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Antiseizure Medications for Adults With Epilepsy
A Review

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IMPORTANCE Epilepsy affects approximately 65 million people worldwide. Persistent seizures are associated with a 20% to 40% risk of bodily injuries (eg, fractures, burns, concussions) over 12-month follow-up. The primary goal of epilepsy treatment is to eliminate seizures while minimizing adverse effects of antiseizure drugs (ASDs).

OBSERVATIONS An epileptic seizure is defined as a sudden occurrence of transient signs and symptoms caused by abnormal and excessive or synchronous neuronal activity in the brain. Focal and generalized epilepsy are the 2 most frequent types of epilepsy; diagnosis is based on the type of seizures. There are 26 US Food and Drug Administration–approved medications for epilepsy, of which 24 have similar antiseizure efficacy for focal epilepsy and 9 have similar efficacy for generalized epilepsy. The decision to initiate an ASD should be individualized, but should be strongly considered after 2 unprovoked seizures or after 1 unprovoked seizure that occurred during sleep and/or in the presence of epileptiform activity on an electroencephalogram and/or in the presence of a structural lesion on the brain magnetic resonance imaging. The ASDs must be selected based on the seizure and epilepsy types, the epilepsy syndrome, and the adverse effects associated with the drug. For focal epilepsy, oxcarbazepine and lamotrigine are first-line therapy, while levetiracetam can be also considered if there is no history of psychiatric disorder. For generalized epilepsy, the selection of the ASD is based on the type of epilepsy syndrome and the patient's sex, age, and psychiatric history. Seizure freedom is achieved in approximately 60% to 70% of all patients. A total of 25% to 50% of patients also experience neurologic, psychiatric, cognitive, or medical disorders, such as mood, anxiety, and attention deficit disorders and migraines. For these patients, selecting an ASD should consider the presence of these disorders and concomitant use of medications to treat them. ASDs with cytochrome P450 enzyme-inducing properties (eg, carbamazepine, phenytoin) may worsen comorbid coronary and cerebrovascular disease by causing hyperlipidemia and accelerating the metabolism of concomitant drugs used for their treatment. They can also facilitate the development of osteopenia and osteoporosis.

CONCLUSIONS AND RELEVANCE Epilepsy affects approximately 65 million people worldwide and is associated with increased rates of bodily injuries and mortality when not optimally treated. For focal and generalized epilepsy, selection of ASDs should consider the seizure and epilepsy types and epilepsy syndrome, as well as the patient's age and sex, comorbidities, and potential drug interactions.

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Epileptic seizures are paroxysmal episodes characterized by transient motor, sensory, psychiatric, autonomic, and visual signs and symptoms resulting from abnormal synchronous neuronal electrical activity propagated through 1 or more brain circuits involving cortical and subcortical structures.[1] Epilepsy is currently defined as the presence of 1 of the following: at least 2 unprovoked seizures occurring more than 24 hours apart, 1 unprovoked seizure and the probability of further unprovoked seizures that is similar to the recurrence risk after 2 unprovoked seizures (ie, at least 60%) occurring over the next 10 years, or a diagnosis of an epilepsy syndrome.[2] The factors associated with seizure recurrence after a first unprovoked seizure include epileptiform discharges in electroencephalographic recordings; a previous brain injury; structural pathology in a neuroimaging study (ie, brain magnetic resonance imaging), such as a stroke or brain tumor; and occurrence during sleep.[3] The frequent co-occurrence of psychiatric or cognitive disturbances and psychosocial problems are recognized in the current definition of epilepsy.[2] Mood and anxiety disorders occur in approximately 35% of patients with epilepsy, while problems with attention and memory can affect up to approximately 25% of patients with epilepsy. These psychiatric and cognitive comorbidities should be considered when selecting a drug to manage epilepsy. This article reviews the management of focal and generalized epilepsy in adults who respond to pharmacotherapy

with antiseizure drugs (ASDs). This review focuses on the most common types of epilepsy treated by general neurologists and primary care clinicians.

Methods

A literature search was conducted using the PubMed database from January 1, 1980, to November 1, 2021, which identified articles on the epidemiology, pharmacologic treatment, and management of focal and generalized epilepsy in adults. The terms used in the literature search are presented in the Supplement. Only English-language articles were selected for inclusion. Randomized clinical trials and meta-analyses were preferentially selected. A total of 1604 articles were identified from the search and 112 were selected for inclusion, including 20 clinical trials, 6 meta-analyses, 2 longitudinal observational studies, 6 practice guidelines, and 78 articles addressing pharmacokinetic and pharmacodynamic properties of ASDs and common medical neurologic and psychiatric comorbidities of epilepsy.

Epidemiologic and Etiologic Aspects

Epilepsy is a chronic disease affecting approximately 65 million people worldwide and about 1% of the US population. It has an incidence of 50 to 100 per 100 000 individuals per year, with higher incidence rates among those younger than 1 year and older than 85 years.[4,5] Epilepsy is more common in low-income countries.[6] Risk factors for epilepsy are multiple. For example, poststroke epilepsy was reported in 12% of patients diagnosed with stroke over a 10-year follow-up period[7] and in up to approximately 3% of patients with severe traumatic brain injury followed up for a 12-month period. Epileptic seizures occurred in up to 80% of patients with brain tumors and approximately 70% to 95% with symptomatic neurocysticercosis. Furthermore, the underlying cause of epilepsy is often associated with the degree of response to therapy with ASDs (Table 1).[8]

Table 1. Causes of Epilepsy

Etiologies	Responsiveness to pharmacotherapy
Structural	
Cerebrovascular diseases (cavernoma, subarachnoid hemorrhage, stroke)	Stroke: 54%; vascular malformation: 50%
Hippocampal sclerosis	11% to 25%
Cerebral dysgenesis (Focal cortical dysplasia)	Approximately 24%
Brain tumors	Variable; 60%-90%, with most favorable outcome for glioneuronal tumors
Head trauma	50%-70%
Infectious	
Neurocysticercosis	>70%
Bacterial/viral meningitis	Variable
Genetic	
Genetic generalized epilepsies (JME,[a] JAE, GTC seizure alone)	60%-80%
Autosomal dominant nocturnal frontal lobe epilepsy	Approximately 70%
Autosomal dominant epilepsy with auditory features	>80%
Unknown	50%-70%
Immune[b]	
anti-GAD-65, anti-NMDA, anti-GABA A/B receptor antibody–associated epilepsies	Usually poor response
Metabolic	
Porphyria	Variable

Abbreviations: GABA, gamma-aminobutyric acid; GAD-65, glutamic acid decarboxylase 65; GTC, generalized tonic-clonic; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; NMDA, *N*-methyl-D-aspartate.

