Epilepsy

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LEARNING OBJECTIVES

1. Apply considerations of quality of life when optimizing care for a patient with epilepsy.
2. Design an appropriate antiepileptic drug (AED) regimen, including monitoring, for a patient with epilepsy.
3. Evaluate an AED regimen on the basis of patient-specific considerations.
4. Evaluate data on emerging treatments, sudden unexpected death in epilepsy, suicidality, and generic formulations.

ABBREVIATIONS IN THIS CHAPTER

AAN	American Academy of Neurology
AED	Antiepileptic drug
AES	American Epilepsy Society
EEG	Electroencephalography
ILAE	International League Against Epilepsy
LGS	Lennox-Gastaut syndrome
SJS	Stevens-Johnson syndrome
SUDEP	Sudden unexpected death in epilepsy
TEN	Toxic epidermal necrolysis

Table of other common abbreviations.

INTRODUCTION

Epilepsy is a common neurologic condition, with an estimated 1.2% of the U.S. population reporting active epilepsy (Zack 2017). This estimate consists of 3 million adults and 470,000 children. Many developments in epilepsy diagnosis and treatment have occurred recently, introducing great opportunity for pharmacists to assist in optimizing pharmacotherapy for epilepsy while focusing on improving patients' quality of life. In addition, several new drugs are available for treating seizures, each with unique considerations for safety, efficacy, and cost. Investigational agents are also being evaluated, including repurposed drugs. Updates have occurred on diagnostic terminology, guidance for timing of treatment initiation for new-onset seizures, and recommendations on education for sudden unexpected death in epilepsy (SUDEP).

Impact of Epilepsy on Quality of Life

Epilepsy can be a significant burden for patients and caregivers. For many patients, the initial challenge to optimizing care includes having a correct diagnosis. Access to neurologists with the skills and diagnostic equipment to differentiate between epileptic seizures and psychogenic nonepileptic seizures is required to minimize the use of ineffective treatments. Accurate seizure classification is critical in selecting an appropriate drug. Not all antiepileptic drugs (AEDs) treat all seizure types, and some drugs can lead to seizure worsening when used for the incorrect seizure type. The Institute of Medicine 2012 committee report on epilepsies strongly encourages discontinuing use of the term *epileptic* to reduce stigma; however, *antiepileptic drug* remains the terminology used in the literature (Institute of Medicine 2012).

Adverse effects contribute to decreased quality of life. Identifying adverse effects through a review of systems or a questionnaire can encourage further discussion with the patient to optimize therapy. Ensuring that patients are taking AEDs that they tolerate well and

minimizing polytherapy will contribute to improved quality of life (St Louis 2009). Children and adolescents who are trying to be socially accepted have increased difficulty when their AEDs cause sedation (Eatock 2007). The Pediatric Epilepsy Side Effects Questionnaire has been developed and validated for use in both the clinical and the research setting for children with a variety of epilepsy diagnoses (Morita 2012). For adults, quality-of-life questionnaires (QOLIE-31 and QOLIE-10) may help assess adverse effects (Cramer 2000).

The challenges of maintaining a good quality of life with an epilepsy diagnosis are well defined. Adults with refractory epilepsy are more likely to have impaired quality of life when facing persistent seizures, depression, anxiety, felt stigma, and a decreased sense of control of their epilepsy (Ridsdale 2017b). *Felt stigma* refers to an individual patient's sense of shame with the diagnosis, and it is appropriate to refer patients to their clinic or local Epilepsy Foundation chapter to explore social connection opportunities or support groups. Patient education provided in groups gives patients the opportunity to connect and share their stories. This outreach can improve self-management and the sense that patients can make choices that improve their health (Ridsdale 2017a). The combination of worrying about seizures and a decrease in social support and self-efficacy is associated with an increased likelihood of depression and felt stigma (Smith 2009). Another type of stigma is enacted stigma, which refers to unfair treatment by others and may be addressed by addressing laws and policies that discriminate or create barriers for patients with epilepsy.

Updates in Diagnosis

In 2010, the International League Against Epilepsy (ILAE) classification taskforce released new guidance defining classification of seizure type (Berg 2010). This new terminology was developed to convey a common language between health care providers when communicating about the different aspects of seizures. In this guidance, seizures are differentiated into three primary types of onset: focal, generalized, and unknown. *Focal* replaces the term *partial*. Seizures that were "partial onset with secondary generalization" are classified as seizures that progress from focal to bilateral tonic-clonic. Generalized seizures are classified by motor or nonmotor (absence) activity. Use of *unknown onset* reflects the difficulty in classifying seizures that are unwitnessed and that occur while the patient is asleep or when observers cannot provide an adequate description (Fisher 2017).

Historically, an epilepsy diagnosis required a patient to have had two seizures at least 24 hours apart (Fisher 2014). An ILAE taskforce expanded the definition to include patients who have had only one seizure but who are at significant risk of seizure recurrence (e.g., recent stroke, brain structure abnormality, abnormal electroencephalography [EEG]). A 2015 guideline group determined that the greatest risk of seizure recurrence is during the first 2 years after an unprovoked seizure, but treating early does not necessarily ensure long-term seizure remission. Several clinical factors may increase the risk of recurrence and lead to beginning treatment after only one seizure, including an EEG with epileptiform abnormalities, a past brain injury such as stroke or trauma, a significant brain structure abnormality, or having a nocturnal seizure (Krumholz 2015).

PHARMACOTHERAPY

More than 23 drugs to treat epilepsy are now available in the United States. This chapter does not include the drugs used to treat seizure emergencies. Drug selection depends on the seizure type and epilepsy diagnosis, with considerations for efficacy, adverse effects, cost, and insurance coverage. Not all patients tolerate typical dosages or schedules, and individualized adjustments may be necessary. Figure 1 presents a treatment algorithm for epilepsy.

Drug Selection for New-Onset Epilepsy

Seizure Type

The generally accepted drugs for new-onset epilepsy are presented according to seizure type in Table 1, which is based on the 2013 UK National Institute for Health and Care Excellence (NICE) guidelines, the 2018 American Academy of Neurology (AAN), and the American Epilepsy Society (AES) treatment guidelines for new-onset epilepsy.

Focal seizures may present with a variety of symptoms, and awareness may be either intact or impaired. Seizures are further described by the presence of motor movements, including automatisms or other motor activity, and by nonmotor onset symptoms, including sensory or autonomic symptoms. Most clinical trials of AEDs are with patients with focal seizures, usually as adjunctive therapy.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of seizure pathophysiology
- AED pharmacology and drug monitoring
- Common AED drug interactions

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Academy of Neurology. Guidelines Related to Seizures and Epilepsy.
- American Epilepsy Society. Epilepsy 101.

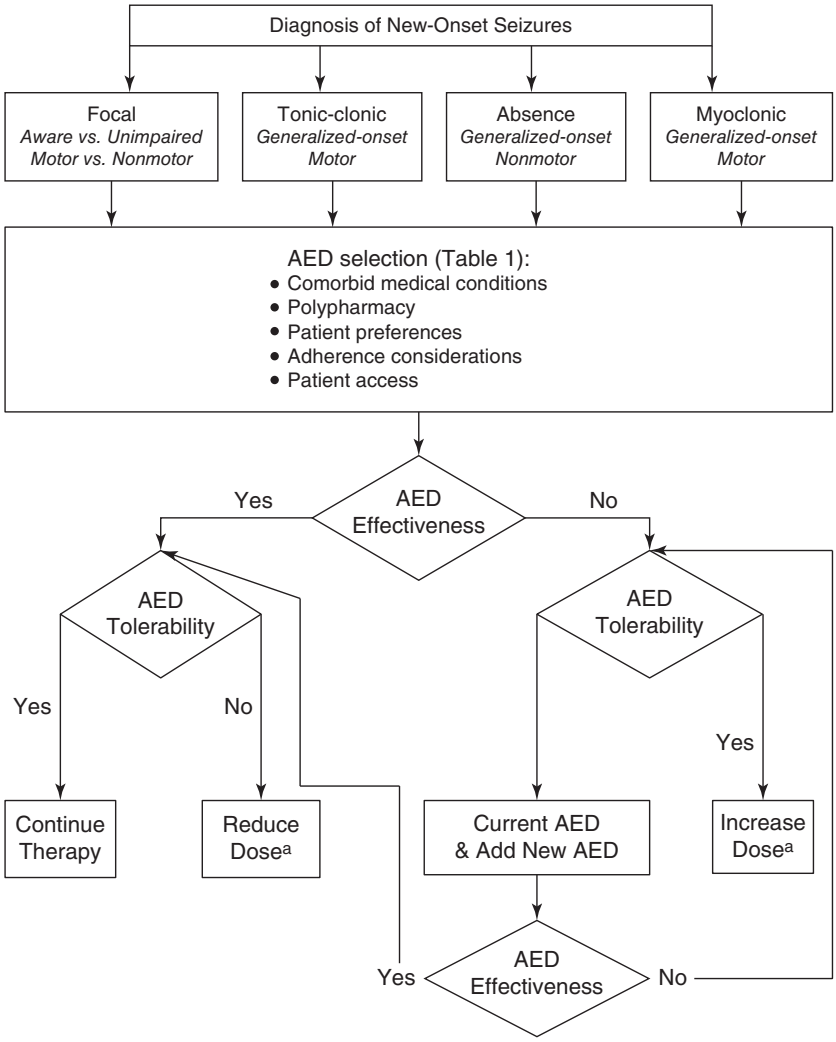

Figure 1. Treatment algorithm for epilepsy.

[a]Consider tapering off ineffective AED if two AEDs used.

AED = antiepileptic drug.

Adapted with permission from: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. Figure 40-1.

Generalized seizures involve bilateral networks in the brain. The activity can be asymmetric, and seizures may manifest with a motor (e.g., tonic-clonic activity) or nonmotor (e.g., absence) presentation. Myoclonic seizures are in the diagnostic classification of generalized seizures and present as sudden, brief, shock-like contractions confined to one muscle or a group of muscles. Juvenile myoclonic epilepsy is a type that often presents during adolescence, typically at 5–16 years of age. Most patients will require long-term treatment, though about 10% may remain seizure free without drugs (Höfler 2014). Several AEDs may worsen myoclonic jerks in these patients (see Table 1). Absence seizures are also in the diagnostic classification of generalized seizures, which present as brief staring spells lasting a few seconds. This seizure often presents in childhood, but many patients grow out of these seizures.

