Chapter 75: Epilepsy

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 54, Epilepsy.

KEY CONCEPTS

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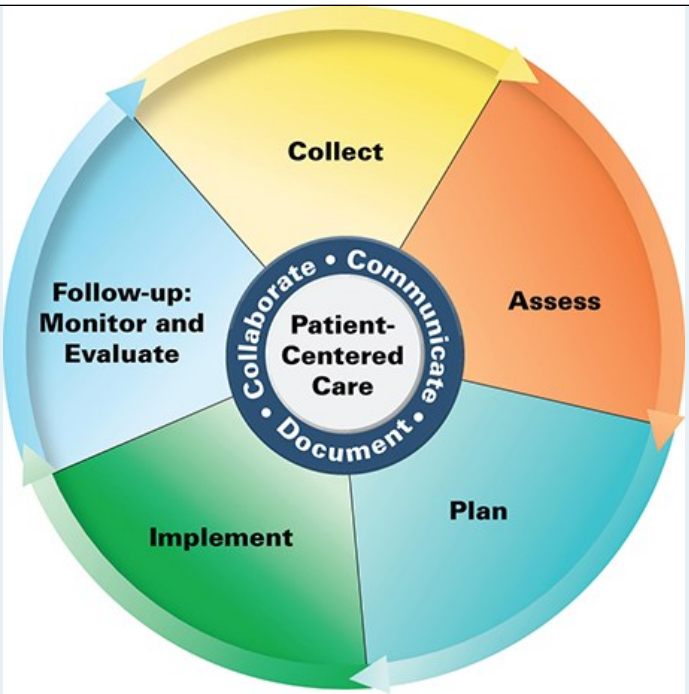
1. The goal of pharmacotherapy is seizure freedom with minimal adverse effects. Between 60% and 80% of patients can achieve this.
2. Accurate classification and diagnosis of seizure type/epilepsy syndrome, including where seizures begin, is critical to selection of appropriate pharmacotherapy.
3. Besides seizure type, antiseizure medication (ASM) selection depends on patient characteristics such as age, sex, ethnicity, susceptibility to adverse medication effects, comorbid conditions, ability to adhere with the prescribed regimen, presence or absence of insurance coverage, and need for therapeutic levels to be reached quickly.
4. Pharmacotherapy for epilepsy is highly individualized and requires dose titration to optimize therapy (maximal seizure control with minimal or no adverse medication effects).
5. If the therapeutic goal is not achieved with monotherapy, a second ASM, preferably with a different mechanism of action, can be added. The patient's ASM can also be switched to an alternative single agent.
6. Patients who do not respond to pharmacotherapy should be referred to a comprehensive epilepsy center to determine if nonpharmacologic treatments such as surgery are potential options.
7. In general, first-generation ASMs are very efficacious but have complex pharmacokinetics, multiple medication interactions, and an increased incidence of adverse effects, which make them more complicated to manage than either the second- or third-generation ASMs.
8. Second-generation ASMs have unique mechanisms of action and are as efficacious as first- and third-generation ASMs with better tolerability. They are generally considered first-line epilepsy pharmacotherapy.
9. Third-generation ASMs should be reserved for failure of other agents due to cost and limited long-term experience.
10. 20% to 35% of patients will have unsatisfactory control with ASMs and will be considered to be treatment-resistant.

PATIENT CARE PROCESS

Patient Care Process for Epilepsy



Collect

- Patient-specific demographics (eg, age, race, sex, pregnancy status, and desire for pregnancy)
- A detailed description of seizure semiology from the patient and a witness of the seizure, including the following:
  - Degree of mental status impairment during the event
  - Presence of ictal motor, sensory, autonomic, or other features at onset of the seizure (Fig. 75-1)
  - Tongue biting, cheek biting, and bladder or bowel incontinence during the seizures
  - Seizure time course and any postictal phenomena (eg, fatigue, headaches, confusion, and psychosis)
- Frequency of seizure events and any precipitating factors
- Information on comorbid medical psychiatric, and neurodevelopmental conditions including depression, anxiety, and learning and development conditions
- Family history of epilepsy, risk factors for epilepsy including injury at birth, history of meningitis or encephalitis, history of traumatic brain injury
- Current and past medications including antiseizure medications (ASMs)
- Duration of past ASM therapy and response to each ASM (eg, decrease or increase in seizure frequency and adverse medication reactions experienced)
- Allergies to medications including ASMs
- Laboratory values for electrolytes and glucose to rule out provoked seizures, baseline test for renal function, liver function, and complete blood count (CBC)
- Magnetic resonance imaging (MRI) of brain without contrast

- Electroencephalogram (EEG)

Assess

- Seizure, epilepsy, and epilepsy syndrome classification (Figs. 75-1 and 75-2)
- Duration of therapy on current ASM regimen
- Seizure freedom on current ASMs or current seizure frequency if not seizure-free (Fig. 75-3)
- Adverse medication reactions experienced on current ASMs (Fig. 75-3)
- Factors for optimal ASM selection including patient-specific factors (Table 75-1)
- Other quality-of-life factors

Plan*

- Determine need for monotherapy (usually at initiation of therapy) or polytherapy (usually after failure of first or second ASM) (Fig. 75-3)
- Select an ASM that has efficacy for the specific seizure type, epilepsy, or epilepsy syndrome (Table 75-5)
- Considering patient-specific factors, select an ASM with:
  - Most tolerable adverse medication reaction profile (Table 75-5)
  - Least incidence of interactions with other medications (Tables 75-3 and 75-5)
  - Least complicated ASM pharmacokinetics (Table 75-2)
  - Utility in treating the patients' other comorbid conditions (Table 75-5)
- Create a patient-specific monitoring plan based on the therapy chosen

Implement*

- Identify initial dose and maintenance dose (Table 75-4) along with appropriate formulation (Table 75-5) and dosage size (eg, 25 mg tablets, 100 mg capsules, 250 mg/5 mL oral solution, 1,500 mg/100 mL of diluted solution for intravenous injection) to meet the patients' needs
- Counsel patient on dose, dose formulation, and how to titrate appropriately
- Provide patient with seizure and adverse medication reaction diary and counsel patient and family on how to record in the diary
- Ensure completion of prior authorizations for insurance coverage as needed
- Ensure prescription is provided on appropriate controlled substance prescription form as needed for any scheduled preparations (Table 75-5)

Follow-up: Monitor and Evaluate

- Treatment response including increase or decrease in seizure frequency and changes in seizure semiology
- Laboratory assessments including CBC, chemistries, liver function tests, and ASM serum concentrations if needed
- Monitor for common dose-related, rare idiosyncratic, and long-term adverse medication reactions
- Monitor for other comorbid conditions such as depression, anxiety, suicidal ideation, and social adjustment
- Monitor for learning and development issues in children

- Monitor seizure triggers
- Monitor adherence

Collaborate with patient, caregivers, and other healthcare professionals.

BEYOND THE BOOK

BEYOND THE BOOK

Use the following webpage (Epipick.org) to help identify the possible epilepsy types. This resource will also help you select appropriate medications for your patient based on patient-specific characteristics and comorbidities.

Use the following link (https://www.ilae.org) to get acquainted with the International League Against Epilepsy (ILAE), a world association of health professionals and scientists working together to understand, diagnose, and treat patients with epilepsy. Of particular interest may be the section on education which provides links to infographics and videos as well as the section on guidelines, which provides current practice guidelines, reports, and position papers.

INTRODUCTION

Epilepsy is a common neurologic condition in which a person is prone to recurrent epileptic seizures. There are many types of epilepsies characterized by different seizure types, ranging in severity and etiologies. While the specific pathophysiologic mechanisms behind different epilepsies are complex, the general pathophysiologic process underlying all epilepsies is disturbed regulation of electrical activity in the brain resulting in synchronized and excessive neuronal discharge.