[a] May have started as childhood absence epilepsy.

[b] Less-frequent causes of epilepsy.

Seizure and Epilepsy Types

In 2017, the International League Against Epilepsy revised its classification of seizure types, epilepsy types, and epilepsy syndromes.[9] Seizure types were classified into focal, generalized, and unknown, based on clinical and electroencephalographic criteria. Focal seizures consist of ictal activity that originates from a distinct brain region. Generalized seizures consist of ictal activity that originates synchronously in both hemispheres. A seizure is classified as "unknown type" when the clinical and EEG data cannot establish whether it is focal or generalized. Epilepsy types are based on the seizure types and include focal epilepsy, generalized epilepsy, combined generalized and focal epilepsy, and epilepsy of unknown type. The epilepsy classification also depends on presence of specific clinical, etiologic, electrophysiologic, neuroimaging, and genetic data. This revised classification underscores the need to consider comorbidities in the comprehensive evaluation and treatment plans of patients with epilepsy.

The diagnosis of epilepsy requires a thorough clinical history that includes a detailed description of the signs and symptoms associated with the seizure as provided by the patient and witnesses and, when possible, videos recorded on cellular telephones (Table 2).[10] The clinical diagnosis is also made based on epileptiform activity (eg, spikes and sharp and slow waves and electrographic seizures) in routine and prolonged EEG studies. A normal EEG result does not exclude the diagnosis of epilepsy. Results of approximately 45% to 50% of routine EEGs of up to 1 hour can be normal in patients with epilepsy. The sensitivity of the EEG for epileptiform discharges increases to approximately 64% with 2-hour sleep-deprived EEGs that include sleep recordings and to approximately 85% with 24-hour ambulatory EEGs.[11] Brain magnetic resonance imaging is performed in patients with focal and generalized epilepsy, but is not required for certain generalized epilepsy syndromes, such as childhood absence, juvenile absence, and juvenile myoclonic epilepsy, when typical clinical and EEG features are present.[12] Referral to a neurologist should always be considered if the seizure and epilepsy types and epilepsy syndrome cannot be clearly established or if the treatment plan cannot be formulated.

Treatment of an Initial Seizure

Whether to prescribe an ASD after the first epileptic seizure depends on whether the seizure is acute, symptomatic, or unprovoked. Acute symptomatic seizures are caused by specific disturbances, such as acute stroke, toxic stimuli (cocaine intoxication,

Table 2. Clinical Presentation of Focal Seizures and Generalized Seizures Seen in Idiopathic Generalized Epilepsy

New nomenclature	Previously known as	Areas of the brain involved	Clinical characteristics
Focal with retained awareness	Simple partial seizure	Electrographic seizure onset and its circuit involve a discrete area of the brain; the area involved determines the signs and symptoms experienced by the patient (motor, sensory, visual, auditory, psychiatric, autonomic)	The patient is aware of surroundings and typically recalls signs and symptoms, such as clonic activity and feelings of deja-vu, panic, and visual hallucinations, and environmental events are intact Seizures may or may not be disabling Seizures are typically less than 1 minute in duration Initial signs and symptoms are identical Can evolve to focal impaired awareness and/or to focal to bilateral tonic-clonic seizures
Focal impaired awareness seizure	Complex partial seizure	Electrographic seizure onset involves a discrete area of the brain, but the circuit propagates the ictal activity to adjacent and/or distant cortical and subcortical structures, which mediate the ictal signs and symptoms	Loss of awareness, unresponsiveness with or without behavioral arrest, and/or purposeless movements of the tongue, mouth, and upper and lower extremities, known as *automatisms* Automatisms may be simple repetitive movements (eg, lip smacking, picking on clothes, hand tapping) or complex (eg, thrashing movements of the extremities and/or the head, flip from supine to prone position) Tonic posturing of the extremities Verbal and nonverbal vocalizations (ictal speech, affect-laden ictal cry) Mean duration ranges from 30 s to 2 min Patients are amnestic to the ictal events Postictal period may be associated with confusion, disorientation, delayed return of verbal functions, and an urge to fall asleep Can be preceded by a focal aware seizure and can evolve to focal to bilateral tonic-clonic seizures
Focal to bilateral tonic-clonic	Secondarily generalized tonic-clonic seizure	Electrographic ictal onset originates in a discrete cortical region and, through its circuit, rapidly propagates to involve cortical and subcortical structures in both hemispheres	May begin with or without focal awareness and focal with impaired awareness A forced head and gaze deviation to one side (ie, adversive head deviation) may be the first clinical sign followed by a tonic contraction in extension of the upper extremity and tonic flexion of the contralateral upper extremity (sign of 4), which is followed by bilateral tonic and then rhythmic contraction of all 4 extremities (clonic activity) The forced head and gaze deviation and tonic contraction of an upper extremity in the early phase of the seizure indicate a focal seizure and correlates with the seizure focus in the contralateral hemisphere The patient is unresponsive and unaware of the surroundings during the seizure and is amnestic to the event After the seizure, the patient is unresponsive for several minutes and remains confused and, at times, agitated on recovery of consciousness for a period There may be a delay in recovery of language functions and transient weakness of the extremities on one side (known as Todd paralysis); the typical duration ranges from 45 s to 3 min
Generalized tonic-clonic seizure		Electrographic ictal activity begins synchronously in bilateral diffuse cortical and subcortical structures.	Initial tonic contraction of all muscles, resulting in a tonic contraction in extension of all 4 extremities for 10-20 s (tonic phase), associated with a cyanotic discoloration of the lips, a short ictal cry, tongue biting, or urinary or fecal incontinence. Tonic phase followed by bilateral rhythmic contraction of the extremities (clonic phase), which represent a repetitive inhibition of the tonic-contraction of the muscles The typical duration of the ictal event is 1-3 min. The postictal state consists of unresponsiveness for a variable period of time (5-20 min) followed by a state of confusion of variable duration. These seizures can occur in any of the idiopathic generalized epilepsy syndromes or can be a form of generalized tonic-clonic seizures of undetermined type