Efficacy

Both prescribers and patients are concerned about selecting a drug that will result in seizure freedom. Clinical trials of AEDs are often designed with an investigational drug added as adjunctive therapy to an existing AED regimen versus placebo. This trial design is mainly because of ethical limitations of exposing patients to only a placebo while their seizures are not well controlled (Perucca 2012). Large, active-control, double-blind clinical trials are lacking that would help better define efficacy, and discussion about how to best design AED studies continues.

Table 1. First-line Treatment of New-Onset Epilepsy in Patients ≥ 13 Yr

Seizure Type	First-line AEDs	Drugs to Avoid
Focal	Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, zonisamide	
Generalized		
Tonic-clonic	Lamotrigine, carbamazepine, oxcarbazepine, valproate	If absence, myoclonic, or juvenile myoclonic seizures suspected, avoid the following: Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Absence	Ethosuximide, valproate	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin
Myoclonic (including juvenile myoclonic epilepsy)	Lamotrigine, levetiracetam, topiramate, valproate	Carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, vigabatrin

Information from: National Institute for Health and Care Excellence (NICE). Epilepsies: Diagnosis and Management; and Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Neurology Jul 2018;81:74-81.

Research has shown that patients with newly diagnosed epilepsy respond in one of four common patterns (Figure 2). In a database of 1098 patients with newly diagnosed epilepsy followed for at least 2 years, 68% of patients were seizure free at the end of observation period. This study provides insight into the erratic nature of epilepsy and how challenging it is to predict clinical response. This study did not detect differences in response on the basis of sex, age, or epilepsy syndrome diagnosis (Brodie 2012).

Patient Considerations

Several factors should be considered when selecting an AED for a patient with a new seizure diagnosis, including comorbid medical conditions, polypharmacy, patient preferences, and patient access to drugs. Most AEDs have several labeled indications or other uses beyond seizures. Valproate, carbamazepine, and lamotrigine are approved for mood stabilization related to bipolar disorder. Gabapentin and pregabalin have efficacy for neuropathic pain. Valproate and topiramate can be prescribed for migraine prophylaxis. Pharmacists can contribute to tailoring the AED to the patient's health conditions.

Adverse effects of AEDs (Table 2) often drive drug selection for epilepsy treatment. All the AEDs have a warning to monitor for suicidal behavior and suicidal thoughts. Significant and life-threatening adverse effects have been associated with most AEDs, including drug reaction with eosinophilia

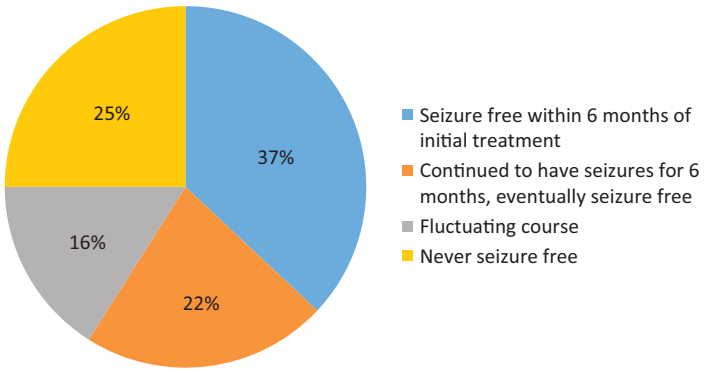

Figure 2. Treatment response patterns in newly diagnosed epilepsy (n=1098).

Information from: Brodie MJ, Barry SJE, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548-54.

Table 2. AED Adverse Effects

Drug	Common	Serious
Brivaracetam	Somnolence/sedation, dizziness, fatigue, nausea/vomiting, irritability, constipation	Hypersensitivity reaction,[a] bronchospasm, angioedema,[a] cerebellar ataxia, impairment of balance, psychiatric symptoms
Cannabidiol	Somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash; insomnia, sleep disorder, infections	
Carbamazepine	Nausea/vomiting, ataxia, dizziness, somnolence, blurred vision, pruritus	SJS,[a] TEN,[a] hypersensitivity reaction,[a] aplastic anemia/agranulocytosis,[a] atrioventricular heart block, hepatic failure,[a] hyponatremia
Clobazam	Somnolence, lethargy, ataxia, aggressive behavior, constipation	SJS,[a] TEN,[a] physical and psychological dependence
Eslicarbazepine	Dizziness, somnolence, nausea, headache, double vision, ataxia, fatigue	SJS,[a] TEN,[a] hyponatremia, hypersensitivity reaction,[a] DRESS[a]
Ethosuximide	Nausea/vomiting, loss of appetite, abdominal discomfort, ataxia, dizziness, headache, somnolence	Agranulocytosis,[a] aplastic anemia,[a] SJS,[a] TEN,[a] DRESS,[a] depression
Everolimus	Stomatitis, infections, rash, fatigue, diarrhea, decreased appetite	Noninfectious pneumonitis, infections, severe hypersensitivity reactions[a], angioedema[a], impaired wound healing, metabolic disorders, myelosuppression
Felbamate	Loss of appetite, nausea/vomiting, insomnia, fatigue, headache	Aplastic anemia,[a] hepatic failure[a]
Gabapentin	Somnolence, sedation, dizziness, ataxia, tremor, peripheral edema, increased weight	DRESS,[a] anaphylaxis,[a] angioedema[a]
Lacosamide	Dizziness, ataxia, nausea, headache, double vision	PR interval prolongation, atrial fibrillation and flutter, DRESS[a]
Lamotrigine	Dizziness, ataxia, somnolence, headache, double vision, blurred vision, nausea/vomiting	SJS,[a] TEN,[a] DRESS,[a] hemophagocytic lymphohistiocytosis[a], aseptic meningitis
Levetiracetam	Somnolence, asthenia, coordination difficulties, dizziness, headache, irritability, fatigue	Behavior abnormalities, psychotic symptoms, SJS,[a] TEN,[a] hematologic abnormalities
Oxcarbazepine	Dizziness, double vision, ataxia, nausea/vomiting, somnolence, fatigue	Hyponatremia, anaphylaxis,[a] angioedema,[a] DRESS,[a] SJS,[a] hematologic abnormalities
Perampanel	Dizziness, somnolence, headache, irritability, mood changes, ataxia	DRESS,[a] aggressive behavior, homicidal thoughts
Phenobarbital	Somnolence, sedation, impaired cognition, depressed affect	Hypersensitivity reactions[a]
Phenytoin	Nystagmus, ataxia, slurred speech, decreased coordination, somnolence, confusion, dizziness, gingival hyperplasia	SJS,[a] TEN,[a] anaphylaxis,[a] DRESS,[a] hematologic abnormalities, hepatic failure[a]
Pregabalin	Peripheral edema, dizziness, somnolence, headache, incoordination, tremor, fatigue, double vision	Angioedema,[a] hypersensitivity reaction[a]
Primidone	Ataxia, dizziness, nausea/vomiting, loss of appetite, somnolence, double vision, nystagmus	Hematologic abnormalities, hypersensitivity reactions[a]

(continued)

Table 2. AED Adverse Effects *(continued)*

Drug	Common	Serious
Rufinamide	Somnolence, nausea/vomiting, headache, fatigue, dizziness	Multiorgan hypersensitivity,[a] DRESS,[a] leukopenia
Tiagabine	Dizziness, somnolence, depression, confusion, asthenia, ataxia	SJS,[a] nonconvulsive status epilepticus
Topiramate	Paresthesia, anorexia, weight loss, fatigue, dizziness, somnolence, word finding difficulty, memory impairment	Metabolic acidosis, vision changes and glaucoma, kidney stones, oligohidrosis and hyperthermia, hyperammonemia
Valproate	Abdominal pain, nausea, vomiting, somnolence, insomnia, tremor, asthenia, alopecia, weight changes, blurred vision	Hyperammonemia, thrombocytopenia, hepatic failure,[a] pancreatitis
Vigabatrin	Weight gain, confusion, somnolence, tremor, memory impairment, double vision, aggressive behavior, fatigue, peripheral edema	Permanent bilateral concentric visual field constriction, central retina damage resulting in decreased visual acuity, hepatic failure[a]
Zonisamide	Weight loss, loss of appetite, ataxia, dizziness, somnolence, agitation, difficulty concentrating and memory, irritability	SJS,[a] TEN,[a] agranulocytosis,[a] DRESS,[a] metabolic acidosis, kidney stones, oligohidrosis and hyperthermia

[a]Use-limiting reactions that require rapid discontinuation of medication because of concerns for morbidity or mortality.

AED = antiepileptic drug; DRESS = drug reaction with eosinophilia and system symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

and system symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). Patients can present with fever, rash, and internal organ involvement, usually the liver, as indicated by elevated liver function tests or hepatomegaly. If these hypersensitivity reactions are suspected, the AED should be withdrawn quickly and supportive treatment provided. Mortality can exceed 10% for DRESS, so rapid diagnosis and treatment are necessary (Cacoub 2011). See the Pharmacogenomics section for a further discussion of the identified genes that increase the risk of hypersensitivity reactions.

Several AEDs can cause undesirable adverse effects, such as weight gain. Topiramate or zonisamide may be considered for a patient who could benefit from weight loss. Declines in bone mineral density have been reported with several AEDs, with the most concern focused on enzyme-inducing agents (carbamazepine, phenytoin, and phenobarbital) (Fraser 2015). Patients should be assessed for risk factors for bone loss, encouraged to participate in weight-bearing exercise, and take calcium and vitamin D, if appropriate.

Table 3 describes mechanisms for AED interactions and additional pertinent therapeutic monitoring that should be considered to optimize patient management.

Formulation Considerations

Most AEDs are introduced to the market with an oral tablet or capsule and liquid formulation that addresses patient needs, particularly for children. Several extended-release formulations have been designed to address a variety of patient-specific needs.

Topiramate is available as two different extended-release formulations: Trokendi XR (Supernus Pharmaceuticals, Rockville, MD) and Qudexy XR (Upsher-Smith Laboratories, Maple Grove, MN). Both are bead-containing capsules approved for seizures and migraine prophylaxis. Trokendi XR is a once-daily dose; unique to this formulation, alcohol use is contraindicated 6 hours before and after a dose. Alcohol alters the release mechanism for Trokendi XR and results in higher concentrations in the beginning of the dosing interval and potentially subtherapeutic concentrations later in the dosing interval. For administration, the capsule should remain intact and not be sprinkled, crushed, or chewed. Qudexy XR is also designed for once-daily dosing. The capsules can be sprinkled on soft food for immediate consumption, but the beads should not be chewed.