Beyond seizures, people with epilepsy face many challenges, including increased risk of neurodevelopmental delay, cognitive impairment, comorbid depression, and anxiety. Furthermore, patients with epilepsy may face educational and vocational challenges, have difficulties with independent living, and be victims of stigma and common public misunderstanding. The International League Against Epilepsy (ILAE) defines epilepsy not only as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures" but also by "the neurobiologic, cognitive, psychological, and social consequences of this condition."[1] Clinicians treating epilepsy must address these common psychosocial issues and comorbidities. Pharmacotherapy should be selected not only to reduce the frequency of seizures as much as possible, but also to minimize adverse medication reactions, address coexisting health and social conditions, and enhance overall quality-of-life (QOL) for patients.

EPIDEMIOLOGY

Epilepsy is the fourth most common neurologic disorder globally and in the United States; only following stroke, migraine, and Alzheimer's disease. In the United States, approximately 3.4 million people suffer from epilepsy with a prevalence of 1.2%. While epilepsy is a chronic disease that can present at all ages, the highest number of new epilepsy cases (incidence) will occur in childhood and the older adult population. Among children, epilepsy has the highest incidence in children under 5 years of age with most new cases occurring under 2 years of age. In older populations, the high frequency of epilepsy is now garnering attention as 1.5% of people older than 65 are affected by epilepsy in the United States.[2,3]

The majority of patients with epilepsy has a good prognosis and will be able to attain seizure freedom. However, the mortality rate of patients with epilepsy is two to three times that of the general population and life expectancy may be reduced.[4] Increased mortality has been attributed to a wide variety of causes including sudden unexplained death in epilepsy (SUDEP).[5] While the exact mechanisms underlying SUDEP are unclear, recent research suggests there may be a cardio-respiratory mechanism involved.[5] Although it is rare in patients with well-controlled epilepsy, SUDEP accounts for up to 15% of all epilepsy-related deaths, with a lifetime risk of 4.6% to 8%.[5]

All individuals with epilepsy experience seizures; however, not all individuals who experience seizures will be diagnosed with epilepsy. Some seizures

are provoked and occur as a result of systemic, toxic, or metabolic insults such as substance use; alcohol, barbiturate, or benzodiazepine withdrawal; or acute neurologic (eg, brain hemorrhage) or systemic illnesses (eg, hypocalcemia, hypoglycemia, uremia, and eclampsia). Furthermore, some patients will have seizures only associated with fever (eg, febrile seizures). In all of these situations, seizure occurrence does not generally constitute epilepsy, but rather are a symptom of the provoking insult. Once the provoking insult is removed or treated, there is not "an enduring predisposition to generate epileptic seizures." Each year, 120 per 100,000 people in the United States will be evaluated for a newly recognized seizure (provoked or unprovoked), but only 40 to 70 cases per 100,000 will be diagnosed with epilepsy. At least 10% of the general population will have at least one seizure from *any* cause in their lifetime.[2,3]

ETIOLOGY

Hundreds of medical conditions can cause epilepsy, ranging from genetic predisposition to acquired injury (eg, stroke or traumatic brain injury). The most common causes vary depending on the population of interest. For instance, childhood-onset epilepsy is predominantly caused by genetic and/or developmental structural abnormalities, while epilepsy with an onset at older age is most often caused by acquired structural injury (eg, stroke or traumatic brain injury). Therefore, epilepsy etiologies can be generally classified into six categories reviewed here: (1) genetic; (2) structural; (3) infectious; (4) metabolic; (5) immune; and (6) unknown.[6] It is important to note that these categories are not mutually exclusive.

Genetic Etiology

Epilepsies with genetic etiology usually present in infancy or childhood with examples being (1) Dravet syndrome associated with mutations in sodium channel, voltage-gated, type I alpha subunit (SCN1A), (2) childhood absence epilepsy (CAE) associated with many different mutations in T-type Ca^{2+} channels and GABA-receptor subunits, and (3) Juvenile Myoclonic Epilepsy (JME) associated with many different mutations including those in the EF-hand containing protein-1 (EFHC1) and intestinal cell kinase (ICK).[7–11] Prior to 2010, genetic epilepsies were labeled as primary generalized epilepsy or idiopathic generalized epilepsy (IGE), as no clear structural brain abnormalities were found to be responsible for the epilepsy.[6] However, as most of these disorders have abnormalities at the molecular level they are now also called genetic generalized epilepsies.[6] Genetic etiologies usually pass from generation to generation but can also arise from sporadic mutations, and cannot be acquired after birth.

Structural Etiology

Structural etiologies refer to abnormalities visible on structural neuroimaging, and are either acquired or of genetic origin.[6] Common epilepsies caused by structural abnormalities include cortical dysplasia, mesial temporal lobe epilepsy, and posttraumatic epilepsy. In general, cortical dysplasia is a common cause of childhood onset medication-resistant epilepsy and is a result of disruptions in neuronal migration, proliferation, and differentiation during brain development, leading to disorganization of the normal structure of the cerebral cortex in certain brain areas. In general, mesial temporal lobe epilepsy is a common type of adult-onset epilepsy responsible for many of the medication-resistant epilepsies seen in tertiary care epilepsy clinics. In this structural form of epilepsy, sclerosis occurs in the hippocampus, the main structure of the mesial temporal lobe, and is characterized by glial scarring, reduced hippocampal volume as seen on magnetic resonance imaging (MRI), and decreased cellular density as seen on biopsy.[12] In contrast, traumatic brain injury epilepsy results from blunt force injury or stroke that causes structural lesions in the brain.[6]

Infectious Etiology

Infections are the most common epilepsy etiology worldwide[6] and typically occurs when a patient develops epilepsy as the sequelae of an infection, not when a patient experiences seizures in the setting of acute infection such as meningitis or encephalitis. In developing countries, the most common acquired infectious epilepsy is from neurocysticercosis, a parasitic infection of the brain that results from ingestion of pork tapeworm eggs, causing subsequent structural injury that promotes the development of epilepsy.[6]

Metabolic, Immune, and Unknown Etiology

Both the metabolic and immune etiologies of epilepsy are less common, although they are increasingly being recognized and understood.[6] An interesting metabolic etiology is Lafora disease, which is associated with abnormal glycogen metabolism and subsequent development of insoluble glycogen inclusion bodies resulting in epilepsy.[13] Immune epilepsies include anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis which

causes autoimmune-mediated central nervous system (CNS) inflammation and resulting epilepsy.[6] While both of these etiologies carry specific treatment implications, treatment implications are evolving. Patients can also present with unprovoked seizures that do not have an identifiable cause, and thus by definition have epilepsy of unknown cause.[6] While standard epilepsy workup procedures need to be followed, it is possible that these epilepsies may be due to an as-yet-unidentified gene or may be the consequence of an as-yet-unrecognized-structural or metabolic disorder.

Risk Factors and Seizure Triggers

While certain risk factors may suggest a predisposition to epilepsy, they are not necessarily causative, as known epilepsy risk factors include premature birth with small gestational weight, perinatal injury (eg, anoxia), history of alcohol withdrawal seizures, history of febrile seizures, and family history of seizures.[14] While the presence of such risk factors aid in establishing the diagnosis of epilepsy and may help in identifying the underlying epilepsy etiology, they may not explain the mechanistic cause of seizures.