(continued)

alcohol withdrawal), or metabolic disorders (hyponatremia, hypoglycemia/hyperglycemia). For these patients, treating the underlying condition is sufficient to minimize seizure recurrence. However, temporary treatment with an ASD may be necessary in acute symptomatic seizures in the setting of a critical illness (eg, stroke, subarachnoid hemorrhage, certain metabolic disturbances), in which a seizure may recur until the underlying condition is stabilized. For example, among 139 inpatients who had a first seizure in the hospital, 85 (61.1%) had recurrent seizures, 35 (41.1%) of whom had a metabolic disturbance. Among the 32 patients whose seizure was caused by an acute stroke, seizures recurred after the initial episode in 15 (47%).[13] The risk of seizure recurrence is lower for patients with provoked seizures (19%) than for patients with spontaneous seizures (65%) at 10-year follow-up.[14] In some strokes, seizures that occur within the first 7 days are considered "symptomatic seizures," which will not require long-term therapy with ASDs,

Table 2. Clinical Presentation of Focal Seizures and Generalized Seizures Seen in Idiopathic Generalized Epilepsy (continued)

New nomenclature	Previously known as	Areas of the brain involved	Clinical characteristics
Absence seizure		Electrographic ictal activity begins synchronously in bilateral diffuse cortical and subcortical structures	Characterized by sudden behavioral arrest, motionless staring with or without subtle eyelid fluttering, and loss of awareness and unresponsiveness for periods ranging between 3 and 15 s Urinary incontinence may occur in some seizures With longer seizures (ie, >10 s), there may be purposeless movements of the hands, mouth, or tongue The patient does not recall the seizure This seizure type can be identified in childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy Occasionally, absence seizures may be the expression of nonmotor seizures of unknown type
Myoclonic seizure		Electrographic ictal activity begins synchronously in bilateral diffuse cortical and subcortical structures	Characterized by sudden, very brief (0.5-1.0 s) involuntary movement of the head and/or segments of 1 or more extremities or of the entire upper and/or lower extremities, which may or may not be associated with loss of awareness The severity of these brief movements (myoclonic jerks) may range from very subtle (eg, the patient feels the jerk, but it is not visible to others) to violent, resulting in falls or dropping objects They may occur as isolated seizures or in clusters, in which case they can evolve into a generalized tonic-clonic seizures; this seizure type can be seen in juvenile myoclonic epilepsy

whereas seizures that occur beyond 1 week fall in the category of "spontaneous seizures" and hence represent focal epilepsy and will have to be treated with long-term ASD therapy.

After 2 spontaneous seizures, the risk of a third seizure increases to 73% within 4 years if untreated,[15] particularly in patients with an underlying predisposing condition, such as history of stroke or brain tumor. The decision to start an ASD after the first or second unprovoked seizure must be individualized and the risks and benefits must be carefully considered. For example, the initiation of an ASD may be more important for individuals whose work requires driving, while it could be delayed in a person planning pregnancy.

General Principles of Pharmacotherapy

The goal of pharmacotherapy with ASDs is to achieve complete seizure remission without adverse events. Patients with generalized epilepsy are more likely to become seizure free (64%-82%) than those with focal epilepsy (25%-70%).[16]

Recurrent seizures are associated with seizure-related injuries in approximately 28% to 40% of patients and a mortality rate that is 1.6 to 9.3 times higher than the general population during the first 2 years after diagnosis.[17-19] Causes of death are typically drowning, status epilepticus, suicide, or sudden unexpected death in epilepsy. Sudden unexpected death in epilepsy consists of a nontraumatic death, not due to drowning, in a patient with epilepsy without an identifiable toxic or anatomical cause of death based on postmortem examination. The incidence of sudden unexpected death in epilepsy is approximately 0.35 cases per 1000 persons-years in patients with newly diagnosed epilepsy, and the incidence increases to approximately 1 to 6 per 1000 person-years in those with chronic epilepsy and to 6 to 9 per 1000 person-years in patients with treatment-resistant epilepsy.[20]

Accurate identification of the seizure type and epilepsy syndrome is important for selecting the ASD (**Table 3**). The ASD should be started as monotherapy at a low dose with a stepwise titration to attain an initial moderate dose that minimizes adverse events (Table 3). If a seizure recurs, the dose should be increased until there are no subsequent seizures, the maximal dose is reached, or adverse events occur, whichever happens first. If persistent seizures occur at optimal doses or if there are persistent adverse events, an alternative ASD should be added until an adequate dose is reached, at which point the first ASD can be tapered to lower doses until it is discontinued.

Intravenous loading should be considered when a rapid attainment of therapeutic serum concentrations of an ASD is necessary, such as for focal and generalized seizures occurring in clusters, defined by recurrent seizures separated by minutes to hours within a 24-hour period.[21] Treatment with more than 1 drug is typically considered in patients with treatment-resistant epilepsy, defined as persistent seizures after a trial with 2 appropriate ASDs at optimal doses.

Serum concentrations can be obtained for any ASD. Drug levels were routinely measured for first-generation ASDs (ie, phenobarbital, primidone, phenytoin, carbamazepine valproic acid, and ethosuximide) and in some of the newer ASDs (eg, lamotrigine) and their "therapeutic range" was used to determine the appropriateness of dose adjustments. Recent evidence suggests that ASD concentrations should be used to monitor drug adherence, help explain adverse events, and identify the need for dose adjustments conditions such as pregnancy, hepatotoxicity, and kidney failure.[22] Furthermore, because seizure remission can often be achieved with low serum concentrations, and high concentrations are not always associated with toxicity, dose changes should be determined based on persistent seizures or adverse events.[22]

Therapeutic Expectations of Pharmacotherapy

The rate of seizure freedom, defined as the absence of seizures over a 5-year period in focal or generalized epilepsy, has been unchanged over the past 20 years, despite the release of 17 new ASDs. For example, a 2000 study from the UK reported seizure freedom