Gabapentin is available as two different extended-release formulations: Gralise (Depomed, Newark, CA) and Horizant (Arbor Pharmaceuticals, Atlanta, GA); however, neither is approved for epilepsy, and data on converting between formulations are not available. Gabapentin extended release (Gralise) for postherpetic neuralgia is once-daily dosing taken with the evening meal to optimize absorption. Gabapentin's release mechanism is designed with polymers that swell, resulting in gastric retention and controlling the release of the drug from the formulation (Chen 2011). Taking the dose with food is required to achieve the optimal performance

Table 3. AED Metabolism and Therapeutic Monitoring

Drug	Role in Drug Interactions	Metabolites and Therapeutic Monitoring
Brivaracetam	Weakly inhibits CYP2C19; may increase phenytoin concentrations; enzyme inducers increase clearance	
Cannabidiol	Inhibitor of CYP2C9, 2C19, UGT1A9, UGT2B7; inhibitor or inducer of CYP1A2 and CYP2B6.	
Carbamazepine	Causes significant enzyme induction	Active epoxide metabolite contributes to efficacy and adverse effects; auto induces metabolism; therapeutic range 4–12 mg/L
Clobazam	Inhibitors of CYP2C19; metabolizers increase active metabolite	
Eslicarbazepine	Inhibits CYP2C19; moderate inducer of CYP3A4; inducers increase clearance	Rapidly metabolized to the *S*-enantiomer of oxcarbazepine metabolite
Ethosuximide	Inducers increase clearance	
Everolimus	Weak CYP3A4 inhibitor enzyme inducers increase clearance	
Felbamate	Inducers increase clearance; increases phenytoin, carbamazepine epoxide, valproate concentrations	
Gabapentin	No interactions with other AEDs	
Lacosamide	Inducers may increase clearance	
Lamotrigine	Metabolism significantly inhibited by valproate; induced by carbamazepine, phenytoin, phenobarbital, and estrogen	
Levetiracetam	No interactions with other AEDs	
Oxcarbazepine	May inhibit CYP2C19 at higher doses	Rapidly metabolized to active MHD, which exerts antiseizure activity. Pharmacokinetic parameters for MHD; inducers increase clearance
Perampanel	Inducers increase clearance	
Phenobarbital	Causes significant enzyme induction	Therapeutic range 10–40 mg/L
Phenytoin	Causes significant CYP 2B6, 3A4 enzyme induction; nonlinear kinetics resulting in greater-than-expected increases in blood concentrations as dose increases	Therapeutic range 10–20 mg/L (total drug concentration); 1-2 mg/L (free concentration)
Pregabalin	No interactions with other AEDs	
Primidone	Significant enzyme inducer	Active metabolites phenobarbital and phenylethylmalonamide; primidone therapeutic range 5–12 mg/L
Rufinamide	Inducers increase clearance; valproate decreases clearance	
Tiagabine	Inducers increase clearance	
Topiramate	Inducers may increase clearance; inhibits CYP2C19 at higher doses	
Valproate	Inducers increase clearance; increases concentrations of lamotrigine, rufinamide, carbamazepine epoxide, ethosuximide	Therapeutic range 50–150 mg/L (total drug concentration); 5-15 mg/L (free concentration)
Vigabatrin	May decrease phenytoin concentrations	
Zonisamide	Inducers increase clearance	

AED = antiepileptic drug; MHD = metabolite monohydroxy derivative.

of the release mechanism. Gabapentin enacarbil (Horizant) has a labeled indication for restless legs syndrome and postherpetic neuralgia. Gabapentin enacarbil is a prodrug that undergoes first-pass hydrolysis, resulting in gabapentin as the active metabolite, which is then eliminated through the kidney.

Extended-release formulations of lamotrigine, levetiracetam, oxcarbazepine and pregabalin are also available. Extended-release lamotrigine theoretically provides the most benefit for patients who are also taking enzyme-inducing AEDs, allowing lamotrigine to be administered once a day rather than twice a day. The area under the curve (AUC) of extended-release lamotrigine can be reduced by 21% when taken with enzyme-inducing AEDs, averaging more variability than when taken without interacting or enzyme-inhibiting drugs (Tompson 2008). This variability may warrant monitoring of extended-release lamotrigine concentrations if seizure frequency changes, if formulations are changed, or if the patient has adverse effects. The therapeutic advantage of extended-release levetiracetam and oxcarbazepine is to reduce dosing frequency. Extended-release levetiracetam had bioequivalence to immediate-release tablets comparing 500 mg twice daily of immediate release with 1000 mg once daily of extended release (Rouits 2009). Extended-release oxcarbazepine, Oxtellar XR (Supernus) is not bioequivalent to immediate-release oxcarbazepine tablets. Compared with immediate release, oxcarbazepine XR has a 19% decrease in AUC and Cmax, whereas the trough concentration is 16% lower. Monitoring the active metabolite concentration may be necessary if the patient has changes in seizure frequency or adverse effects.

Pharmacogenomics

Treatment of seizures is evolving on the basis of pharmacogenomics. Enzymes that contribute to variability in drug disposition include CYP2C9 and CYP2C19. Data on other metabolic pathways, including CYP3A4 and glucuronidation, have not yet provided clinically relevant evidence of polymorphisms that affect drug disposition or treatment response (Balestrini 2018). Table 4 includes the drugs and genes with established evidence. Although severe cutaneous reactions including SJS and TEN are rare, they can be devastating when they occur. In one study, risk of SJS/TEN was increased for patients who had *HLA-B*15:02* (OR 5.77 (CI 3.49-9.55) or *HLA-A*24:02* (OR 3.15 (CI 1.86-5.32) (Shi 2017). Patients who do not carry these genes may still develop a severe rash, indicating that other mechanisms are contributing to risks not yet understood (Illing 2017).

Increasingly, there is progress on identifying genes that cause certain epilepsy syndromes. Unfortunately, gene-targeted therapy is not yet a clinical reality for treating epilepsy. Sodium channel polymorphisms have been identified, but developing a drug that targets this gene is lacking. Progress has been made in determining that some drugs may be less efficacious with specific polymorphisms. For example, patients with the sodium voltage-gated channel α subunit 1 gene are less likely to have improved seizure control when taking sodium channel blockers (Walker 2015).

Table 4. AED Clinically Significant Pharmacogenomic Considerations

Drug	Gene	Potential Clinical Consequences	At-Risk Populations
Carbamazepine	*HLA-B*15:02*	Associated with risk of developing SJS and TEN	Higher frequency of this allele in Asian populations
	*HLA-A*31:01*	Associated with risk of developing SJS and TEN	Found in Northern European and Japanese populations
Clobazam	*CYP2C19* poor metabolizers	Increased active metabolite	
Lacosamide	*CYP2C19* poor metabolizers	Decreased metabolite concentrations; however, not deemed clinically significant	
Oxcarbazepine	*HLA-B*15:02*	Associated with risk of developing SJS and TEN	Higher frequency of this allele in Asian populations
Phenytoin	*HLA-B*15:02*	Associated with risk of developing SJS and TEN	Higher frequency of this allele in Asian populations
	CYP2C9 poor metabolizers	Increased risk of adverse effects, lower doses recommended	

AED = antiepileptic drug; DRESS = drug reaction with eosinophilia and system symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Information from: PharmGKB [homepage on the Internet].

The role of pharmacogenomic screening remains controversial for AEDs. A Hong Kong study evaluated the cost-effectiveness of *HLA-B*15:02* screening. Three scenarios were evaluated: current practice with genetic testing before prescribing carbamazepine, an ideal situation with same-day, one-time, genetic testing before receiving any AED, and extended screening in addition to ideal testing to include avoidance of phenytoin, if appropriate. The study identified that this screening was not cost-effective under any of the studied scenarios (Chen 2016). Under current practice, and with the many AEDs now available, providers often avoid selecting carbamazepine. However, in some clinical situations, carbamazepine or oxcarbazepine may be preferred, and it may be appropriate to obtain genetic testing before therapy initiation.

Drugs for Refractory Epilepsy

Despite the availability of many AEDs, some patients do not obtain acceptable seizure control, or they have unacceptable adverse effects. If a drug is deemed a failure because of adverse effects, trying a second drug is appropriate. In general, the second drug is added while the patient is still taking the first drug, and once the new drug reaches a therapeutic dose, the first drug can be tapered. If the patient has urgent adverse effects, a drug may be abruptly discontinued as a new drug is added. If a drug is deemed a failure because of a lack of efficacy, it is reasonable to consider changing to a different treatment or adding a second drug. Table 5 provides the generally accepted drugs for refractory epilepsy according to seizure type and is based on the UK NICE guidelines and the 2018 AAN and the AES treatment guidelines for treatment-resistant epilepsy.

Polytherapy

For patients whose disease does not respond to monotherapy because of a lack of efficacy, clinical trial data are limited to guide the decision regarding which combinations of AEDs might work better together. Pharmacokinetic interactions and adverse effects should be primary considerations when selecting an additional AED (Abou-Khalil 2017). If drugs have a similar mechanism of action, the likelihood of adverse effects increases. A post hoc analysis of lacosamide clinical trial data showed that subjects taking additional AEDs with primarily sodium channel–blocking effects did not tolerate the maximal dose of lacosamide as well as subjects taking AEDs with other mechanisms of action (Sake 2010).

Analysis of a large private insurance claims database evaluated whether persistence on therapy and health care use differed among adult patients taking two concomitant AEDs with a combination of mechanisms of action (Margolis 2014). Persistence on therapy was viewed as a marker for tolerability and efficacy. Drug combinations were grouped into four categories: sodium channel blockers, g-aminobutyric acid (GABA) analogs, synaptic vesicle protein 2A binding, and multiple mechanisms. Patients taking combinations of AEDs affecting GABA or combinations of AEDs affecting sodium channel blocking had more hospital admissions and ED visits. Persistence on AED therapy was higher in patients taking drugs with different mechanisms of action. Although this study provides no insight on specific drug combinations, it supports the broader concept of selecting a second drug with a different mechanism of action. Table 6 includes a summary of AED mechanisms of action.