Many factors trigger seizures in susceptible individuals, with two of the best known seizure triggers being hyperventilation and photostimulation (eg, flashing lights or rapidly changing or alternating images) in certain genetic epilepsies including juvenile myoclonic epilepsy and childhood absence epilepsy. Additional triggers include physical and emotional stress, sleep deprivation, sensory stimuli, and hormonal changes occurring around the time of menses, puberty, or pregnancy, as all of these have been associated with the onset of or an increased frequency of seizures. Lastly, medications such as theophylline, high-dose phenothiazines, antidepressants (especially bupropion), alcohol, and substance use have all been associated with lowering seizure threshold and provoking seizures in patients with epilepsy.[15]

PATHOPHYSIOLOGY

The underlying general pathophysiologic process for all epilepsies is neuronal hyperexcitability and hypersynchronization. Initially during a seizure, a small number of hyperexcitable neurons fire abnormally in synchrony resulting in breakdown of normal membrane conductances and inhibitory synaptic currents. This allows the excess excitability to spread, either locally to produce a focal seizure, or the seizure is propagated by physiologic pathways and networks to involve more remote areas, or more widely to produce a generalized seizure.[16]

In general, neuronal hyperexcitability occurs because there is an enhanced predisposition of a neuron to depolarize and discharge when stimulated. While this may occur as the result of multiple mechanisms, alterations in the number, type, and biophysical properties of voltage- or ligand-gated K^+, Na^+, Ca^{2+}, and Cl^- ion channels in neuronal membranes are thought to play a significant role.[17] In fact, many of the available antiseizure medications (ASMs) have mechanisms of actions that act on these specific ion channels, highlighting the importance of these channels in promoting hyperexcitability. Carbamazepine and phenytoin reduce neuronal excitability by binding sodium channels in their inactive state and slowing channel recovery from inactivation, thereby preventing hyperexcitable neurons from rapidly and repetitively firing; this also blocks firing in a use-dependent fashion.[18,19] Benzodiazepines, in contrast, bind to the gamma subunit of the $GABA_A$ receptor leading to an increase in chloride ion conductance and inhibition of action potentials.[20] Mutations within these ion channels have been associated with multiple different epilepsies.[11] While the exact nature of these alterations has not been fully elucidated, these genetic alterations may result in differences between the various genetic epilepsies.

Other mechanisms of epileptogenesis, which may play roles in hyperexcitability, are related to alterations in vesicle trafficking and neurotransmitter release. For instance, synaptic vesicle protein 2A ($SV2_A$), a protein responsible for the fusion of vesicles to the membrane, is upregulated in certain models of epilepsy, and is the target of the second- and third-generation ASMs, levetiracetam and brivaracetam, respectively.[21] Alterations in neurotransmitter uptake and metabolism may also play a role in the pathogenesis of epilepsy.[22] An example of this comes from vigabatrin, which is an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T).[23] As this enzyme is responsible for the metabolism of the inhibitory neurotransmitter GABA, this medication is thought to increase GABA through GABA-T inhibition.[23]

Additionally, there are many other possible hyperexcitability promoting mechanisms that may be important in the pathophysiology of epilepsy, including possible biochemical modifications of receptors, modulation of second messaging systems and gene expression, and changes in extracellular ion concentrations.[22] Hyperexcitability that results in increased firing of random individual neurons does not result in epileptic seizures, as synchronization of excessive neuronal firing is required.[24] The intrinsic organization of local circuits of certain cerebral structures including the hippocampus, the neocortex, and the thalamus contributes to synchronization and promotes generation of epileptiform activity. That is why many

epileptic networks originate in these specific brain regions.[24,25] Modifications in the ratio and function of inhibitory circuits in these structures play an important role in promoting epileptogenesis, as a large number of these neurons are interconnected and can become simultaneously inhibited, and then synchronously excited. Although under normal circumstances, these neurons are asynchronous, it is believed that under abnormal circumstances, they become synchronous and act as pacemakers promoting epileptiform activity. Sprouting and reorganization of neuronal projections in abnormal tissue or after neuronal injury (eg, head trauma or stroke) may also lead to increased connectivity between neurons and a chronic susceptibility to seizures.[24] Therefore, both excitation and inhibitory connections lie at the heart of the pathophysiologic mechanisms behind epileptogenicity.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Epilepsy

Focal Aware Seizures

- Patients retain awareness of themselves and their environment including external stimuli.

Focal Impaired Awareness Seizure

- Patient has impaired awareness at any time during the seizure
- May be able to respond to questions during the seizure, but inappropriate response
- May not recall actions after event

Motor signs

- Automatisms: automatic behaviors like lip smacking, chewing, picking at clothing
- Atonic: loss of tone, going limp
- Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg
- Spasm: trunk flexion
- Hyperkinetic: thrashing/pedaling
- Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg
- Tonic: extension or flexion postures

Nonmotor signs

- Autonomic: flushing, sweating, piloerection, salivation, pallor
- Behavior arrest: pausing, freezing, activity arrest
- Cognitive: language problems, thinking problems, memory phenomenon, and feelings of familiarity (déjà vu) or unfamiliarity (jamais vu)
- Emotion: feelings of fear, depression, joy, anger, extreme aberration of behavior
- Sensory: numbness, tingling, sounds (ringing/buzzing), smells, tastes, visions (hallucinations), vertigo

Focal to Bilateral Tonic–Clonic

- Focal seizure with impaired awareness which progresses to bilateral convulsive features such as with tonic–clonic motor features

Generalized Onset

- Impaired awareness

Motor signs (more common symptoms described below only)

- Tonic–clonic: sudden sharp tonic stiffening of muscles with a subsequent period of clonic movements such as rhythmic jerking of arms and legs (previously called "grand mal")
- Clonic: rhythmic jerking or twitching of arm, shoulder, face, or leg
- Myoclonic: arrhythmic jerking of arm, shoulder, face, or leg
- Atonic: loss of tone, going limp
- Epileptic spasms: trunk flexion

Nonmotor/absence (more common symptoms described below only)

- Typical: sudden arrest of behavior, blank stare with brief upward rotation of the eyes lasting 2 to 30 seconds
- Eyelid myoclonia: lid jerks

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[3] They can manifest physically in a variety of ways and can range from intense involuntary repetitive muscular contractions (eg, convulsions) to subtle alterations in sensation or consciousness. The new basic seizure classification is based on three key features: (1) where in the brain the seizure originates; (2) the individual's level of awareness during a seizure; and (3) other seizure features.[26]

1 Seizures can be classified into an initial three categories depending on how they begin in the brain (eg, onset): (1) focal seizures (previously called partial seizures) that start in a network of cells on one side of the brain; (2) generalized seizures (previously called primary generalized) that start in a bilaterally distributed network (eg, a network encompassing both sides of the brain); and (3) unknown onset which can later be recategorized when it becomes clear how seizures begin in a particular individual's brain.[26] Understanding seizure onset is important, as it has significant treatment and prognostic implications affecting choice of seizure medication and eligibility for epilepsy surgery. Examples of this include patients with generalized-onset seizures who may have a seizure exacerbation when treated with certain ASMs (eg, treating childhood absence epilepsy with carbamazepine)[27] or patients with medication-resistant focal-onset seizures who may be good candidates for surgical resection, while those with generalized-onset seizures are not.