Table 3. Antiseizure Drugs

Antiseizure drug	Seizure types drug is effective for	Mechanism of action	Common and serious adverse events	Effect on metabolism of other drugs	Hepatic cytochrome P450 isoenzymes and biotransformation mechanisms	Laboratory/ diagnostic monitoring for potential adverse events
First generation						
Phenytoin	Focal and GTC seizures; may worsen myoclonic seizures	Sodium channel blockade	Gingival hyperplasia (60%) and hirsutism, osteopenia/ osteoporosis, cardiac arrhythmia (0.8%), SJS (1-10 per 10 000 new users)[a]	Greatest increase	Inducer (CYP3A, CYP2C9, CYP2C19, UGT, PGP)	Monitor for osteopenia/ osteoporosis, lipid profile (cholesterol and LDL)
Ethosuximide	Absence seizures	T-type calcium blockade	Depression, irritability, psychotic symptoms, SJS[a]	NA	NA	
Carbamazepine	Focal and GTC seizures; may worsen myoclonic seizures	Sodium channel blockade	Hyponatremia (1%-40%), neutropenia, osteopenia/ osteoporosis, SJS (1-10 per 10 000 new users)[a]	Greatest increase	Inducer (CYP1A2, CYP3A, CYP2C9, CYP2C19, PGP, UGT)	Monitor for osteopenia/ osteoporosis, lipid profile (cholesterol and LDL), serum sodium
Valproic acid[b]	Focal, GTC, absence, and myoclonic seizures	Sodium channel blockade; GABA potentiation	Thrombocytopenia/ neutropenia (1%-30%), weight gain (up to 70%), osteopenia/ osteoporosis, pancreatitis (1 in 3000 to 1 in 5000 cases)	Greatest decrease	Inhibitor (CYP2C9, epoxyde hydrolase, UGT)	Monitor for osteopenia/ osteoporosis, platelet count, LFTs
Second generation						
Gabapentin	Focal and GTC seizures; may worsen myoclonic seizures	P/Q-type calcium channel blockade	Weight gain (2%-3%), peripheral edema (2%-8%)	NA	NA	
Lamotrigine[b]	Focal and GTC seizures; may worsen myoclonic seizures	Sodium channel blockade; some effect on GABA potentiation	Headaches (1%-5%), insomnia (5%-10%), tremor (4%-10%), rash (5%-17%), SJS (1-10 per 10 000 new users)[a]	NA	Inducer (UGT), inhibitor (UGT, CYP2C19)	
Topiramate[b]	Focal and GTC seizures	Sodium channel blockade; some effect on GABA potentiation	Weight loss (4%-17%), memory problems and word finding difficulties (1%-11%), nephrolithiasis (3%)	Mild increase (moderate increase at >200 mg/d)	Inducer (CYP3A4), inhibitor (CYP2C19)	Metabolic acidosis
Levetiracetam	Focal and GTC seizures; may worsen myoclonic seizures	Binding to SV2a protein	Psychiatric symptoms (7%-25%)	NA	NA	
Oxcarbazepine	Focal and GTC seizures; may worsen myoclonic seizures	Sodium channel blockade	Hyponatremia (1%-46%), osteopenia/ osteoporosis, SJS[a]	Mild increase (moderate increase at >900 mg/d)	Inducer (CYP3A4), inhibitor (CYP2C19)	Monitor for osteopenia/ osteoporosis, serum sodium
Zonisamide[b]	Focal, GTC, and myoclonic seizures	Sodium and calcium channel blockade	Psychiatric symptoms (1%-9%), memory problems and word finding difficulties (10%-15%), SJS, nephrolithiasis (4%)	NA	NA	Metabolic acidosis
Third generation						
Lacosamide	Focal and GTC seizures	Slow sodium channel inactivation	Dizziness (16%-30%), drowsiness (5%-17%), cardiac arrhythmia	NA	NA	Electrocardiogram (PR interval)
Eslicarbazepine	Focal seizures	Sodium channel blockade	Hyponatremia (1%-2%), SJS[a]	Mild increase	Inducer (CYP2C9, CYP3A4), inhibitor (CYP2C19)	Serum sodium

Abbreviations: ASD, antiseizure drug; CYP, cytochrome P450; GABA, γ-aminobutyric acid; GTC, generalized tonic-clonic; LDL, low-density lipoprotein; LFTs, liver function tests; PGP, P-glycoprotein; SJS, Stevens-Johnson syndrome; UGT, glucuronosyltransferase.

[a] HLA-B*1502 should be tested in any patient of Asian descent, particularly Han Chinese, to minimize the risk of severe rash.

[b] ASDs with >2 mechanisms of action.

in 64% of 470 patients followed up over a 5-year period.[23] In a 2018 study by the same investigators, 65% of 1795 patients were seizure-free.[24] Remission from seizures was more frequent in patients with generalized epilepsy compared with those with focal epilepsy (68.1% vs 62.5%).

Poor adherence to ASDs has been identified in approximately 30% to 40% of patients with epilepsy and is a cause of approximately 45% of breakthrough seizures.[25] ASDs with extended-release formulations (carbamazepine, oxcarbazepine, valproic acid, levetiracetam, topiramate) or a long half-life (lamotrigine, zonisamide, eslicarbazepine) that can be given once a day may improve adherence.

Patients diagnosed with treatment-resistant epilepsy[26] should be referred to an epilepsy center for consideration of alternative therapeutic options (eg, surgery, neuromodulation therapies [such as vagal nerve stimulation and deep brain stimulation], ketogenic diets) and to exclude the possibility of "pseudoresistance." Pseudoresistance results from 1 of the following: use of the wrong ASD for the type of seizure and epilepsy (Table 3) or paroxysmal epileptic seizures due to some psychiatric disorders (panic disorder, conversion disorder presenting as psychogenic nonepileptic seizures),[27] some sleep disorders (ie, cataplectic event, parasomnias), migraines and migraine equivalents, transient ischemic episodes, movement disorders (paroxysmal dyskinesia, tremor), and syncopal episodes.[28] Approximately 1 of every 4 to 5 patients referred to an epilepsy center with a diagnosis of treatment-resistant epilepsy does not have epilepsy.[29]

Selecting the Antiseizure Drug

The level of evidence of the efficacy and tolerability of ASDs and recommendations were reviewed in several practice guidelines.[30-35] The choice of ASDs is multifactorial and depends on the drug's efficacy for the seizure and epilepsy types and epilepsy syndrome (Tables 3 and 4); tolerability profile, which includes the drug's potential adverse effects that can often be associated with the patient's age, sex, and race (Tables 3, 4, and 5); pharmacokinetic and pharmacodynamic interactions with concomitant medications (Table 3); potential therapeutic and/or iatrogenic effects on comorbid disorders (Table 4); and drug costs.