New Agents

Brivaracetam

Brivaracetam is an analog of levetiracetam with broad-spectrum activity against focal seizures approved both for adjunctive therapy and monotherapy to treat individuals 16 years and older with focal seizures (UCB, Inc., Smyrna, GA). Brivaracetam selectively binds to synaptic vesicle

Table 5. Drugs for Refractory Seizures

Seizure Type	Adjunctive Options	Third Line
Focal	Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, zonisamide	Eslicarbazepine, lacosamide, perampanel, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin
Generalized tonic-clonic	Clobazam, lamotrigine, levetiracetam, topiramate, valproate	
Absence	Lamotrigine	Clobazam, clonazepam, levetiracetam, topiramate, zonisamide
Myoclonic (including juvenile myoclonic epilepsy)	Lamotrigine, levetiracetam, valproate, topiramate	Clobazam, clonazepam, zonisamide

Information from: National Institute for Health and Care Excellence (NICE). Epilepsies: Diagnosis and Management; Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. Neurology 2018;91:82-90.

Table 6. AED Mechanisms of Action

	Mechanism	Drugs
Decrease excitation	Sodium channel blockade	Carbamazepine, eslicarbazepine, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rufinamide
	Multiple mechanisms, including sodium channel blockade	Felbamate, topiramate, valproate, zonisamide
	High-voltage activated calcium channel blockade	Felbamate, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate
	T-calcium channel modulation	Ethosuximide, valproate, zonisamide
	Calcium channel A2δ subunit binding	Gabapentin, pregabalin
	Glutamate receptor antagonist	Felbamate, perampanel, phenobarbital, primidone, topiramate
	Synaptic vesicle 2A binding	Brivaracetam, levetiracetam
	Carbonic anhydrase inhibition	Acetazolamide, topiramate, zonisamide
Enhance inhibition	Enhance GABA	Clobazam, felbamate, phenobarbital, primidone, tiagabine, topiramate, valproate, vigabatrin

AED = antiepileptic drug; GABA = g-aminobutyric acid.

glycoprotein 2A, a protein-coding gene that regulates voltage-gated neurotransmitter release.

Three randomized, double-blind, placebo-controlled, multicenter trials evaluated the efficacy and tolerability of brivaracetam in patients with uncontrolled partial-onset seizures. In these studies, an adequate trial of at least two or three anticonvulsants was assessed for up to 12 weeks of treatment (Klein 2015; Biton 2014; Ryvlin 2014). The primary end point assessed the percent reduction in baseline-adjusted partial-onset seizure frequency per week for adjunctive brivaracetam over placebo. The 50% or greater responder rate was 32.7% (50 mg/day, p=0.008), 38.9% (100 mg/day, p<0.001), and 37.8 (200 mg/day, p<0.001). Compared with placebo, brivaracetam often caused more dizziness, somnolence, irritability, and fatigue. Compared with levetiracetam, brivaracetam was better tolerated. In fact, two-thirds of patients who changed from levetiracetam to brivaracetam because of behavioral adverse effects such as irritability, anxiety, anger, and agitation had symptom resolution (Lattanzi 2016; Yates 2015).

Cannabidiol

In 2014, the AAN released a position statement about using cannabinoids, stating that "for patients with epilepsy, data are insufficient to support or refute the efficacy for reducing seizure frequency." A New Drug Application for a pure plant-derived cannabidiol product was submitted to the FDA in the fourth quarter of 2017 for the treatment of Dravet syndrome and LGS, and the FDA CNS Advisory Committee recommended approval in April 2018 with final approval by the FDA in June 2018. Even though the FDA has approved this nonsynthetic cannabidiol product for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older, the Drug Enforcement Administration has 90 days to reschedule this product from schedule I to another schedule for wide use.

Cannabidiol and tetrahydrocannabinol are active cannabinoids found in cannabis. Both cannabinoids have anticonvulsant properties. However, unlike tetrahydrocannabinol, cannabidiol lacks cannabinoid receptor-independent mechanisms associated with psychoactive properties and therefore has minimal psychoactive properties (not more than 0.15% (w/w) tetrahydrocannabinol) (Greenwich Biosciences, Inc., Carlsbad, CA). Cannabidiol is highly lipophilic (Koctanol-water around 6–7) with a large volume of distribution (around 32 L/kg) and rapid distribution into the brain and tissues (around 6%) (Devinsky 2014). Cannabidiol is extensively metabolized, predominantly by the liver by CYP3A4, CYP2C9, and CYP2C19.

Use of cannabidiol to manage treatment-resistant seizures, including Dravet syndrome and LGS, has been studied systematically in three double-blind, placebo-controlled trials. A double-blind, placebo-controlled trial of 120 patients with Dravet syndrome and drug-resistant seizures evaluated the safety and efficacy of cannabidiol oral solution (Devinsky 2017). All patients entered a 4-week baseline period in which the frequency of epilepsies was recorded by a trained caregiver. Patients were then randomized to receive either placebo or the cannabidiol solution in addition to standard anticonvulsant therapy, which was titrated over 14 days to 20 mg/kg/day given

in divided doses. Results showed a 2-fold reduction in seizure frequency per month (12.4 to 5.9, p=0.01), together with a 50% reduction in convulsive seizure frequency, compared with placebo (OR 2.0; 95% CI, 0.93–4.30; p=0.08). The most common adverse effects in the cannabidiol group compared with placebo included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal liver function tests. It has been shown to cause drug interactions. An evaluation of patients in an open-label cannabidiol compassionate use study showed statistically significant increases in concentrations of the active metabolite of clobazam, eslicarbazepine, topiramate, zonisamide, and rufinamide (Gaston 2017).

Clobazam

Clobazam was introduced as an anxiolytic agent in 1975 and was later determined to have strong anticonvulsant properties. Clobazam has a labeled indication as an adjunctive therapy for Lennox-Gastaut syndrome (LGS) in patients 2 years and older. This form of childhood epilepsy occurs at 2–6 years of age and accounts for 1%–4% of all childhood epilepsies (Lunbeck, Deerfield, IL). Clobazam is a benzodiazepine but differs from classic agents by the placement of the nitrogen atom at positions 1 and 5 rather than 1 and 4 in the second ring. Clobazam binds to the $GABA_A$ receptor between the α and the g_2 subunit rather than the α_2 and the g_2 subunit, as with other benzodiazepines. This binding activity leads to hyperpolarization of the neuron by increasing the frequency of chloride channel opening.

The efficacy and tolerability of clobazam has been evaluated as add-on therapy for LGS. One study found that 56.3% of subjects with atonic and myoclonic seizures had a 50% reduction in seizures (Ng 2007). Two multicenter, randomized, double-blind studies of 306 patients established clobazam efficacy in LGS as adjunct therapy in which low (0.25 mg/kg/day), medium (0.5 mg/kg/day), and high (1 mg/kg/day) doses of clobazam showed a dose-related decrease in the number of atonic seizures. Mean decreases per week in atonic seizures were 68.3% (p<0.0001) (high dose), 49.4% (p=0.0015) (medium dose), and 41.2% (p=0.0120) (low dose) (Ng 2011; Conry 2009). Clobazam is also associated with the development of tolerance in about one-third of patients within the first 3 months of therapy. The dose can be increased to improve seizure control.

Eslicarbazepine

Eslicarbazepine has a labeled indication for the treatment of focal seizures in individuals 4 years and older (Sunovion Pharmaceuticals Inc., Marlborough, MA). Eslicarbazepine is a third-generation, acetate prodrug, structurally related to carbamazepine and rapidly metabolized by hydrolytic first-pass to (S)-licarbazepine and (R)-licarbazepine.

The efficacy and tolerability of eslicarbazepine was evaluated in three multicenter, randomized, double-blind, placebo-controlled parallel-group studies. Patients with at least four simple or complex partial seizures who did not respond to one to three previously prescribed AEDs were enrolled (Gil-Nagel 2013; Ben-Menachem 2010; Elger 2009). For each study, the primary end point assessed was the median percent change in seizure frequency and 50% responder rate. Patients were enrolled in a pretreatment phase for 8 weeks to determine pretreatment seizure frequency. Once enrolled, 749 patients were randomized to receive placebo or an initial dose of eslicarbazepine, which was then titrated weekly over 2 weeks to 1200 mg/day, depending on the randomized dose and study. Patients were then maintained on the randomized dose for another 12 weeks. At daily dosages of 800 and 1200 mg, eslicarbazepine improved seizure control. Rash was less common in patients taking eslicarbazepine (1%) than in patients taking oxcarbazepine (11%) and carbamazepine (10%) (Shorvon 2000; Mattson 1992). Likewise, the incidence of hyponatremia (less than 134 mEq/L) is more common with carbamazepine (26%) and oxcarbazepine (46%) than with eslicarbazepine (2.5%) (Berghuis 2017; Toledano 2017).

Everolimus

Everolimus is an antineoplastic drug with a labeled indication for patients 2 years and older with tuberous sclerosis complex–associated focal seizures (Novartis Pharmaceuticals Corp, East Hanover, NJ). Tuberous sclerosis complex is an autosomal-dominant mutation on chromosome 9 of the *TSC1* or chromosome 16 of the *TSC2* gene whereby the mammalian target of rapamycin pathway is activated. Everolimus was evaluated in clinical trials to determine whether it could improve seizure control as adjunctive treatment in patients with tuberous sclerosis complex. Patients were randomized to one of three arms: placebo, everolimus titrated to a target trough concentration of 3–7 ng/mL, or everolimus titrated to a target trough concentration of 9–15 mg/mL. The primary outcome was defined as a change from baseline in seizures frequency between the two treatment arms versus placebo. Both the low-dose (29.3%, p=0.0028 vs. placebo) and the high-dose (39.6%, p<0.0001 vs. placebo) groups had significantly better seizure reductions than placebo (14.9%). Common adverse effects included mouth ulceration, stomatitis, and fever (French 2016). This is one of the first drug studies that targets the underlying disease causing seizures rather than just the symptoms.