Focal Seizures

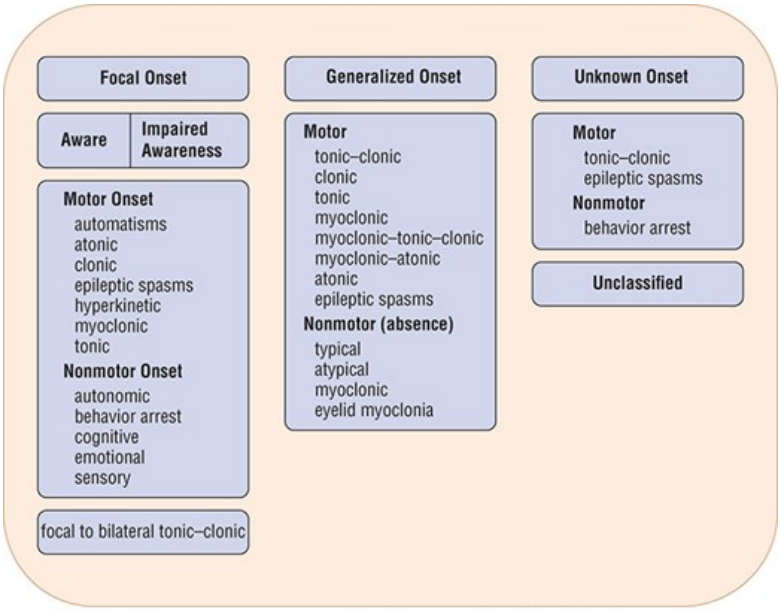
In general, focal seizures may be characterized by whether the patient retains awareness of themselves and their environment including external stimuli (eg, being asked questions) during the seizure, even if immobile and unable to talk or respond. When awareness is retained the seizure is termed a "focal aware seizure" corresponding to what has historically been termed "simple partial seizure." A focal impaired awareness seizure corresponds to the prior term "complex partial seizure" and is an appropriate classification if the person has impaired awareness at any time during the seizure (eg, they are aware in the beginning but lose awareness at the end, or if they have a vague idea of what is occurring and know that someone is speaking to them but respond inappropriately).[26]

Focal seizures can be further subgrouped by earliest most prominent motor sign (eg, automatisms, clonic, myoclonic) or nonmotor sign (eg, autonomic or sensory symptoms) at seizure onset. If motor signs are present, then some type of movement will occur during the seizure such as twitching and jerking (eg, myoclonus), stiffening (tonic contraction), or automatic movements (automatisms) such as smacking lips, rubbing hands, and picking at clothes. Nonmotor signs include changes in sensation, emotions, thinking, or experience. The symptoms felt by the individual at the very beginning of a seizure is sometimes called an aura, although this term is now discouraged. Motor or nonmotor symptoms that may appear at onset are

listed in Fig. 75-1.[26]

FIGURE 75-1

ILAE 2017 Classification of seizure types—expanded version. (*Reprinted, with permission, from 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(4):522–530.*)



Focal seizures may propagate beyond one brain hemisphere to also involve the contralateral hemisphere. This seizure type is called "focal to bilateral tonic–clonic" and is a special seizure type which previously was called "partial onset with secondary generalization" or "secondarily generalized tonic–clonic (GTC) seizure." The term "to bilateral" is preferred to distinguish this focal-onset seizure from a generalized-onset seizure. During this type of seizure, the person usually becomes unconscious and displays bilateral convulsive features such as tonic–clonic motor features.[26,28]

Focal aware seizures may manifest clinically in a variety of ways and can vary depending on where the abnormal firing occurs. For example, seizures manifesting as abnormal movements such as clonic movements (eg, twitching or jerking) of the arm, shoulder, face, or leg indicate seizure activity in motor pathways. Feelings of numbness or tingling indicate sensory or somatosensory involvement and may indicate parietal lobe involvement. Sensory symptoms can also include feelings of fear, depression, joy, anger, or memory phenomena such as feelings of familiarity (déjà vu) or unfamiliarity (jamais vu) that may indicate temporal lobe seizure activity. Visual disturbances or hallucinations may indicate seizure activity involving the occipital lobe, while ringing or buzzing sounds in the ears may indicate seizure activity in auditory areas of the brain. Autonomic symptoms such as sweating, salivation, or pallor indicate seizure activity in autonomic areas of the brain.[28,29]

Focal impaired awareness seizures may manifest with any of the signs and symptoms described for focal aware seizures except that the patient does not retain awareness. They may still be able to perform routine tasks such as walking, but such movements are not purposeful or planned and after the event is over they may not recall their actions. The patient may be able to respond to questions during the seizure, although they may not respond appropriately. The degree of alteration in awareness and responsiveness may be so subtle that witnesses may not recognize that anything is overtly wrong. For example, they may simply display behavioral arrest and stare off into space for a minute. They may also display subtle automatisms such as lip smacking, chewing, or picking at their clothing without purpose. On the other hand, some patients may display extreme aberrations of behavior, and some are even mistakenly diagnosed as having psychotic episodes. After the seizure (postictal period), the patient may display altered consciousness, drowsiness, confusion, or even paranoia for a variable period of time and frequently go into a deep sleep.[28,29]

Generalized-Onset Seizures

Generalized-onset seizures start in a network that is bilaterally distributed to both brain hemispheres and have previously been referred to as primary generalized seizures. These types of seizures involve impaired awareness and are divided into motor and nonmotor (eg, absence) seizures. Generalized "absence" seizures are not synonymous with an "absent stare" which typically accompanies the behavioral arrest that occurs in other seizure types.[26]

Generalized-onset seizures can have a variety of motor symptoms with the major motor category being tonic–clonic. These generalized-onset tonic–clonic seizures were previously called "grand mal" seizures. During these seizures the patient experiences loss of consciousness, followed by a sudden sharp tonic contraction (stiffening) of muscles with a subsequent period of rigidity and clonic movements, oftentimes described as jerking of the arms and legs. During the seizure, the patient may cry or moan, due to muscles in the larynx being activated or they may lose sphincter control with bladder and/or bowel incontinence or bite their tongue. Postictally, after consciousness is regained, the patient may experience confusion, drowsiness, lack of coordination, soreness throughout the body, and amnesia for the event.[28,29]

It is important to remember that bilateral tonic–clonic seizures can also result from focal propagation to contralateral hemispheres and that these seizures must be differentiated from generalized-onset tonic–clonic seizures. Generalized manifestations of seizures can be asymmetrical or symmetrical, rendering the distinction from focal-onset seizures difficult, but certain distinguishing features such as very early motor or nonmotor signs that may be characteristic of focal-onset seizures, and characteristic findings on EEG aid in distinguishing between the two. Other forms of generalized motor seizures may happen but the generalized tonic–clonic (GTC) seizure is most common and most distinct.[6,28]

In contrast to other motor seizure categories in which there is a sudden onset of increased tone, a sudden loss of muscle tone occurs in *atonic seizures*. Atonic seizures are not preceded by myoclonic or tonic features and can be very brief. They may present as a head drop, the dropping of a limb, or a slumping to the ground (due to loss of postural tone). These patients often wear protective headware to prevent trauma and atonic seizures are one hallmark of Lennox–Gastaut syndrome.[6,28]

Typical generalized nonmotor seizures, aka "absence" seizures, can manifest as typical absence seizures, atypical absence, absence seizures with myoclonia, or absence seizures with eyelid myoclonia. Most commonly, typical absence seizures manifest as a sudden onset interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes indicating the abrupt onset and offset of impaired consciousness. The staring and behavioral arrest lasts 2 to 30 seconds during which time the patient is unaware of the environment and unresponsive. The patient has neither a warning that the seizure is going to occur, nor does the patient have postictal confusion or lethargy after the seizures. After cessation of the seizure, the patient will often return to the previous activity as if nothing had happened. These absence seizures generally occur in young children through adolescence. It is important to differentiate these seizures from focal unaware seizures; in general, absence-type seizures are much briefer than the staring spells associated with focal unaware seizures and have minimal postictal manifestations.[6,28,29]

Seizures of Unknown Onset

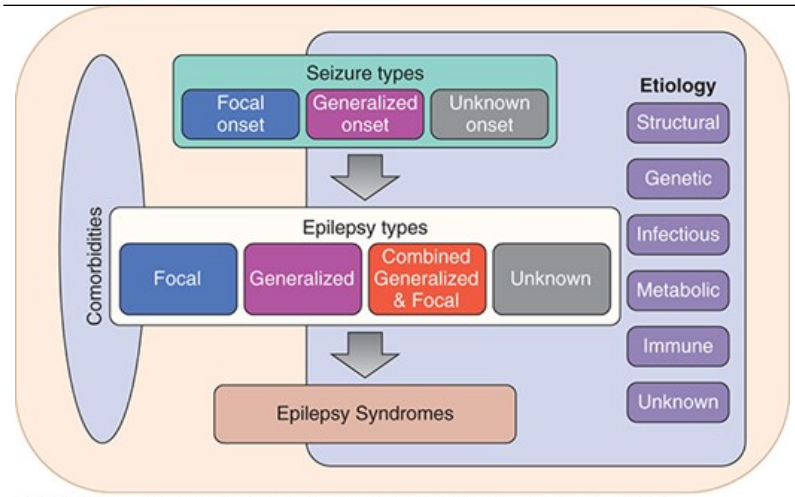
Seizures of unknown onset are classified based on presence of motor or nonmotor features; however, in some cases it may be impossible to classify a seizure at all. Although this should be a rare occurrence, in such cases this seizure would be an unclassified seizure.[26]

