; in fact, topiramate demonstrated a higher risk of cleft lip or palate compared to lamotrigine in the more recent North American AED pregnancy registry findings.[23] A recent American Academy of Neurology guideline suggested that avoidance of valproic acid and polytherapy was advisable to reduce risks of birth defects.[21] The same guidelines identified a risk of poor cognitive outcomes among

children born to women taking valproate. Notably, brain development occurs up to the third trimester, so avoidance of valproate should be considered beyond the first trimester. The effects of valproate are dose related, so if a pregnant woman or a woman planning pregnancy needs valproate, she should be maintained on the lowest dose possible and if possible on monotherapy (**Case 4-3**). Data from pregnancy registries are constantly being gathered, and it might be a while before the exact risks for each drug are known. No specific anomalies have been associated with the other newer AEDs, but too few data are available to determine whether they are safe. More information on this topic is available in the article ''Pregnancy, Epilepsy and Women's Issues'' by Dr Page B. Pennell in this issue of CONTINUUM.

Antiepileptic Drug Selection in the Elderly

Older patients tend to have lower thresholds for developing side effects. Effects on cognition, alertness, and gait stability are of particular concern.[26] Both hepatic and renal clearance decrease with age over 65. For these reasons, it is preferable to titrate slowly and to lower target doses. Other pharmacokinetic

KEY POINT

- Planning for pregnancy in women with epilepsy is crucial not only to construct a treatment approach, but also to predetermine a baseline, or minimal drug level, required to maintain seizure freedom.

Case 4-3

A 15-year-old girl presented with a history of three generalized tonic-clonic seizures. She had a family history of seizures on the maternal side. Her EEG revealed a pattern of 4-Hz generalized polyspike-and-wave discharges that become activated during photic stimulation and associated with myoclonus. Although she was an avid high school basketball player, she felt slower and noticed some weight gain and tremor since starting extended-release valproate, which was initiated by another physician at a dose of 500 mg every night at bedtime.

The patient began lamotrigine therapy and after reaching 100 mg daily achieved a level of 5.5 μg/mL; her valproate dose was then reduced over several weeks until it was off. Two weeks later, she experienced a generalized convulsion; her lamotrigine level was found to be 2.8 μg/mL.

Comment. This patient with juvenile myoclonic epilepsy was experiencing side effects of valproate. While valproate is an effective agent for this type of epilepsy, its use should be avoided, if possible, in women of childbearing potential because of its known teratogenic potential and the risk of cognitive dysfunction in children born to mothers receiving valproate. Ideally, valproate should be removed and another broad-spectrum drug, such as levetiracetam, lamotrigine, or zonisamide, started. Along with valproate, topiramate has also recently been associated with an increased teratogenicity.[24] One reasonable approach, as was done in this case, would be to add lamotrigine 25 mg every other day and slowly increase the dose until a therapeutic drug level is attained, at which point a gradual reduction of valproate could take place.

Planning of pregnancy in women with epilepsy is crucial not only to construct a treatment approach, but also to predetermine a baseline or minimal drug level required to maintain seizure freedom. Close monitoring during pregnancy in a woman with epilepsy is essential, particularly when the patient is taking lamotrigine; among lamotrigine's quirks is the difficulty in maintaining therapeutic levels during pregnancy. Lamotrigine clearance often rises substantially during pregnancy, which may increase the risk of breakthrough seizures as the level drops.[25] It is recommended that lamotrigine levels be followed monthly during pregnancy; it is also common practice among epileptologists to preemptively increase lamotrigine doses in anticipation of a dramatic drop in a pregnant patient's lamotrigine level, which typically reaches its nadir during the second trimester.

Valproate inhibits the hepatic glucuronidation pathway responsible for metabolizing lamotrigine, so when it is removed, lamotrigine clearance doubles, resulting in a lower serum level. This is likely the reason for the patient's breakthrough seizure.

issues in the elderly may include reduced serum albumin leading to higher free (active) fraction of highly protein-bound drugs such as phenytoin, carbamazepine, and valproate.[27]

CONCLUSION

Both drugs and patients have unique characteristics. The treating physician must consider all of these when determining the best fit for a particular patient. The ultimate goal is freedom from seizures as well as from side effects. Since AEDs are taken long term in many cases, present and future effects need to be considered.

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