Perampanel

Perampanel has a labeled indication for the adjunctive treatment of generalized tonic-clonic seizures as well as adjunctive and monotherapy for partial seizures in adults and adolescents 12 years and older (Eisai Inc., Woodcliff Lake, NJ). The efficacy of perampanel was studied in three randomized, double-blind, placebo-controlled, multicenter trials of adults and adolescents who did not respond to at least two AEDs and were currently being treated with one to three AEDs, with complex partial seizures with or without secondarily generalized seizures (French 2013, 2012; Krauss 2012). For each study, the primary end point was the median percent change

in seizure frequency and 50% responder rate. All patients entered a 6-week baseline phase during which eligibility was assessed and were enrolled in the study if five or more partial seizures occurred. Once enrolled, 1331 patients were randomized to receive placebo or an initial dose of 2 mg/day of perampanel, which was then titrated weekly by 2 mg/day over 6 weeks to 12 mg/day, depending on the randomized dose and study. Patients were then maintained on the randomized dose for another 13 weeks. At daily dosages of 4, 8, and 12 mg, perampanel improved seizure control. A boxed warning about serious or life-threatening psychiatric and behavioral adverse effects associated with perampanel includes aggression, hostility, irritability, anger, and homicidal ideation and threats. These effects typically occur within the first 6 weeks of therapy. Psychiatric behavior incidence is 6%, 12%, and 20% for placebo, 8 mg/day, and 12 mg/day, respectively.

Monitoring and Evaluation

Efficacy

Efficacy is monitored by interviewing the patient or caregiver to determine seizure control. Occasionally, the patient is unaware of having a seizure, especially if the patient has focal seizures that lack significant motor involvement and the patient lives alone. In these and similar situations, additional strategies must be used. Historically, blood concentrations were used as a metric for assessing adherence and as a surrogate for efficacy (Paschal 2008). The newer AEDs lack a clear correlation between blood concentrations and efficacy, and manufacturers do not recommend regular concentration monitoring. Despite this, many neurologists still order AED blood concentrations, which may be used for monitoring and adjusting drug doses because of interacting codrugs, changes in physiology during pregnancy, changes in liver or kidney functioning or when changing formulations or manufacturers (Landmark 2016). Most AEDs have an established reference range that analytical laboratories have determined from the literature and clinical trials.

Some AEDs have a therapeutic concentration range according to evidence confirming a relationship between concentration and effect. These established ranges are noted in Table 3 and are not absolute guides to treatment. Optimal use of concentrations includes obtaining a concentration once a patient has achieved improved seizure control to determine the patient's individual therapeutic range. Subsequent concentrations are then interpreted with respect to the patient's individual drug-taking behavior, codrugs, and comorbidities (Patsalos 2008).

Safety

Monitoring of adverse effects is critical to assessing the safety of AED treatment. Assessing the patient for adverse effects through the patient interview is recommended. Inquiring about fatigue, increased sleep or daytime napping, difficulty with concentration or memory, and difficulty with balance or coordination will provide assessment data for determining how well a drug is being tolerated. If family members or caregivers are available, they may provide valuable insight into changes in behavior of which the patient may unaware. Using a targeted review of systems may also reveal symptoms the patient does not recognize as AED adverse effects.

Before beginning a new AED, baseline laboratory results should be obtained, including electrolytes, kidney function, CBC, and liver function tests (Harden 2000). In addition, laboratory data should be obtained to assess for safety at least once a patient's condition is stable on a drug. More frequent monitoring of blood counts is required when felbamate is prescribed and at the beginning of valproate treatment to monitor platelet counts.

Decision to Discontinue Treatment

Current literature supports considering AED withdrawal if patients are seizure free for 2 or more years, if seizure control was obtained on one drug, when neurologic examination and EEG are normal, and if patient has no history of seizure relapse after drug withdrawal. If seizures return after AED withdrawal, time may be needed to regain good seizure control (Schmidt 2017).

The Akershus study was designed as a prospective, randomized, double-blind, placebo-controlled study with subjects who were seizure free for at least 2 years who were assigned to either withdrawing their AED or remaining on their AED and followed for 12 months (Lossius 2008). The goal of the study was to determine the benefit-risk of AED withdrawal. More patients had seizure relapse in the withdrawal arm, but the relative risk (2.46; 95% CI, 0.85–7.08) was not statistically different. Patients in the withdrawal group had improved neuropsychological functioning but no differences in quality of life or EEG findings. Previous use of carbamazepine and a normal neurologic examination were predictors of seizure freedom.

A recent meta-analysis examined the risk of seizure recurrence in adults and children if AEDs are discontinued early (less than 2 years) and later (more than 2 years) after seizure remission (Strozzi 2015). Discontinuing drugs early in children is associated with an increased risk of recurrence when the seizures are focal or the EEG is abnormal (RR 1.34; 95% CI, 1.13–1.59). Data were insufficient to make a recommendation for children with generalized seizures or for adults.

The lack of clear evidence requires the decision to be shared by both providers and patients. Weighing the potential benefits of freedom from AED treatment and adverse effects compared with the risk of seizure recurrence is an important discussion. The schedule to decrease AED doses is based on pharmacokinetic parameters with close monitoring for seizure recurrence. If a patient is taking several AEDs, withdrawing one drug at a time provides a buffer to reestablish the drug regimen if seizures occur.

UPDATES IN SPECIAL POPULATIONS

Women's Health

Teratogenicity

The AAN and the AES issued their special report on AEDs and teratogenicity in 2009, and this document is under revision. The highest risk of major congenital malformations is with exposure to valproate, which has an odds ratio of 6.7–9.3, depending on the registry (Meador 2016). Exposure to carbamazepine, lamotrigine, levetiracetam, or phenytoin resulted in a risk of major congenital malformations with odds ratios of 2–3 with a 95% CI of 1.2–5. There is a greater risk with exposure to phenobarbital and topiramate (OR 4.2–5.5; 95% CI, 2.4–9.7). Beyond teratogenicity risk, in utero exposure to valproate results in reduced neurocognitive abilities. Children at age 6 exposed to valproate have statistically significantly lower IQs than children exposed to carbamazepine, lamotrigine, or phenytoin. The analysis accounted for maternal IQ, preconception folic acid, and gestational age at delivery (Meador 2013). Data on the newest AEDs are lacking.

Pharmacists actively involved in prepregnancy planning and education should advise women it is ideal to be seizure free for at least 9 months before pregnancy (Abe 2014). Folic acid should be taken while trying to become pregnant or while at risk of pregnancy, ideally for at least 1–3 months before conception. The optimal folic acid dose has not been well defined, so at least 1 mg/day is recommended. For AEDs that are subject to pharmacokinetic changes during pregnancy, individual therapeutic ranges should be determined from prepregnancy therapeutic drug monitoring. This information will help the team adjust doses during pregnancy to maintain concentrations to reduce the risk of seizures breaking through.

Pharmacokinetic Changes During Pregnancy

Pharmacokinetic changes can be expected because of physiologic changes during pregnancy. Absorption may be altered because of the nausea and vomiting that can occur during pregnancy. Distribution may be altered because of increases in blood volume and resulting decreases in protein binding. Metabolism may be altered because of changes in enzyme function as a result of hormone changes. Elimination is increased because of increased blood flow and glomerular filtration rates (Tomson 2013). Because most drugs have not been systematically studied, an individualized prepregnancy therapeutic range should be established, if possible, and closely followed and monitored during pregnancy for an increase in seizures and a decline in drug blood concentrations. Concentrations should be checked before pregnancy (baseline), once during the first and second trimesters, monthly during the final trimester, and postpartum. If AED doses are changed, concentrations should be checked once at steady state. Drug doses should be increased appropriately to decrease the risk of having a seizure, to protect the mother and fetus (Reisinger 2013).

Lamotrigine has a lower relative risk of congenital malformations and good efficacy for many seizure types. During most pregnancies, lamotrigine monotherapy clearance will increase as the pregnancy progresses and then return to baseline at about 3 weeks postpartum (Polepally 2014).

Children

Recent clinical trial data brought clarity to the treatment of childhood absence epilepsy. A large, randomized, double-blind trial addressed the relative difference in efficacy and tolerability between ethosuximide, valproate, and lamotrigine (Glauser 2010). The study included 451 children, and the primary outcome was freedom from treatment failure, with failure defined as continued seizures or excessive drug toxicity, evaluated at weeks 16 and 20. There was no difference between ethosuximide and valproate (53% and 58% respectively, p=0.35), whereas patients taking lamotrigine were less likely to meet the study outcome, probably because of a lack of seizure control (29%, p<0.0001). Adverse effects were not significantly different between the drugs. The children who did not have treatment failure at 4 months were followed up to 12 months to evaluate longer-term efficacy and safety. The results were similar to those obtained in the previous study. Ethosuximide and valproate were not significantly different in rates of freedom (45% and 44%, respectively; p=0.82) from treatment failure, whereas patients taking lamotrigine were less likely to achieve freedom from treatment failure (21%, p<0.001) (Glauser 2013). The third analysis of this study population invited the subjects who had treatment failure in the first study to continue into an open-label arm in which subjects were randomized to one of the two drugs that had not previously failed for them (Cnaan 2017). The results were again similar to those obtained in the previous two studies. Ethosuximide and valproate were not significantly different in rates of freedom from treatment failure (57% and 49%, respectively; p=0.062), whereas lamotrigine had higher rates of lack of seizure control (p<0.0001). Subjects taking valproate had more attention difficulties across all three studies, as measured by the Conners' Continuous Performance Test. Commonly, attention-deficit/hyperactivity disorder can coexist with epilepsy, especially with absence seizures in children. Once the seizures are controlled, stimulants (e.g., methylphenidate, dextroamphetamine) can be initiated cautiously because of the potential for lowering the seizure threshold.

Older Adults

The prevalence of epilepsy in patients older than 65 is estimated as 15.2 in 1000 individuals, and incidence is 6.1 in 1000 individuals (Ip 2018). Both incidence and prevalence increase with age. Identifiable causes of seizures in older adults are more likely the result of cerebrovascular disease or tumor than in younger adults (Stefan 2014). Choosing an appropriate AED for an older adult patient can be challenging because of polypharmacy, risks of drug interactions, and

Patient Care Scenario

K.T., a 16-year-old male adolescent (height 72 in, weight 75 kg [165 lb]), receives a diagnosis of generalized seizures. His history reveals that he has myoclonic jerks a few mornings every week. He also reports some depression and anxiety symptoms. K.T. is an avid soccer player and is in college preparation courses. How best should this patient's epilepsy be managed?