Classification of Epilepsies and Epilepsy Syndromes

A seizure is only a symptom that occurs within epilepsy; therefore, seizure classification is distinct from but related to the classification of epilepsies and epilepsy syndromes. The starting point of epilepsy classification is identification of the seizure type, understanding that some patients may have multiple different seizure types. After seizure types are determined, the epilepsy should be classified into one of four categories: (1) focal epilepsy in which a patient only has focal-onset seizures; (2) generalized epilepsy in which a patient displays evidence of only generalized-onset seizures; (3) combined generalized and focal epilepsy; and (4) unknown in which the epilepsy type is unknown (see Fig. 75-2).[6]

FIGURE 75-2

ILAE framework for classification of the epilepsies. *(Reprinted, with permission, from Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–521.)*



After establishing the epilepsy type, an epilepsy syndrome should be determined if possible. In general, while knowing the etiology and specific comorbid characteristics of a patient with epilepsy is important during seizure and epilepsy classification, these parameters can be unknown and are not necessary. However, when determining epilepsy syndromes (the most specific level of epilepsy classification possible), knowing definitive etiology and specific comorbid characteristics is critical (see Fig. 75-2). Epilepsy syndromes are characterized by a known etiology and by a cluster of signs and symptoms including distinctive comorbidities such as intellectual and psychiatric dysfunction that customarily occur together. Other signs and symptoms include type of seizure, specific electroencephalogram (EEG) findings, specific imaging features, anatomy, precipitating factors, age of onset, severity, chronicity, and diurnal and circadian cycling.[6] Common epilepsy syndromes include childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and juvenile myoclonic epilepsy (JME).[6] They are often grouped together and called the idiopathic generalized epilepsies (IGEs) or the genetic generalized epilepsies (GGEs). Other well-recognized syndromes are West syndrome, Lennox–Gastaut syndrome (LGS), and Dravet syndrome.[6]

Diagnosis

Epilepsy is a clinical diagnosis, meaning that it is made on the basis of medical signs and patient-reported symptoms, rather than any one diagnostic test. A person is considered to have epilepsy if they meet any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome.[30]

Accurate diagnosis also depends on the neurologic examination and diagnostic techniques such as EEG and brain imaging. The neurologic examination is generally nonfocal, and focal findings may suggest a nonepilepsy diagnosis or help identify an epilepsy etiology (eg, stroke). The EEG can identify abnormal brain wave patterns that are associated with certain seizure types and epilepsy syndromes and is one of the most common and important diagnostic tests that can be performed for a patient with epilepsy. However, an abnormal epileptiform EEG is found in only approximately 50% of the patients who have epilepsy and sometimes several EEGs must be obtained before convincing epileptiformver activity is detected. Video EEG is the gold standard for diagnosing epilepsy and involves hospital admission to facilitate recording video and continuous EEG monitoring until the patient has a typical event. However, this is not the standard for most patients and is generally reserved for cases unresponsive to medication or difficult to characterize.[31,32]

Brain imaging with either a computed tomography scan (CT) or MRI can detect structural lesions that aid in the diagnosis of seizures and epilepsy types. A CT is commonly performed in patients who present after their first seizure, as a way to evaluate for a brain tumor, cerebral bleeding, or gross anatomical injury. An MRI is preferred for validation of an epilepsy diagnosis as it is the preferred imaging technique to identify more subtle structural abnormalities (eg, sclerosis in the mesial temporal lobes and traumatic brain injury).[32]

There are no diagnostic laboratory tests for epilepsy; however, in some cases, particularly following generalized convulsive seizures, serum prolactin levels obtained within 10 to 20 minutes can be transiently elevated.[33] Other laboratory tests can be done to rule out treatable causes of seizures (eg,

hypoglycemia, altered electrolyte concentrations, infections) that do not represent epilepsy.

TREATMENT

Desired Outcomes

1 ASM therapy is the mainstay of epilepsy treatment; however, all available ASMs are symptomatic treatments which only prevent seizures from occurring. None have been proven to have any disease modifying or antiepileptogenic properties and no ASMs are curative. Surgery is the only possibly curative therapy and only a select number of patients qualify for surgery (see section "Nonpharmacologic Therapy"). Therefore, the majority of patients with epilepsy will be on life-long ASM therapy. The goal of ASM therapy is eliminating the occurrence of seizures within the shortest possible duration of time and with minimal impact on QOL. In most patients the desired outcome is complete seizure freedom with little to no medication adverse effects. However, in 20% to 35% of patients, complete seizure freedom may not be possible[34] and more obtainable goals that balance seizure control with patient-specific QOL factors and wishes (eg, decrease in the number of seizures with minimized adverse effects) should be established.

General Approach to Treatment

When a patient presents after a single isolated seizure, one of three treatment decisions can be made: (1) treat, (2) possibly treat, or (3) do not treat, with the ultimate decision being based on the probability of the patient having a second seizure. The probability of recurrent seizures is higher if certain findings are present, including brain imaging abnormalities (eg, stroke, trauma, CNS infection, cerebral palsy, and other cognitive developmental disabilities), EEG with epileptiform abnormalities (characterized by spikes or sharp waves), or a nocturnal seizure.[35] For patients with any of the above findings present, the probability of seizure recurrence may be 2 to 2.5 times that of those without those findings.[35] The decision on whether to start ASM therapy after a single seizure depends on clinician judgment and available clinical evidence. Some clinicians choose to start ASM treatment after one seizure with a definite abnormal MRI or epileptiform EEG while others do not initiate treatment until a second seizure has occurred. In general, patients who have had two or more unprovoked seizures should be started on ASMs.[30,35]

2 Once the decision to initiate therapy has been determined, accurate identification of seizure type and epilepsy diagnosis is critical for treatment, as an ASM must be effective for the specific seizure type and epilepsy, or epilepsy syndrome, being treated. For instance, if a patient is diagnosed with the epilepsy syndrome, childhood absence epilepsy (CAE), then an ASM that is effective for that syndrome (eg, ethosuximide) should be selected, and an ASM that may exacerbate that syndrome (eg, phenytoin or carbamazepine) should be avoided. Only after an accurate diagnosis is obtained, can a care plan, including selection and/or optimization of ASM therapy, be developed.[27]

3 During ASM selection, several possible first-choice agents are identified based on the type of epilepsy, and then narrowed down to an ideal single medication based on patient-specific characteristics including age, sex, susceptibility to adverse effects, comorbid medical conditions, interactions with other medications, ability to adhere to a prescribed regimen, and cost of therapy/insurance coverage (Table 75-1). Patient-specific characteristics must be taken into consideration as individuals may be better suited to receive one ASM over another. For instance, children may be more susceptible to neuropsychiatric adverse effects and ASMs with those effects should be avoided. Females with childbearing potential should not be on ASMs with unacceptable teratogenicity, and ASMs with adverse cognitive effects should be avoided in older adults as they may be more susceptible. On the other hand, patients with comorbid conditions, such as migraine headache, bipolar disorder, or neuropathy, may benefit from the use of particular ASMs that can also treat those comorbid conditions (eg, topiramate for the treatment of epilepsy and migraine, lamotrigine for the treatment of epilepsy and bipolar, pregabalin for the treatment of epilepsy and neuropathy).