Efficacy

Until 1990, there were 6 primary ASDs (phenytoin, phenobarbital, primidone, carbamazepine, valproic acid and benzodiazepines) that were first-line therapy for managing epilepsy. In many low-income countries, these drugs, referred to as *first-generation* ASDs because they were the first to be approved by the US Food and Drug Administration, remain the only drugs available. Eight ASDs were approved between 1990 and 2010 and are referred to as *second-generation* ASDs (Table 3). Among these, levetiracetam, lamotrigine, oxcarbazepine, and topiramate have become the most frequently prescribed today. Ten drugs became available in the past decade and are referred as *third-generation* ASDs (Table 3). Eight of these ASDs are used in patients with treatment-resistant epilepsy, while eslicarbazepine and lacosamide are currently prescribed to patients with newly diagnosed focal epilepsy.

Except for ethosuximide, which is only indicated for absence seizures, all ASDs are indicated for focal epilepsy. Head-to-head comparison trials among first-generation ASDs demonstrated that carbamazepine and phenytoin were the most effective for focal epilepsy, followed by valproic acid.[36,37] Valproic acid was the most effective drug for idiopathic generalized epilepsy syndromes.[38]

A review of 15 multicenter randomized double-blind clinical trials that directly compared the efficacy and tolerability between first- (carbamazepine, phenytoin, and valproic acid), second- (lamotrigine, oxcarbazepine, topiramate, gabapentin, and zonisamide), and third-generation ASDs (lacosamide) in patients with newly diagnosed epilepsy[36,37,39-51] suggested a comparable efficacy among these ASDs for focal epilepsy, except for a lower efficacy for gabapentin. In 3 trials, lamotrigine had better tolerability than phenytoin and carbamazepine.[40,44,45] For generalized and unclassified tonic-clonic seizures, these clinical trials found no differences in efficacy among the pairs of drugs compared.

Currently, the Standard and New Antiepileptic Drugs trials (SANAD) I and II are the 2 largest randomized unblinded trials of monotherapy published in patients with newly diagnosed focal and generalized epilepsy. Participants were followed up for 2 years. Dose titrations were made by the treating clinician based on clinical response. Outcome measures consisted of time to 12 months of seizure remission and time to treatment failure resulting from intolerable adverse events or poor seizure control.

For focal epilepsy, 1721 patients were randomized to receive carbamazepine, oxcarbazepine, lamotrigine, gabapentin, or topiramate in SANAD I and 990 patients were randomized to receive lamotrigine, zonisamide, or levetiracetam in SANAD II. In both studies, lamotrigine showed superior effectiveness, which was based mainly on better tolerability.[52,53] In this study, lamotrigine's antiseizure efficacy was comparable to that of zonisamide and levetiracetam, but it had less unacceptable adverse events (9.7% for lamotrigine vs 17.9% for topiramate, 13.8% for oxcarbazepine, 13.2% for carbamazepine, and 9.2% for gabapentin). In SANAD I, lamotrigine and carbamazepine had the shortest times to 12 months of seizure remission, compared with oxcarbazepine, gabapentin, and topiramate, while lamotrigine and oxcarbazepine had the longest time to treatment failure compared with carbamazepine, gabapentin, and topiramate. In SANAD II, levetiracetam and zonisamide were associated with more adverse events than lamotrigine (≥1 adverse event was reported in 33% of patients receiving lamotrigine, 45% receiving zonisamide, and 44% receiving levetiracetam), but the 3 drugs did not differ in efficacy.[52,53]

For generalized or unclassifiable epilepsy, 716 patients were randomized to receive valproic acid, lamotrigine, or topiramate in SANAD I and 520 patients were randomized to receive valproic acid or levetiracetam in SANAD II. Valproic acid was superior in efficacy to lamotrigine in both SANAD I and SANAD II and to levetiracetam in SANAD II.[54,55] Inadequate seizure control at final follow-up was 10% for lamotrigine and 3.8% for valproic acid in SANAD I. In SANAD II, inadequate seizure control was more frequent for levetiracetam (36%) than valproic acid (26%). However, the potential for serious teratogenic adverse events with valproic acid and topiramate preclude their use in women of reproductive age, unless there are no other options.[56]

A meta-analysis of 4 randomized trials that included 2856 patients found no significant differences in the associations of carbamazepine, levetiracetam, zonisamide, and the newer ASDs—lacosamide and eslicarbazepine—for the outcomes of efficacy and adverse effects.[57]

Table 4. Choice of Commonly Prescribed Antiseizure Drugs in the Setting of Comorbid Disorders[a]