ANSWER

This patient likely has juvenile myoclonic epilepsy. He is of the typical age that this type of epilepsy presents. He will likely achieve seizure freedom with the right medication. In addition, he will need to ensure healthy habits, including getting regular sleep, avoid alcohol (and when older-consume in moderation), and good medication adherence. Preferred choices for this type of epilepsy include levetiracetam, topiramate, and valproate. The first choice for this patient is valproate. Topiramate is not first choice because of its adverse effect profile, including weight loss, oligohidrosis, and attention or concentration disturbance. For a young athlete and student, these are not desirable and could be harmful. Because it is difficult to predict which patients will have mood adverse effects with levetiracetam, it is not first choice for this patient because of his current symptoms of depression and anxiety. Valproate has good efficacy for this type of epilepsy and may help with his mood. Monitoring for sedation, tremor, and weight gain is required. A baseline CBC and liver function test should be collected before initiating treatment.

1. National Institute for Health and Care Excellence (NICE). Epilepsies: Diagnosis and Management.
2. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Neurology 2018;81:74-81.

adverse effects that are particularly undesirable in older adult patients. Only carbamazepine, gabapentin, lamotrigine, and levetiracetam have been included across the clinical trials of older adult patients. The first two studies compared lamotrigine with immediate-release carbamazepine. The two drugs had similar efficacy, but lamotrigine was better tolerated, and patients were more likely to continue taking lamotrigine (Nieto-Barrera 2001; Brodie 1999).

A large randomized, double-blind Veterans Affairs trial compared gabapentin, lamotrigine, and immediate-release carbamazepine. Subjects (mean age 72 years) randomized to lamotrigine were less likely to terminate early because of adverse effects than were those randomized to gabapentin ($p=0.015$) or carbamazepine ($p<0.0001$), whereas rates of seizure freedom were comparable for all three drugs (Rowan 2005). These early studies included immediate-release carbamazepine, which left open the clinical question of whether extended-release carbamazepine would have been better tolerated. A separate study comparing lamotrigine with extended-release carbamazepine showed no difference in time to drug withdrawal ($p=0.336$) (Saetre 2007).

The two most recent studies also included levetiracetam, which has a much lower risk of drug interactions. A randomized, double-blind clinical trial compared extended-release carbamazepine, lamotrigine, and levetiracetam in the treatment of focal epilepsy in older adults (Werhahn 2015).

Patient Care Scenario

L.V. is a 45-year-old woman (height 64 in, weight 104 kg [230 lb]) who has a history of refractory focal seizures. She currently takes levetiracetam and lamotrigine. L.V.'s spouse reports she is irritable since levetiracetam has been added. The patient also takes metformin, simvastatin, hydrochlorothiazide, and escitalopram. How best should this patient's condition be managed?

ANSWER

The adjunctive treatment options for focal seizures according to the current guidelines include carbamazepine, gabapentin, oxcarbazepine, topiramate and zonisamide. Gabapentin is associated with weight gain and, because of its short half-life, needs to be dosed three or four times daily. The risk of hyponatremia caused by carbamazepine and oxcarbazepine is increased because of concomitant hydrochlorothiazide. Topiramate has several mechanisms of action and may cause weight loss, making it a preferred choice for this patient. Zonisamide could also be considered if the patient does not have a sulfa allergy. However, discussion with the patient about the pros and cons of each drug should occur, and the patient's preference should drive the choice, if possible.

1. National Institute for Health and Care Excellence (NICE). Epilepsies: Diagnosis and Management.
2. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. Neurology 2018;91:82-90.

The treatment retention rates at 58 weeks for carbamazepine, levetiracetam, and lamotrigine were 45.8%, 61.5%, and 55.5%, respectively. Retention was significantly better for levetiracetam than for carbamazepine (p=0.02). Retention was not significantly different between levetiracetam and lamotrigine (p=0.36) or between lamotrigine and carbamazepine (p=0.15). The three drugs were similar in the rates of seizure freedom. The most recent data are a subset analysis from a large, randomized, unblinded study that compared levetiracetam with extended-release valproate and extended-release carbamazepine. Seizure freedom was not significantly different, but time to treatment withdrawal was significantly longer for subjects taking levetiracetam (Pohlmann-Eden 2016).

EMERGING TREATMENTS

Fenfluramine

Structurally related to amphetamine, fenfluramine has a central serotonergic activity whereby serotonin is released from storage vesicles and reuptake is prevented. In 2012, fenfluramine was evaluated in an observational study of 12 patients with Dravet syndrome and was granted Breakthrough Therapy designation in February 2018 (Ceulemans 2012). Seven patients became seizure free for at least 1 year with a mean fenfluramine dose of 0.34 mg/kg/day (range 0.12–0.9 mg/kg/day) when added to current AED therapy. Reported adverse effects included fatigue, reduced appetite, excessive sleep, and nonclinical thickening of one or two cardiac valves (n=2).

A prospective, open-label study evaluated the safety and efficacy of fenfluramine in nine patients with Dravet syndrome (Schoonjans 2017). Patients were excluded from the study if they had a cardiovascular history, including pathology or treatment for high blood pressure, glaucoma, stimulant use, or hypersensitivity to fenfluramine. After a 3-month pretreatment period, fenfluramine was added to the current AED therapy at a dose of 0.25–1.0 mg/kg/day, which was titrated to a maximum dose of 20 mg/day on the basis of efficacy and safety. The patients had a 75% mean reduction in seizure frequency (28%–100%). Somnolence and anorexia were the most common adverse effects, with no reports of cardiac structure or function change.

PHARMACIST CONSIDERATIONS

Patient Education

SUDEP Risk

Greater emphasis has been placed on educating patients and caregivers about the risks of SUDEP, resulting in a new 2017 guideline addressing the incidence rates and risk factors (Harden 2017). The definition of SUDEP is a sudden, unexpected, witnessed or unwitnessed, nontraumatic, non-drowning death in a patient with epilepsy with or without evidence of seizure, and excluding documented status epilepticus. Postmortem examination does not reveal a structural or toxicologic cause for death. Pharmacists can address patient concerns and provide guidance on the importance of drug adherence. Feedback from families who have lost loved ones to a seizure without having a conversation about the risk of SUDEP has led to a broad conversation between providers and patients to better understand what education is needed. Studies have tried to determine the incidence rate of SUDEP, and though there is study heterogeneity, it is estimated that for adults with epilepsy, 1 in 1000 will die of SUDEP. In children, it is estimated that 1 in 4500 will die of SUDEP (Harden 2017).

Risk factors for SUDEP include having generalized tonic-clonic seizures, having a higher frequency of seizures, not being seizure free for 1–5 years, and the lack of additional drug therapy in patients refractory to treatment. According to the available data, nonadherence to AEDs increases mortality risk. The RANSOM study analyzed a large data set of 33,658 patients; quarterly drug possession ratios were calculated according to the number of days with supplies of an AED divided by the number of days in the quarter. Nonadherence was defined as less than 0.80. Patients identified as nonadherent had an increased risk of mortality that was 3 times higher after controlling for other variables. In addition, nonadherence was associated with a higher incidence of ED visits and hospitalizations (Faught 2008).

Good seizure control through medication adherence is critical to reducing the risk of SUDEP. Patient education and collaboration is necessary to improve adherence through pillboxes, mobile device applications, or other creative approaches. Encourage patients to avoid their known seizure triggers, including exhaustion and alcohol or drug ingestion. Patients who continue to have poor seizure control should be referred to an epilepsy specialist. All attempts should be made to optimize seizure control.

AED-Associated Suicide and Suicidality

Health professionals should be familiar with the 2008 FDA warning that AEDs are associated with an increased risk of suicidal thoughts or actions. This association was based on a meta-analysis of clinical trial data. The health professional community debated about the data sources, how the analysis was conducted, and whether the warning should have been applied to the entire class of drugs. One of the primary limitations of the FDA analysis was its inclusion of data from spontaneous reports of suicidal thoughts/action that were inconsistently collected across clinical trials (Hesdorffer 2009). Of the AEDs included in the FDA analysis, only topiramate and lamotrigine had statistical significance toward increased risk of suicidal thoughts or actions (Mula 2013). Most of the trials were adjunctive therapy studies, making it difficult to determine whether one drug or a combination of drugs resulted in the adverse reaction. Suicidal behavior varied with geographic regions across the studies, suggesting challenges with data collection (Hesdorffer 2010).

Despite the criticism, the FDA's warning regarding AEDs and suicidality has resulted in improved awareness by providers, leading to more frequent discussions with patients about the risk and discussion of mood.

Generic Substitution and Equivalence

Over the past 40 years, the epilepsy community has greatly debated about the generic substitution of AEDs. The AES issued a position statement in 2007 that called for additional investigation of drug substitution beyond the FDA-required bioequivalence studies. Until such studies were available, the AES opposed substitution without prescriber and patient approval and any legislation or formularies that would limit patient access to branded AEDs (Liow 2007). This concern stemmed from reports of decreased efficacy when patients were changed from brand to generics. A systematic review later showed that these reports were retrospective and had design limitations. Prospective studies showed no significant differences between the products for pharmacokinetic parameters of bioequivalence (Yamada 2011).

However, the ongoing controversy between generics and brand led to the Equivalence among Generic Antiepileptic Drugs (EQUIGEN) trial, jointly sponsored by AES, the Epilepsy Foundation, and the FDA. The trial used two study designs to evaluate two generic lamotrigine products that were deemed the most disparate on the basis of bioequivalence data submitted to the FDA. The single-dose crossover bioequivalence study of 49 patients with epilepsy not regularly prescribed lamotrigine evaluated the two generics and brand lamotrigine. The mean ratios of the AUC for the comparisons (generic to generic, and each generic to brand) ranged from 99% (CI, 96.9–101.2) to 99.6% (CI, 97.3–101.9). The mean ratios of the Cmax for the comparisons ranged from 96% (CI, 92.6–99.6) to 106.4% (CI, 102.6–110.4), well within the FDA requirements for determining bioequivalence if the 90% CI interval is within 80%–125% (Berg 2017). The study design also included a comparison of the two generics, which required subjects to take both generics for 2 weeks over four 2-week phases. This allowed for characterization of the inter- and intrasubject variability of the pharmacokinetic parameters at steady state. Patients with epilepsy taking immediate-release lamotrigine 100, 200, 300, or 400 mg twice daily for at least 28 days were eligible to participate. This study included data from 33 subjects and determined no differences between the two lamotrigine manufacturers for either the Cmax or the AUC (Privitera 2016).