TABLE 75-1

Factors to Consider When Making ASM Selection

1. ASM efficacy for the specific seizure type, epilepsy, or epilepsy syndrome
2. Selection of an ASM that can also treat the patient's other comorbid conditions
3. Selection of an ASM with the most tolerable adverse effect profile, considering patient-specific factors including age and sex
4. Interactions with other medications
5. Ability to adhere to a prescribed regimen (eg, three or four times daily dosing) and insurance coverage, as this can affect ASM adherence and effectiveness
6. Need to quickly reach therapeutic levels

Pharmacokinetic interactions are a common complicating factor in ASM selection and an appreciation of pharmacokinetic variability is necessary when selecting therapy (Table 75-2). In general, ASM interactions can occur in any of the pharmacokinetic processes (eg, absorption, distribution, metabolism, or elimination); however, their effects on metabolic pathways are particularly complex and significantly affect management. Knowledge of ASM metabolic pathways as well as induction or inhibitory effects on liver enzymes (Table 75-3) can aid in ASM optimization. Caution should be used when ASMs are added to or withdrawn from a drug regimen.

TABLE 75-2

Antiseizure Medication Pharmacokinetic Data

ASM	$t_{1/2}$ (Hours)	Time to Steady State (Days)	Unchanged (%)	V_D (L/kg)	Clinically Important Metabolite	Protein Binding (%)
First Generation						
Carbamazepine	12-17	21-35 for completion of autoinduction	3	0.8-2	10,11-epoxide	76
	34 (10,11-epoxide)					
Clonazepam	30-40	3-10	2	3.2	No	85
Ethosuximide	17-56	7-10	10-20	0.6-0.7	No	22
Phenobarbital	53-180	12-24	25-50	0.5-1	No	50
Phenytoin	22	7-10	unknown	0.5-1	No	90
Primidone	7-22	2-4	<1	0.4-1	Phenylethylmelanomide (PEMA); Phenobarbital (PB)	34
	10-25 (PEMA)					
	75-126 (PB)					
Valproic acid	9-16	2-4	<3	0.14-0.23	No	90
Second Generation						

Felbamate	16-22	3-4	40-50	0.73-0.85	No	25
Gabapentin	5-7	1-2	100	58 L	No	<3
Lamotrigine	12-60	3-15	10	0.9-1.3	No	55
Levetiracetam	6-8	2	66	0.7	No	<10
Oxcarbazepine	2 9 (MHD)	2-3	2	49 L	10-monohydroxy-carbazepine (MHD)	40
Tiagabine	7-9	2	2		No	96
Topiramate	21	4	70	0.6-0.8	No	15-41
Zonisamide	63	14	35	1.45	No	40
Third Generation						
Brivaracetam	9		<10	0.5	No	40
Cenobamate	50-60	14	6.8	40-50 L	No	60
Eslicarbazepine	13-20	4-5	67	0.87	S-licarbazepine; oxcarbazepine	<40
Lacosamide	13	3	40	0.6	No	<15
Perampanel	105	14-21	74-80	77 L	No	96
Pregabalin	6	1-2	90	0.5	No	0
Third Generation Approved for Specific Epilepsy Syndromes						
Cannabadiol	56-61	7	Minor	20,963-42,849 L	7-OH cannabadiol	>94
Clobazam	36-42	7-14	2	100 L	N-desmethylclobazam	80-90
Fenfluramine	20		<25	11.9	norfenfluramine	50
Rufinamide	6-10		<2	50 L	No	34
Stiripentol	4.5-13	Varies	0.1	Related to body weight	No	99
Vigabatrin	5-11		80	1.1	No	0

ASM, antiseizure medication; MHD, monohydroxycarbazepine derivative; PEMA, phenylethylmelanomide; PB, phenobarbital; V_D, volume of distribution.

Data from References 17-20, 23, and 36-56.

TABLE 75-3

Antiseizure Medication Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Medications	Major Hepatic Enzymes	Renal Elimination (%)	Induces	Inhibits
First Generation				
Carbamazepine	CYP3A4	3	CYP1A2; CYP2B6; CYP2C9/19; CYP3A; GT	None
Clonazepam	CYP3A	2	None	None
Ethosuximide	CYP3A4; CYP2E1	10-20	None	None
Phenobarbital	CYP2C9; CYP2C19	25	CYP 3A4/2C9/2C19/1A2; GT	None
Phenytoin	CYP2C9; CYP2C19	unknown	CYP3A; CYP2C; GT	
Primidone		<1		
Valproate	GT; β-oxidation	<3	None	CYP2C9; GT epoxide hydrolase
Second Generation				
Felbamate	CYP3A4; CYP2E1; other	50	CYP3A4	CYP2C19; β-oxidation
Gabapentin	None	Almost completely	None	None
Lamotrigine	GT	10	GT	None
Levetiracetam	None (undergoes nonhepatic hydrolysis)	66	None	None
Oxcarbazepine (MHD is the active metabolite.)	Cytosolic system	<1 (27 as MHD)	CYP3A4; CYP3A5; GT	CYP2C19
Tiagabine	CYP3A4; CYP1A2; CYP2D6; CYP2C19	2	None	None
Topiramate	Not known	70	CYP3A (dose dependent)	CYP2C19
Zonisamide	CYP3A4	35	None	None
Third Generation				
Brivaracetam	CYP2C19	<10	None	CYP2C19 (weak), GT epoxide hydrolase

Cenobamate	UGT2B7/B4; CYP2E1; CYP2A6; CYP2B6; CYP2C19; CYP3A4/5	6.4	CYP2B6; CYP2C8; CYP3A4	CYP 2B6; CYP2C19; CYP3A
Eslicarbazepine	Undergoes hydrolysis	67	GT (mild)	CYP2C19
Lacosamide	CYP2C9/19; CYP3A4	40	None	CYP2C19
Perampanel	CYP3A4/5; CYP1A2; CYP2B6	Undefined	CYP3A4/5; CYP2B6; GT	CYPA3A4/5; CYP2C8; GT
Pregabalin	None	100	None	None
Third Generation with Indications for Specific Epilepsy Syndromes				
Cannabadiol	CYP2C19; CYP3A4; GT	Minor	CYP1A2; CYP2B6; GT	CYP2C8/9/19
Clobazam	CYP3A4; CYP2C19; CYP2B6	2	CYP3A4 (weak)	CYP2C9
Fenfluramine	CYP1A2; CYP2B6; CYP2D6	<25	None	None
Rufinamide	Hydrolysis	2	CYP3A4 (weak)	CYP2E1 (weak)
Stiripentol	CYP1A2; CYP2C19; CYP3A4	0.1	CYP1A2; CYP2B6; CYP3A4	CYP1A2; CYP2B6; CYP3A4; CYP 2C8/19
Vigabatrin	None	Almost completely	CYP2C9	None

CYP, cytochrome P450 isoenzyme system; GT, glucuronyltransferase; MHD, monohydroxy derivative, 10-OH-carbazepine.

Data from References 17-20, 23, and 36-56.

When selecting ASM therapy, a patient's ability to adhere to a prescribed regimen and their insurance coverage are of extreme importance, as these factors can impact outcomes. For instance, a prescribed regimen requiring multiple daily doses may result in nonadherence for a patient who finds it difficult to remember to take medicines leading to decreased seizure control. Switching to an alternative with fewer daily doses may improve outcomes in that case. Similarly, an ASM that is not covered by insurance or is expensive may also promote nonadherence or adversely affect the patient by causing financial hardship. Ultimately, ASM effectiveness results from the interaction of all of these specific factors.