Comorbid condition	Favor	Use with caution	Observations
Mood disorders	Lamotrigine, oxcarbazepine, valproic acid, clonazepam	Levetiracetam, topiramate, zonisamide	Increased risk in patients with personal and first-degree family history of psychiatric disease
Anxiety disorders	Valproic acid, gabapentin, pregabalin, clonazepam	Lamotrigine, levetiracetam, topiramate, zonisamide	Increased risk in patients with personal and first-degree family history of psychiatric disease
Cognitive impairment/ Intellectual disability	Lamotrigine, lacosamide, oxcarbazepine, eslicarbazepine, valproic acid	Topiramate, zonisamide, benzodiazepines, barbiturates, levetiracetam	Valproic acid: start slow titration Lamotrigine: may cause paradoxical agitation in cognitively impaired patients suffering from autism Eslicarbazepine and levetiracetam: monitor psychiatric symptoms
Neuropathic pain	Carbamazepine, oxcarbazepine, gabapentin, pregabalin, topiramate, lacosamide		Carbamazepine and oxcarbazepine: monitor for hyponatremia in the elderly and with concomitant use of SSRIs and diuretics
Migraine disorder	Topiramate, valproic acid, gabapentin, zonisamide	Lamotrigine, oxcarbazepine, eslicarbazepine	Gabapentin and zonisamide: conflicting data to support or refuse its use in migraines
Tremor	Topiramate, gabapentin, zonisamide, clonazepam, primidone	Lamotrigine, valproic acid	
Cardiovascular disease	Levetiracetam, topiramate	Any EI-ASD, valproic acid, lacosamide, lamotrigine	Valproic acid: increased risk of metabolic syndrome Lacosamide: monitor PR interval Lamotrigine: use with caution in cardiac conduction disorders
Hematologic dyscrasias (eg, thrombocytopenia, leukopenia, agranulocytosis)	Levetiracetam, lacosamide, lamotrigine, topiramate, benzodiazepines	Valproic acid, Carbamazepine, Oxcarbazepine	Levetiracetam and lamotrigine: can cause leukopenia in rare cases
Oncologic diseases	Levetiracetam, lacosamide, lamotrigine,	Any EI-ASD, valproic acid	EI-ASDs: may decrease the efficacy of chemotherapy Valproic acid: may worsen leukopenia and thrombocytopenia caused by chemotherapy
Hepatic dysfunction	Levetiracetam, gabapentin, pregabalin, topiramate, zonisamide, lacosamide	Valproic acid, clobazam, barbiturates, lamotrigine, phenytoin, felbamate	Topiramate, zonisamide, lacosamide: dose adjustment necessary
Kidney dysfunction	Lamotrigine, oxcarbazepine, eslicarbazepine, valproic acid	Levetiracetam, lacosamide, gabapentin, pregabalin, topiramate	Levetiracetam, lacosamide, gabapentin, pregabalin, and topiramate: dose adjustment necessary
Allergic reactions	Gabapentin, levetiracetam, lacosamide, valproic acid	Lamotrigine, oxcarbazepine, eslicarbazepine, carbamazepine, topiramate, zonisamide, phenytoin, phenobarbital	Lamotrigine, oxcarbazepine, eslicarbazepine, carbamazepine, phenytoin: test for HLA-B15:02 allele before prescribing in individuals of Asian descent; do not use if result is positive
Obesity	Topiramate, zonisamide	Valproic acid, gabapentin, pregabalin	
Osteopenia/osteoporosis	Levetiracetam, lacosamide, lamotrigine	Any EI-ASD, valproic acid	

Abbreviations: EI-ASD, enzyme-inducing antiseizure drug; SSRI, selective serotonin reuptake inhibitor.

[a] Antiepileptic drugs used in treatment-resistant epilepsy were not included.

Table 5. Antiseizure Drugs (ASDs) for Women of Reproductive Age and Major Congenital Malformations of ASDs

ASD of choice for women of reproductive age	Epilepsy type	
	Focal	Generalized/unknown
First option	Levetiracetam, Lamotrigine	Levetiracetam, Lamotrigine
Second option	Oxcarbazepine, Zonisamide[a], Lacosamide[a]	Zonisamide[a]
Third option	Carbamazepine[b]	
ASD	**Major congenital malformations and/or poor cognition in neonates**	**Level of recommendation for AED plasma level monitoring[c]**
First generation		
Phenobarbital	High risk: 5.5% (cardiovascular malformations, oral clefts)	Data inadequate
Phenytoin	Moderate risk: 2.9% (cleft palate, poor neonatal cognition)	Probably useful
Ethosuximide	Unknown[d]	Data inadequate
Carbamazepine	Moderate risk: 3% (posterior cleft palate)	Probably useful
Valproate	High risk: 11% (neural tube defects, hypospadias, cardiovascular malformations, facial clefts, poor neonatal cognition)	Data inadequate
Second generation		
Lamotrigine	Low risk: 2%	Probably useful
Gabapentin	Unknown	Not established
Topiramate	High risk: 4.2% (cleft lip, clef palate, hypospadias, SGA)	Not established
Felbamate	Unknown[d]	Not established
Tiagabine	Unknown[d]	Not established
Levetiracetam	Low risk: 2.4%	Possibly useful
Oxcarbazepine	Low risk: 2.2%	Possibly useful
Zonisamide	Unknown[d]	Not established
Pregabalin	Unknown[d]	Not established
Third generation		
Lacosamide	Unknown[d]	Not established
Rufinamide	Unknown[d]	Not established
Clobazam	Unknown[d]	Not established
Perampanel	Unknown[d]	Not established
Eslicarbazepine	Unknown[d]	Not established
Brivaracetam	Unknown[d]	Not established
Cannabidiol	Unknown[d]	Not established
Cenobamate	Unknown[d]	Not established

Abbreviations: AED, antiepileptic drug; SGA, small for gestational age.

[a] Insufficient data on teratogenic effects.

[b] Teratogenic effects identified.

[c] The American Academy of Neurology practice guidelines recommends checking AED levels at baseline before conception and monthly thereafter. Moreover, the lack of level of evidence should not discourage the clinician from monitoring AED concentration during pregnancy.

[d] Unknown indicates that there are no reliable data on the frequency and types of teratogenic effects.

In the generalized epilepsy syndromes, the ASD selection is based on the type of seizure. Ethosuximide, valproic acid, and lamotrigine are effective for absence seizures; valproic acid, levetiracetam, zonisamide, topiramate, lamotrigine, and lacosamide are effective for myoclonic and generalized tonic-clonic seizures. These 6 ASDs have broad-spectrum efficacy and can be considered as first-line therapy in generalized tonic-clonic seizures of unknown type. In contrast, 6 ASDs prescribed for focal epilepsy (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, gabapentin, and pregabalin) may worsen myoclonic and absence seizures in idiopathic generalized epilepsy syndromes.[58]

Rescue medications consist of benzodiazepines and are used to stop prolonged generalized or focal seizures or abort clusters of acute repetitive seizures.[21] Benzodiazepines effective against seizures include midazolam, lorazepam, clonazepam, and diazepam, which are available in intranasal (midazolam, diazepam), intramuscular (midazolam), oral (midazolam, clonazepam, lorazepam, diazepam), or rectal (diazepam) formulations for use at home and intravenous formulations (lorazepam, midazolam, diazepam) for in-hospital use.[59]