A recent analysis examined lamotrigine, carbamazepine, and oxcarbazepine reports of adverse reactions made to the FDA (Rahman 2017). The intent was to compare reports of brand, generic, and authorized generics to determine whether adverse effects differed. The final data set included 46,177 reports (27,150 for lamotrigine, 13,950 for carbamazepine, and 5077 for oxcarbazepine) collected in 2004–2015. Calculating odds ratios, the authors found no significant differences in reports except for an increased reporting of suicide with generics compared with brand and authorized generics. Limitations in the data source include bias in patient or provider reporting and potential duplicative reports, despite data cleaning. Although this study provides some reassurances that adverse effects are comparable, it did not include an assessment of reports in changes in efficacy and seizure control, which is also of great interest.

Despite the reassurance these data provided, additional data should be considered. Changes in drug appearance can cause unintended anxiety for the patient and caregivers. A study examining a large database of insurance claims for prescription drugs determined that the odds ratio of nonadherence, as defined by a failure to fill a prescription within 5 days of the elapsed days' supply, was increased (1.53; 95% CI, 1.07–2.18) when a new fill for an AED differed in color from the last fill (Kesselheim 2013). An increased odds ratio was not detected when the shape of the drug changed. Implications of this study are limited because of the nature of claims data, including not knowing if the drug is consumed. Data analysis of another large database determined whether seizures were linked with between-generic drug switches. No statistical difference occurred in seizure frequency in patients whose drug manufacturer was switched at refill compared with patients whose prescriptions were refilled with the same drug manufacturer (Kesselheim 2016).

Practice Points

- **Given the many AEDs available, optimal AED therapy recommending AEDs requires knowledge of pharmacokinetics and adverse effects for ideal patient outcomes.**
- **When a second AED is required for seizure control, data analyses suggest that selecting a drug with a different mechanism of action improves tolerability.**
- **Cannabidiol is now FDA approved and waiting for DEA scheduling. Controlled substance laws in several states will need to be changed for the drug to be available.**
- **Pharmacogenomics in epilepsy is still limited but is expected to expand and potentially change practice.**
- **The risk of SUDEP is higher with decreased medication adherence.**

CONCLUSION

Pharmacists play a significant role in optimizing drug selection for patients with epilepsy. Newer AEDs have differing mechanisms of action, pharmacokinetic profiles, and adverse effects that can affect patient care. Because of the challenges in clinical trial design, efficacy data can be particularly difficult to generate. Decisions about drugs require knowledge about pharmacokinetics and adverse effects to make the best recommendations for patients. Pharmacists are in position to advocate the safe and cost-effective use of drugs, including appropriate use of generics, to improve quality of life for people with epilepsy.

REFERENCES

Abe K, Hamada H, Yamada T, et al. Impact of planning of pregnancy in women with epilepsy on seizure control during pregnancy and on maternal and neonatal outcomes. Seizure 2014;23:112-6.

Abou-Khalil B. Selecting rational drug combinations in epilepsy. CNS Drugs 2017;31:835-44.

Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett 2018;667:27-39.

Ben-Menachem E, Gabbai AA, Hufnagel A, et al. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. Epilepsy Res 2010;89:278-85.

Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-85.

Berg M, Welty TE, Gidal BE, et al. Bioequivalence between generic and branded lamotrigine in people with epilepsy. JAMA Neurol 2017;74:919.

Berghuis B, van der Palen J, de Haan GJ, et al. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia 2017;58:1227-33.

Biton V, Berkovic SF, Abou-Khalil B, et al. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia 2014;55:57-66.

Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999;37:81-7.

Brodie MJ, Barry SJE, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548-54.

Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.

Ceulemans B, Boel M, Leyssens K, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia 2012;53:1131-9.

Chen C, Cowles VE, Hou E. Pharmacokinetics of gabapentin in a novel gastric-retentive extended-release formulation: comparison with an immediate-release formulation and effect of dose escalation and food. J Clin Pharmacol 2011;51:346-58.

Chen Z, Liew D, Kwan P. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94.

Cnaan A, Shinnar S, Arya R, et al. Second monotherapy in childhood absence epilepsy. Neurology 2017;88:182-90.

Conry JA, Ng YT, Paolicchi JM, et al. Clobazam in the treatment of Lennox-Gastaut syndrome. Epilepsia 2009;50:1158-66.

Cramer JA, Arrigo C, Van Hammée G, et al. Comparison between the QOLIE-31 and derived QOLIE-10 in a clinical trial of levetiracetam. Epilepsy Res 2000;41:29-38.

Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791-802.

Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011-20.

Eatock J, Baker GA. Managing patient adherence and quality of life in epilepsy. Neuropsychiatr Dis Treat 2007;3:117-31.

Elger C, Halász P, Maia J, et al. BIA-2093-301 Investigators Study Group. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. Epilepsia 2009;50:454-63.

Faught E, Duh MS, Weiner JR, et al. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM study. Neurology 2008;71:1572-8.

Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475-82.

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522-30.

Fraser LA, Burneo JG, Fraser JA. Enzyme inducing antiepileptic drugs and fractures in people with epilepsy: a systematic review. Epilepsy Res 2015;116:59-66.

French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 2012;79:589-96.

French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia 2013;54:117-25.

French JA, Lawson JA, Yapici Z et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): A phase 3, randomised, double-blind, placebo-controlled study. The Lancet 2016;388(10056):2153-63.

Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;58:1586-92.

Gil-Nagel A, Elger C, Ben-Menachem E, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: integrated analysis of pooled data from double-blind phase III clinical studies. Epilepsia 2013;54:98-107.

Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia 2013;54:141-55.

Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362:790-9.

Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors. Neurology 2017;88:1674-80.

Harden CL. Therapeutic safety monitoring: what to look for and when to look for it. Epilepsia 2000;41(suppl 8):S37-44.

Hesdorffer DC, Berg AT, Kanner AM. An update on antiepileptic drugs and suicide: are there definitive answers yet? Epilepsy Curr 2010;10:137-45.

Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? Epilepsia 2009;50:978-86.

Höfler J, Unterberger I, Dobesberger J, et al. Seizure outcome in 175 patients with juvenile myoclonic epilepsy – a long-term observational study. Epilepsy Res 2014;108:1817-24.

Illing PT, Purcell AW, McCluskey J. The role of HLA genes in pharmacogenomics: unravelling HLA associated adverse drug reactions. Immunogenetics 2017;69:617-30.

Institute of Medicine (US) Committee on the Public Health Dimensions of the Epilepsies; England MJ, Liverman CT, Schultz AM, et al., eds. Epilepsy Across the Spectrum: Promoting Health and Understanding. Washington, DC: National Academies Press, 2012. Available at https://www.ncbi.nlm.nih.gov/books/NBK91506/. Accessed June 14, 2018.

Ip Q, Malone DC, Chong J, et al. An update on the prevalence and incidence of epilepsy among older adults. Epilepsy Res 2018;139:107-12.

Kesselheim AS, Bykov K, Gagne JJ, et al. Switching generic antiepileptic drug manufacturer not linked to seizures. Neurology 2016;87:1796-801.

Kesselheim AS, Misono AS, Shrank WH, et al. Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. JAMA Intern Med 2013;173:202.

Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia 2015;56:1890-8.

Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012;78:1408-15.

Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults. Neurology 2015;84:1705-13.

Landmark CJ, Johannessen SI, Tomson T. Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring. Epileptic Disord 2016;18:367-83.

Lattanzi S, Cagnetti C, Foschi N, et al. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. Neurology 2016;86:1344-52.

Liow K, Barkley GL, Pollard JR, et al. American Academy of Neurology. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. Neurology 2007;68:1249-50.

Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus study). Epilepsia 2008;49:455-63.

Margolis JM, Chu BC, Wang ZJ, et al. Effectiveness of antiepileptic drug combination therapy for partial-onset seizures based on mechanisms of action. JAMA Neurol 2014;71:985.

Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic–clonic seizures in adults. N Engl J Med 1992;327:765-71.

Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12:244-52.

Meador KJ, Loring DW. Developmental effects of antiepileptic drugs and the need for improved regulations. Neurology 2016;86:297-306.

Morita DA, Glauser TA, Modi AC. Development and validation of the Pediatric Epilepsy Side Effects Questionnaire. Neurology 2012;79:1252-8.

Mula M, Kanner AM, Schmitz B, et al. Antiepileptic drugs and suicidality: an expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. Epilepsia 2013;54:199-203.

Ng Y, Collins SD. Clobazam. Neurotherapeutics 2007;4:138-44.

Ng YT, Conry JA, Drummond R, et al. OV-1012 Study Investigators. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology 2011;77:1473-81.

Nieto-Barrera M, Brozmanova M, Capovilla G, et al. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. Epilepsy Res 2001;46:145-55.

Paschal AM, Hawley SR, St Romain T, et al. Measures of adherence to epilepsy treatment: review of present practices and recommendations for future directions. Epilepsia 2008;49:1115-22.

Patsalos PN, Berry DJ, Bourgeois BFD, et al. Antiepileptic drugs best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239-76.

Perucca E. What clinical trial designs have been used to test antiepileptic drugs and do we need to change them? Epileptic Disord 2012;14:124-31.

Pohlmann-Eden B, Marson AG, Noack-Rink M, et al. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed

epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol 2016;16:149.

Polepally AR, Pennell PB, Brundage RC, et al. Model-based lamotrigine clearance changes during pregnancy: clinical implication. Ann Clin Transl Neurol 2014;1:99-106.

Privitera MD, Welty TE, Gidal BE, et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. Lancet Neurol 2016;15:365-72.

Rahman MM, Alatawi Y, Cheng N, et al. Comparison of brand versus generic antiepileptic drug adverse event reporting rates in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). Epilepsy Res 2017;135:71-8.

Reisinger TL, Newman M, Loring DW, et al. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. Epilepsy Behav 2013;29:13-8.

Ridsdale L, Philpott SJ, Krooupa AM, et al. People with epilepsy obtain added value from education in groups: results of a qualitative study. Eur J Neurol 2017a;24:609-16.

Ridsdale L, Wojewodka G, Robinson E, et al. Characteristics associated with quality of life among people with drug-resistant epilepsy. J Neurol 2017b;264:1174-84.