Optimizing Dose

4 Once an ASM has been selected, it should be initiated at an appropriate starting dose, and gradually titrated up to a therapeutic maintenance dose based on individual ASM recommendations (Table 75-4). Titration to an adequate therapeutic dose usually occurs over a few weeks and is necessary to allow the patient to slowly adjust to dose-related adverse effects. Some individuals, such as older adults who are sensitive to falls, sedation, and other neurocognitive adverse effects, need to have lower doses started and titrated more slowly. In such cases, titration can last over many weeks or months and may have a lower goal dose. In patients with multiple recent seizures, a therapeutic dose needs to be reached much more quickly, and a rapid titration over days instead of weeks is appropriate. For such patients, loading doses, either administered orally or intravenously, may be indicated. When used in this manner, it is important to select ASMs that can be administered safely as loading doses, as medications like lamotrigine and carbamazepine require slow titration and should not be used in patients who require loading to reach therapeutic levels quickly (Table 75-4).

TABLE 75-4

Antiseizure Medication Dosing and Target Serum Concentration Ranges

Generic Medication Name (Brand Name)	Initial Total Daily Dose (TTD)	Usual Effective TDD Range	FDA-Recommended Max TDD	Target Serum Concentration Range	Dosing Notes
First Generation					
Carbamazepine (Tegretol, Tegretol XR)	400 mg (>12 yrs) 200 mg (6-12 yrs) 10-20 mg/kg (<6 yrs)	400-1,200 mg (>12 yrs) 200-1,000 mg (6-12 yrs) 10-35 mg/kg (<6 yrs)	1,600 mg (>12 yrs) 1,000 mg (6-12 yrs) 35 mg/kg (<6 yrs)	4-12 mcg/mL (mg/L; 17-51 µmol/L)	Doses higher than FDA-recommended max have been used in clinical practice.
Clonazepam (Klonopin)	Up to 1.5 mg (≥18 yrs) 0.01-0.03 mg/kg (<10 yrs or <30 kg)	1-8 mg (≥18 yrs) 0.01-0.05 mg/kg (<10 yrs or <30 kg)	20 mg (≥18 yrs) 0.05 mg/kg (<10 yrs or <30 kg)	20-70 ng/mL (mcg/L; 63-222 nmol/L)	Initial adult TDD may be up to 1.5 mg/day although lower TDD is typically initiated (eg, 0.5-1 mg/day).
Ethosuximide (Zarontin)	500 mg (≥6 yrs) 250 mg (3-6 yrs)	500-1,500 mg (≥6 yrs) 20 mg/kg (3-6 yrs)	1,500 mg (All ages)	40-100 mcg/mL (mg/L; 283-708 µmol/L)	FDA-recommended maximum TDD is not explicitly identified, but doses ≥1,500 mg should only be used with strict monitoring.
Phenobarbital (Various)	300 mg (≥18 yrs) 5 mg/kg (<18 yrs) (15-20 mg/kg LD)	300-600 mg (≥18 yrs) 4-8 mg/kg (<18 yrs)	600 mg (≥18 yrs) 300 mg (<18 yrs)	10-40 mcg/mL (mg/L; 43-172 µmol/L)	FDA-recommended doses are not available but usual dose ranges and max doses listed here are commonly used in practice.
Phenytoin (Dilantin)	300 mg (≥18 yrs) 5 mg/kg (<18 yrs) (15-20 mg/kg LD)	300-600 mg (≥18 yrs) 4-8 mg/kg (<18 yrs)	600 mg (≥18 yrs) 300 mg (<18 yrs)	Total: 10-20 mcg/mL (mg/L; 40-79 µmol/L) Unbound: 0.5-3 mcg/mL (mg/L; 2-12 µmol/L)	Patients >6 yrs may require the minimum adult TDD of 300 mg; 600 mg is the maximum recommended TDD in adults; however, higher TDD may be used in practice if serum levels are still within therapeutic range.
Primidone (Mysoline)	100-125 mg (≥8 yrs)	750-1,000 mg (≥8 yrs)	2,000 mg (≥8 yrs)	5-10 mcg/mL (mg/L; 23-46 µmol/L)	
Valproic acid, Divalproex, Valproate (Depakene, Depakote DR, Depakote ER, Depacon)	10-15 mg/kg (≥10 yrs)	20-30 mg/kg (≥10 yrs)	60 mg/kg (≥10 yrs)	50-100 mcg/mL (mg/L; 347-693 µmol/L)	

Second Generation					
Felbamate (Felbatol)	1,200 mg (≥14 yrs) 15 mg/kg (2-14 yrs)	1200-3,600 mg (≥14 yrs) 15-45 mg/kg (2-14 yrs)	3,600 mg (≥14 yrs) 45 mg/kg (2-14 yrs)	30-60 mcg/mL (mg/L; 126-252 µmol/L)	Pediatric dosing listed is for LGS.
Gabapentin (Neurontin)	300-900 mg (≥12 yrs) 10-15 mg/kg (3-11 yrs)	900-1,800 mg (≥12 yrs) 25-40 mg/kg (3-11 yrs)	3,600 mg (≥12 yrs) 50 mg/kg (3-11 yrs)	2-20 mcg/mL (mg/L; 12-117 µmol/L)	In patients ≥12 yrs, TDDs up to 3,600 mg/day have been tolerated for short durations; TDDs up to 4,800 mg/day have been described in the literature.
Lamotrigine (Lamictal, Lamictal XR)	25 mg (>12 years) 0.3 mg/kg (2-12 yrs)	225-375 mg (>12 yrs) 4.5-7.5 mg/kg (2-12 yrs)	500 mg (>12 yrs) 300 mg (2-12 yrs)	4-20 mcg/mL (mg/L; 16-78 µmol/L)	Dosing recommendations differ if on VPA, CBZ, PB, PHT, PRM, or VPA; refer to PI for specific dose recommendations for patients on those concomitant ASMs.
Levetiracetam (Keppra, Keppra XR)	1,000 mg (≥16 yrs) 20 mg/kg (6-15 yrs) Varies by age (<6 yrs)	2,000-3,000 mg (≥16 yrs) 20-60 mg/kg (6-15 yrs) Varies by age (<6 yrs)	3,000 mg (≥16 yrs) 60 mg/kg (6-15 yrs) Varies by age (<6 yrs)	12-46 mcg/mL (mg/L; 70-270 µmol/L)	Refer to PI for specific age-based dose recommendations for <6 yrs; XR formulation is only approved for ages ≥12 years; an initial TDD of 500 mg can be used for older patients; FDA-approved maximum doses are listed although higher doses have been used in clinical practice.
Oxcarbazepine (Trileptal, Oxtellar XR)	600 mg (>17 yrs) 8-10 mg/kg-max 600 mg (2-16 yrs)	1,200-2,400 mg (>17 yrs) 900-1,800 mg (2-16 yrs)	2,400 mg (>17 yrs) Varies by age (2-16 yrs)	3-35 mcg/mL (MHD) (mg/L; 12-138 µmol/L)	Pediatric dosing listed varies based on weight, refer to PI for specific weigh-based dose recommendations; XR formulation is approved for ages 6 and older.
Tiagabine (Gabitril)	4 mg if on other ASMs that are inducers and <4 mg if not on inducers (≥12 yrs)	32-56 mg if on other ASMs that are inducers and <32-56 mg if not on inducers (≥12 yrs)	56 mg if on other ASMs that are inducers and <56 mg if not on inducers (≥12 yrs)	0.02-0.2 mcg/mL (mg/L; 0.05-0.5 µmol/L)	Not FDA approved in patients under 12 years
Topiramate (Topamax, Trokendi XR)	25-50 mg (≥10 yrs) 25 mg (2-9 yrs)	200-400 mg (≥ 10 yrs) 150-400 mg based on weight (2-9 yrs)	400 mg (≥10 yrs) Varies based on weight (2-9 yrs)	5-20 mcg/mL (mg/L; 15-59 µmol/L)	Pediatric listed dosing varies based on weight; refer to PI for specific weight-based dose recommendations; XR formulation approved for ages 6 and up; maximum recommended TDD is 400 mg; however, up to 1,600 mg has been described for specific situations (eg, status epilepticus).
Zonisamide (Zonegran)	100 mg (>16 yrs)	200-400 mg (>16 yrs)	600 mg (>16 yrs)	10-40 mcg/mL (mg/L; 47-188 µmol/L)	FDA approved pediatric dosing recommendations not available.
Third Generation					