Pharmacokinetic and Pharmacodynamic Properties

Interactions With Other Drugs

Younger (aged 18-35 years) patients with epilepsy take a mean of 3.5 concomitant drugs and older (aged >65 years) patients with epilepsy take a mean of 7 concomitant drugs that can have pharmacokinetic and pharmacodynamic interactions with ASDs.[60] Six drugs (phenobarbital, primidone, phenytoin, carbamazepine, oxcarbazepine [at doses >900 mg/d], and topiramate [at doses >200 mg/d]) have enzyme-inducing properties, which can increase the clearance of several concomitant drugs by 30% to 70% and limit their efficacy unless the drug dose is adjusted (Table 3). Drugs that require adjustments when prescribed with 1 of these 6 drugs include other ASDs, anticoagulants, antibiotic and anti-HIV drugs, chemotherapeutic and immunosuppressant agents, psychotropic drugs, antidiabetic drugs, statins, steroids, and oral contraceptives.[61] Three ASDs (valproic acid, felbamate, and cenobamate) decrease the clearance of other ASDs, psychotropic drugs, calcium channel blockers, and anticoagulants[61] and may cause toxicity unless their dose is adjusted. The combination of ASDs and drugs with similar pharmacodynamic properties can lead to iatrogenic effects. For example, the risk of hyponatremia associated with carbamazepine and oxcarbazepine is higher when a diuretic drug is simultaneously prescribed.[62]

Therapeutic or Iatrogenic Effects

Certain ASDs have pharmacodynamic properties that can improve or worsen common comorbidities associated with epilepsy (Table 4). ASDs with mood-stabilizing (carbamazepine, valproic acid, lamotrigine, and oxcarbazepine), antidepressant (lamotrigine), and anxiolytic (gabapentin, pregabalin, and benzodiazepines [clonazepam]) properties can help with managing mood and/or anxiety disorders, which affect approximately 30% of these patients with epilepsy.[63] Conversely, their discontinuation can unmask these conditions.[64] Likewise, ASDs with negative psychotropic properties (phenobarbital, primidone, levetiracetam, topiramate, zonisamide, and perampanel) can cause psychiatric adverse events, such as symptoms of depression, anxiety, impulsive behavior, and

poor frustration tolerance, particularly in patients with past or current personal or family psychiatric history.[65]

Two ASDs, topiramate and valproic acid, may prevent migraine headaches, which affect up to 30% of patients with epilepsy.[66] Topiramate and zonisamide can cause significant weight loss, while weight gain can occur with valproic acid (4-6 kg), gabapentin (1-3 kg), and pregabalin, typically in a dose-dependent manner.[67]

Enzyme-inducing ASDs (EI-ASDs) can cause osteopenia and osteoporosis in up to 45% of patients.[68] A study from the Women's Health Initiative followed up 1385 people receiving ASDs (681 EI-ASDs and 663 other ASDs) and 137 282 nonusers aged 50 to 79 years for a mean of 7.7 years. The use of ASDs was associated with increased risk of fractures (3.35% vs 2.10%; hazard ratio [HR], 1.44 [95% CI, 1.30-1.61]). The annual fracture rate was higher with the use of EI-ASDs than other ASDs (3.69% vs 2.86%; HR, 1.29 [95% CI; 1.04-1.61]).[69] In a cross-sectional study of 71 patients (42 adults) with epilepsy who were receiving long-term EI-ASD therapy, 59% had osteopenia, which was independent of vitamin D serum concentrations. Bone density was inversely correlated with the duration of ASD use in the adults ($P = .003$).[70]

Exposure to these drugs has also been associated with an increased risk of cardiovascular disease, perhaps mediated in part by adverse effects of EI-ASDs, such as increased serum low-density lipoprotein cholesterol, C-reactive protein, and homocysteine. For example, in a prospective study, 34 patients with epilepsy taking carbamazepine or phenytoin were switched to lamotrigine or levetiracetam (non–EI-ASDs). Serum samples of total cholesterol, non–high-density lipoprotein cholesterol, triglycerides, and C-reactive protein serum concentrations were drawn before and 6 weeks after the switch of the ASD and compared with those of 16 healthy participants not receiving ASDs. Patients who were switched from the EI-ASDs had significant declines in total cholesterol (−24.8 mg/dL), atherogenic (non–high-density-lipoprotein) cholesterol (−19.9 mg/dL), triglycerides (−47.1 mg/dL) (all $P < .0001$), and C-reactive protein (−31.4%; $P = .027$). These changes were significant when compared with changes observed in healthy participants ($P < .05$).[71] A retrospective study compared the incidence of stroke between 3812 adult patients with epilepsy and 15 248 control participants with a similar type and prevalence of comorbidities. The cumulative incidence of stroke was 3-fold higher for the patients with epilepsy than for the control participants (24.08 vs 7.96 per 1000 person-years; HR, 2.92 [95% CI, 2.58-3.30]).[72] Changes can include thickening of the intima-media of carotid arteries and their branches. In a large population-based study of 31 479 patients with epilepsy, 11 803 were treated with EI-ASDs and 19 676 were treated with non–EI-ASDs. Myocardial infarction occurred in 1.4% of patients compared with 0.7% of controls and ischemic stroke occurred in 1% of patients compared with 0.5% of controls ($P < .001$) (HR for cardiovascular disease, 1.21 [95% CI, 1.06-1.39] and increased up to 2.38 [95% CI, 1.52-3.56] after more than 10 years of exposure to EI-ASDs in a dose-dependent manner).[73] A 2021 population-based study documented an increased risk of cardiovascular disease associated with any ASD exposure. In a study of 10 241 patients (mean age, 49.6 y; 52.2% men), any history of ASD use was associated with an increased risk of cardiovascular disease (adjusted HR, 1.58 [95% CI, 1.51-1.63]; $P < .001$) and there were no differences in this association between EI-ASDs and non–EI-ASDs (adjusted HR, 0.95 [95% CI, 0.86-1.05]; $P = .30$) (no absolute data were available).[74] These studies may suggest an increased risk of cardiovascular disease in patients with epilepsy.