Rouits E, Burton I, Guénolé E, et al. Pharmacokinetics of levetiracetam XR 500mg tablets. Epilepsy Res 2009;84:224-31.

Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 2005;64:1868-73.

Ryvlin P, Werhahn KJ, Blaszczyk B, et al. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia 2014;55:47-56.

Saetre E, Perucca E, Isojärvi J, et al. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. Epilepsia 2007;48:1292-302.

St Louis EK. Minimizing AED adverse effects: improving quality of life in the interictal state in epilepsy care. Curr Neuropharmacol 2009;7:106-14.

Sake JK, Hebert D, Isojärvi J, et al. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs 2010;24:1055-68.

Schmidt D, Sillanpää M. Stopping epilepsy treatment in seizure remission: good or bad or both? Seizure 2017;44:157-61.

Schoonjans A, Paelinck BP, Marchau F, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. Eur J Neurol 2017;24:309-14.

Shi YW, Min FL, Zhou D, et al. *HLA-A*24:02* as a common risk factor for antiepileptic drug–induced cutaneous adverse reactions. Neurology 2017;88:2183-91.

Shorvon S. Oxcarbazepine: a review. Seizure 2000;9:75-9.

Smith G, Ferguson PL, Saunders LL, et al. Psychosocial factors associated with stigma in adults with epilepsy. Epilepsy Behav 2009;16:484-90.

Stefan H, May TW, Pfäfflin M, et al. Epilepsy in the elderly: comparing clinical characteristics with younger patients. Acta Neurol Scand 2014;129:283-93.

Strozzi I, Nolan SJ, Sperling MR, et al. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev 2015;2:CD001902.

Thiele EA, Marsh ED, Grench JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391:1085-96.

Toledano R, Jovel CE, Jiménez-Huete A, et al. Efficacy and safety of eslicarbazepine acetate monotherapy for partial-onset seizures: experience from a multicenter, observational study. Epilepsy Behav 2017;73:173-9.

Tompson DJ, Ali I, Oliver-Willwong R, et al. Steady-state pharmacokinetics of lamotrigine when converting from a twice-daily immediate-release to a once-daily extended-release formulation in subjects with epilepsy (the COMPASS study). Epilepsia 2008;49:410-7.

Tomson T, Landmark CJ, Battino D. Antiepileptic drug treatment in pregnancy: changes in drug disposition and their clinical implications. Epilepsia 2013;54:405-14.

Walker LE, Mirza N, Yip VLM, et al. Personalized medicine approaches in epilepsy. J Intern Med 2015;277:218-34.

Werhahn KJ, Trinka E, Dobesberger J, et al. A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy. Epilepsia 2015;56:450-9.

Yamada M, Welty TE. Generic substitution of antiepileptic drugs: a systematic review of prospective and retrospective studies. Ann Pharmacother 2011;45:1406-15.

Yates SL, Fakhoury T, Liang W, et al. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav 2015;52:165-8.

Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy – United States, 2015. MMWR Morb Mortal Wkly Rep 2017;66:821-5.

Self-Assessment Questions

1. A 12-year-old girl with uncontrolled seizures was initiated on a new antiepileptic drug (AED) 1 month ago. Today, she returns to the clinic with her family for a follow-up. Her mother tells you that her seizures are better controlled but that she is concerned that the patient is having difficulty completing her homework to the same standards and does not seem to enjoy playing with her friends and dolls as she did in the past. Which one of the following is best to recommend when seeing this patient?

   A. Assess the patient for adverse effects.
   B. Recommend changing the AEDs.
   C. Assess for attention-deficit/hyperactivity disorder symptoms.
   D. Recommend a visit with a psychologist.

Questions 2 and 3 pertain to the following case.

R.S. is a 29-year-old woman. Although in relatively good health, she recently had a focal seizure lasting less than 1 minute at a family event. R.S. works in a high-paced environment as an accountant for a large firm. She manages her stress well by exercising on a regular basis and consistently sleeps about 8 hours per night without sleep aids. R.S.'s urine toxicology and EEG are negative, her genetic panel is pending, and she reports no unusual activities.

2. In the ED, R.S. has another focal seizure that lasts less than 30 seconds. The neurologist on call decides to initiate an AED. Which one of the following is best to recommend for R.S.?

   A. Carbamazepine
   B. Valproate
   C. Phenytoin
   D. Levetiracetam

3. Three months later, R.S. presents to the clinic, having had two seizures in the past month, with the following genetic report: CYP1A2 – 1*/1* normal metabolizer, CYP2C19 – 1*/1* normal metabolizer, CYP2C9 – 1*/2* intermediate metabolizer, CYP2D6 – 4*/4* poor metabolizer, HLA 1502 – positive, and HLA 3101 – negative. The neurologist asks you to interpret this report. Given the data you have about the patient, which one of the following drugs is best to recommend for R.S.?

   A. Oxcarbazepine
   B. Valproate
   C. Phenytoin
   D. Topiramate

4. A 24-year-old man was cross country skiing down a "bunny hill" when the edge of one of his skies nicked an uneven rock, catapulting him forward into some brush where he hit his head. A few hours later, he felt lightheaded and started sweating. About 2 minutes later, his entire body became rigid, he lost consciousness, and fell to the floor followed by bilateral muscle contractions. Which one of the following best describes this patient's seizures using the new International League Against Epilepsy (ILAE) taskforce's practical clinical definition of seizure type?

   A. Focal motor seizure
   B. Focal non-motor seizure
   C. Generalized motor seizure
   D. Generalized absence seizure

Questions 5–7 pertain to the following case.

V.T. is an 18-year-old man with a seizure disorder (diagnosed 4 years ago) along with several migraine headaches each month. His seizures involve passing out, followed by rapid, repetitive jerks on one side of the body. V.T.'s current AED therapy includes valproate delayed release 1000 mg by mouth twice daily (around 30 mg/kg/day). Other medications include escitalopram 10 mg by mouth day for depression and lisinopril 10 mg by mouth for hypertension. Neurologic examination is normal, but seizures are characteristic of juvenile myoclonic seizures.

5. V.T.'s current juvenile myoclonic seizures are partly controlled, and his neurologist wants to initiate one of the following AEDs. Which one of the following is best to recommend adding as V.T.'s adjunctive therapy?

   A. Carbamazepine
   B. Phenytoin
   C. Topiramate
   D. Lamotrigine

6. Several months later, V.T. returns to the clinic. His current home drugs include valproate delayed release 1000 mg by mouth twice daily, clobazam 20 mg by mouth twice daily, and cannabidiol (CBD) oil 200 mg daily (self-initiated about a week ago). V.T. is curious about the common adverse effects associated with CBD oil. Which one of the following is the best response to give V.T.?

   A. Constipation
   B. Increased drowsiness
   C. Kidney toxicity
   D. Increased salivation

7. Six months later, V.T. returns to the clinic with the same medication list and states that he feels tired all the time. He asks you which of his current medications is most likely causing his drowsiness. Which one of the following is the best response?

   A. Clobazam
   B. Escitalopram
   C. Valproate

D. Pravastatin

8. A 15-year-old female adolescent had brief staring spells over the past week, and is having difficulties paying attention in school. These seizures last a few seconds and are replicated following 3 minutes of hyperventilation with a pinwheel. Which AED do you recommend?

   A. Carbamazepine
   B. Valproate
   C. Ethosuximide
   D. Levetiracetam

9. A patient with treatment-resistant focal seizures has previously taken carbamazepine and phenytoin without benefit. Her current drugs are levetiracetam 1250 mg twice a day and lamotrigine 125 mg twice a day. She continues to have a seizure a month. She does not have any other health conditions or take any other co-drugs. Which one of the following is best to recommend as an adjunctive AED?

   A. Perampanel
   B. Brivaracetam
   C. Oxcarbazepine
   D. Lacosamide

10. A 73-year-old woman was initiated on levetiracetam for focal seizures 12 months ago. She is in the clinic for a 6-month follow-up. She reports her seizures are well controlled. Her husband states she is now significantly more tired, naps almost every day in the afternoon, and has been more irritable. Which one of the following laboratory tests would best help assess this patient's adverse effects?

    A. Liver function tests
    B. Kidney function tests
    C. Levetiracetam concentration
    D. Sodium concentration

11. A 24-year-old man had a significant rash while taking phenytoin. Pharmacogenomic testing showed that he carries the *HLA-B*15:02* allele. Which one of the following is best to recommend for this patient?

    A. Lamotrigine
    B. Carbamazepine
    C. Oxcarbazepine
    D. Zonisamide

Questions 12–14 pertain to the following case.

L.T. is a 26-year-old woman who wishes to begin planning for pregnancy. She takes lamotrigine 100 mg twice daily and has been seizure free for 13 months.

12. Which one of the following is best to recommend for L.T. now, before pregnancy?

    A. Change to the least teratogenic AED.
    B. Discontinue lamotrigine.
    C. Begin folic acid.
    D. Avoid alcohol.

13. One year later, L.T. returns to the clinic. She is 5 months pregnant. Her lamotrigine dose is 100 mg twice daily. Her prepregnancy lamotrigine blood concentrations were 7–8 mg/L; her concentration from 3 days ago was 6.2 mg/L. L.T. shares she is using a pillbox because she worries about having a seizure while pregnant. She also worries about the lamotrigine concentration decreasing. Which one of the following is best to educate L.T. about regarding her seizure drug?

    A. Patient adherence
    B. Drug interaction
    C. Increased clearance
    D. Generic substitution

14. Which one of the following is the best plan for addressing L.T.'s decreased lamotrigine blood concentration?

    A. Increase the dose to 200 mg twice daily; check a concentration next trimester.
    B. Increase the dose to 200 mg twice daily; check a concentration in 1 week.
    C. Increase the dose to 125 mg twice daily; check a concentration next trimester.
    D. Increase the dose to 125 mg twice daily; check a concentration in 1 week.

15. A 68-year-old woman is given a diagnosis of focal seizures 4 months after an ischemic stroke. Her current drug regimen includes lisinopril 10 mg once daily, hydrochlorothiazide 25 mg once daily, aspirin 325 mg once daily, atorvastatin 40 mg once daily, and sertraline 50 mg once daily. Her health conditions include hypertension, cardiovascular disease, chronic kidney disease, and depression. Which one of the following is best to recommend for this patient?

    A. Lamotrigine
    B. Levetiracetam
    C. Carbamazepine
    D. Phenytoin