Approximately 3% to 16% of patients with epilepsy develop a drug hypersensitivity to an ASD.[75] The risk increases 5-fold in those with a history of an ASD rash.[76] Most ASD rashes present as a maculopapular rash, but Stevens-Johnson syndrome and/or toxic epidermal necrolysis occurs in 1 to 8 new cases per 10 000 new ASDs users (Table 3).[77] Individuals of Asian descent, particularly Han Chinese, should be tested for the HLA-B15:02 allele before the prescription of carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, and lamotrigine, which should be avoided in those with a positive result because these individuals are at increased risk of a severe rash, including Stevens-Johnson syndrome.[78]

ASDs in Pregnancy

Potential teratogenic effects must be considered when selecting an ASD for women of child-bearing age, particularly because approximately 50% of pregnancies are unplanned.[79-81] Lamotrigine and levetiracetam have the lowest rates of congenital malformations (2%-2.9% for lamotrigine and 2.4%-2.8% for levetiracetam), which are comparable to those of healthy women receiving no medications,[82,83] followed by oxcarbazepine (2.2%-3%).[83] Conversely, valproic acid has the highest risk of teratogenic effects (up to 11%), which are dose-dependent and include central nervous system (2%), cardiac (8%), urologic (5%), and facial malformations (2%).[82,84] Additionally, children exposed to valproate in utero had a dose-dependent lower intelligence quotient (7-10 points) at 6 years of age, compared with children exposed to phenytoin, lamotrigine, and carbamazepine,[56,85] and an increased risk of autism.[86] Therefore, valproate should be avoided in women of gestational age unless no other options are available, in which case valproate should be prescribed at doses lower than 650 mg per day.[87,88] Topiramate is associated with a 4.2% risk of congenital abnormalities, including cleft lip and cleft palate (1.4%),[83] while cardiac malformations have been associated with phenytoin in approximately 1% of patients and phenobarbital in approximately 4% of patients.[84]

During pregnancy, monthly monitoring of blood levels has been recommended in the American Academy of Neurology guidelines for lamotrigine, oxcarbazepine, levetiracetam, carbamazepine, and phenytoin, because these drugs are metabolized more rapidly during pregnancy (Table 5).[89] For example, lamotrigine's clearance increases by 76% in the first trimester of pregnancy, 153% in the second trimester, and 219% in the third trimester,[90] requiring a dose adjustment. Women with epilepsy should be co-treated by neurologists and obstetricians with expertise in epilepsy during pregnancy. Folate supplementation (1-4 mg/d) should be prescribed for all women during pregnancy because it decreases the risk of malformations and has been associated with higher cognitive functions in children at 6 years of age.[85,89] Breastfeeding is encouraged during the first 6 months after delivery, because it is associated with improved outcomes in all developmental domains regardless of the maternal ASD.[90,91]

Discontinuing Antiseizure Drugs

Discontinuation of ASDs is often considered after a seizure-free period of at least 2 years. However, even in these patients, seizure

recurrence can occur in approximately 30% to 50% of patients.[92] A randomized double-blind placebo-controlled clinical trial of 1013 patients with a 2-year follow-up period and an unblinded observational study of 330 patients with a 5-year follow-up period found a higher seizure recurrence among patients who discontinued ASDs compared with those who continued receiving medication (41% vs 22% and 50% vs 28%).[92,93] A meta-analysis of 10 studies that included 1769 patients with epilepsy with a median follow-up of 5.3 years reported a seizure recurrence of 46% after medication discontinuation.[94]

This risk of seizure recurrence is highest in the first 6 to 12 months after ASDs are discontinued and decreases after the second year. Factors associated with seizure recurrence include a shorter period without a seizure, a history of focal epilepsy, EEG findings with interictal epileptiform discharges, a history of myoclonic seizures or multiple seizure types, poor initial response to treatment, family history of epilepsy, mesial temporal sclerosis (neuronal loss of hippocampus and amygdala), and older age (>50 y) at the onset of epilepsy.[95,96] The decision to withdraw ASDs must be individualized and based on the patient's preferences. For example, patients who must drive or have job requirements that include operating machinery and those with fear of seizure recurrence may decide to continue receiving medication. Slowly tapering ASDs (ie, over 6 months) should be considered for carbamazepine, oxcarbazepine, barbiturates, and benzodiazepines because they may be associated with withdrawal seizures.[92]

Treatment-Resistant Epilepsy

Treatment-resistant epilepsy is defined by persistent seizures after 2 trials with an appropriate ASD at optimal doses, administered as single- or multiple-drug therapy.[26] Drug-resistant epilepsy occurs in approximately 30% to 40% of all patients with epilepsy, but it is more frequent in focal (40%) than in generalized epilepsy.[23] In generalized epilepsy, seizure remission varies by syndrome. Remission rates are 92% for generalized tonic-clonic seizures alone,[97] 59% to 90% for juvenile myoclonic epilepsy,[98] and 37% to 84% for childhood and juvenile absence epilepsy over a mean follow-up of 25.8 years.[99,100]

Treatment-resistant epilepsy typically requires trials of therapy with ASDs that have different mechanisms of action and newer drugs, such as perampanel, cannabidiol, and cenobamate (Table 3). The addition of second- or third-generation ASDs can result in a 50% reduction of seizure frequency in 30% to 40% of patients, while seizure freedom occurs in less than 5% of patients.

Epilepsy surgery consists of resection of the area of the brain from which seizures originate, known as the *epileptogenic zone*. Surgery is associated with seizure remission in approximately 40% to 70% of patients, with the best outcomes observed in lesional focal epilepsy (eg, cavernoma).[101] Anterotemporal lobectomy is the most frequently performed resective surgery, yielding 5-year seizure remission in 66% of patients.[102] Other types of surgical procedures include a small cortical resection (topectomy) or a hemispherectomy.

Neuromodulation is a palliative therapy considered when resective surgery is not an option. Neuromodulation consists of intermittent electrical stimulation of brain circuits, which disrupts neuronal hyperexcitability and reduces seizure frequency over time. Types of neuromodulation include vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation of thalamic nuclei (Supplement). The vagus nerve stimulation has been used since 1997 and is indicated for treatment-resistant focal epilepsy, but has also been used to manage generalized epilepsy and Lennox-Gastaut syndrome.[103] In a meta-analysis of 74 clinical studies, including 3321 patients with intractable epilepsy, vagus nerve stimulation was associated with a reduction in seizure frequency of greater than 50% after 1 year in approximately 30% to 50% of patients.[104]

Limitations

This review has several limitations. First, some relevant articles may have been omitted. Second, only English-language articles were selected for inclusion. Third, this review was limited to the pharmacologic treatment of the common types of epilepsy in adults who respond to ASDs. Newer therapies reported in the treatment-resistant epilepsy literature were not included. Fourth, a formal assessment of quality of the evidence was not performed. Fifth, this review is limited by the quality of available evidence.

Conclusions

Epilepsy affects approximately 65 million people worldwide and is associated with increased rates of bodily injuries and mortality when not optimally treated. For focal and generalized epilepsy, selection of ASDs should consider the seizure and epilepsy types and epilepsy syndrome as well as the patient's age and sex, comorbidities, and potential drug interactions.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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