Brivaracetam (Briviact)	100 mg (≥16 yrs) 50-100 mg if >50 kg or 1-3 mg/kg if <50 kg (1 mo – 15 yrs)	100-200 mg (≥16 yrs) 50-200 mg if >50 kg or 1-6 mg/kg if < 50 kg (1 mo – 15 yrs)	200 mg (≥16 yrs) Varies based on weight (1 mo- 15 yrs)	Not defined	Pediatric dosing listed for patients <50 kg varies based on weight; refer to PI for specific weight-based dose recommendations.
Cenobamate (Xcopri)	12.5 mg (≥18 yrs)	200-400 mg (≥18 yrs)	400 mg (≥18 yrs)	Not defined	Not FDA approved in pediatrics.
Eslicarbazepine (Aptiom)	400 mg (≥18 yrs) 200-400 mg (4-17 yrs)	800-1,600 mg (≥18 yrs) 400-1,200 mg (4-17 yrs)	1,600 mg (≥18 yrs) 1,200 mg (4-17 yrs)	Not defined	Pediatric dosing listed is weight-based; refer to PI for specific weight-based dose recommendations.
Lacosamide (Vimpat)	100-200 mg (>17 yrs) 100 mg if >50 kg and 2 mg/kg if <50 kg (4-17 yrs)	200-400 mg (>17 yrs) 200-400 mg if >50 kg or 4-8 mg/kg if <50 kg (4-17 yrs)	400 mg (>17 yrs) 400 mg if >50 kg or 8 mg/kg if <50 kg (4-17 yrs)	Not defined	Dosing listed is for focal onset and generalized onset tonic–clonic seizures
Perampanel (Fycompa)	2 mg	8-12 mg	12 mg	Not defined	Dosing listed is for patients >4 yrs with focal onset seizures or >12 yrs with generalized onset tonic–clonic seizures.
Pregabalin (Lyrica)	150 mg (≥17 yrs) 2.5 mg/kg if >30 kg and 3.5 mg/kg between 11-29 kg (4-17 yrs)	150-600 mg (≥17 yrs) 2.5-10 mg/kg if >30 kg and 3.5-14 mg/kg between 11-29 kg (4-17 yrs)	600 mg (≥17 yrs) 600 mg if >30 kg and 14 mg/kg between 11 and 29 kg (4-17 yrs)	Not defined	
Third Generation with Indications for Specific Epilepsy Syndromes					
Cannabadiol (Epidiolex)	5 mg/kg (≥2 yrs)	10-20 mg/kg (≥2 yrs)	20 mg/kg (≥2 yrs)	Not defined	Dosing listed is for Dravet Syndrome and LGS.
Clobazam (Onfi)	5 mg if ≤30 kg and 10 mg if >30 kg (≥2 yrs)	5-20 mg if ≤30 kg and 10-40 mg if >30 kg (≥2 yrs)	20 mg if <30 kg and 40 mg if >30 kg (≥2 yrs)	0.03-0.3 ng/mL (mcg/L; 0.1-1.0 nmol/L)	Dosing listed is for LGS.
Fenfluramine (Fintepla)	0.2 mg/kg if not on STP and 0.1 mg/kg if on STP and CLB (≥2 yrs)	0.35 mg/kg if not on STP and 0.2 mg/kg/day if on STP and CLB (≥2 yrs)	26 mg if not on STP and 17 mg if on STP and CLB (≥2 yrs)	Not defined	Dosing listed is for Dravet Syndrome.

Rufinamide (Banzel)	400-800 mg (≥17 yrs) 10 mg/kg (1-16 yrs)	1,600-3,200 mg (≥17 yrs) 10-45 mg/kg (1-16 yrs)	3,200 mg (≥17 yrs) 3,200 mg (1-16 yrs)	Not defined	Dosing listed is for LGS. FDA labeling states the efficacy of TDD <3,200 mg is unknown; however, doses <3,200 mg are commonly used in clinical practice.
Stiripentol (Diacomit)	50 mg/kg (≥2 yrs)	50 mg/kg (≥2 yrs)	3,000 mg (≥2 yrs)	4-22 mg/L (mcg/mL; 17-94 µmol/L)	Dosing listed is for patients with Dravet Syndrome who are also on CLB. STP should only be used in combination therapy with CLB.
Vigabatrin (Sabril)	1,000 mg (≥17 yrs) 350-500 mg depending on weight (2-16 yrs) 50 mg/kg (Infants)	1,000-3,000 mg (≥17 yrs) 1,050-2,000 mg depending on weight (2-16 yrs) 50-150 mg/kg (Infants)	3,000 mg (≥17 yrs) Varies by weight (2-16 yrs) 150 mg/kg (Infants)	0.8-36 mcg/mL (mg/L; 6-279 µmol/L)	Infant dosing listed is for infantile spasms; adult and non-infant pediatric dosing listed is for refractory focal seizures.

CLB, clobazam; CBZ, carbamazepine; DR, delayed-release; FDA, Food and Drug Administration; ER, extended-release; LD, loading dose; LGS, Lennox-Gastaut Syndrome; MHD, 10-monohydroxycarbazepine derivative; PB, phenobarbital; PHT, phenytoin; PI, prescribing information; PRM, primidone; STP, Stiripentol; TDD, total daily dose; yrs, years; VPA, valproate; XR, extended release.

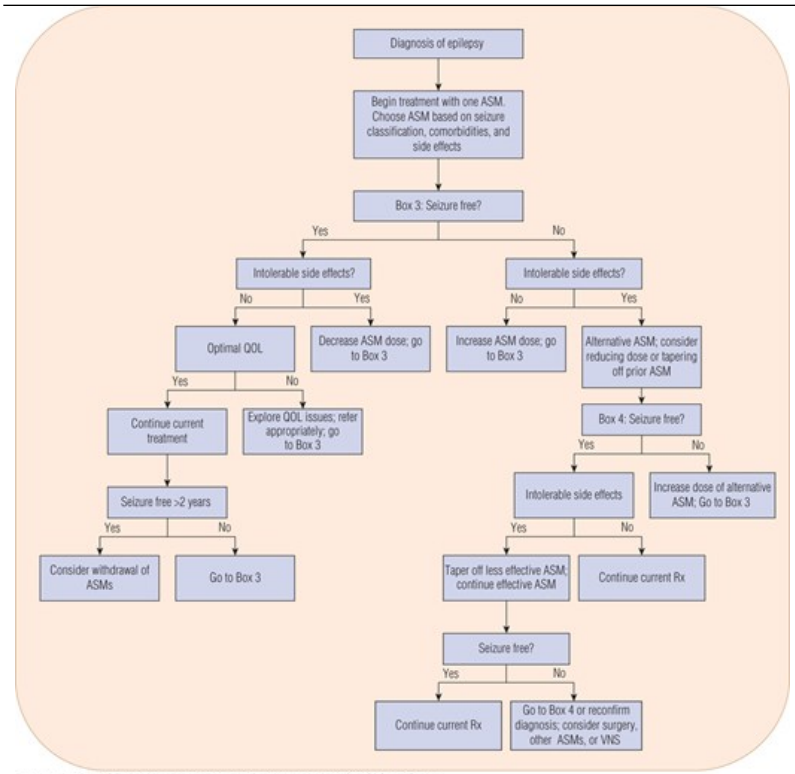
Data from References 17-20, 23, and 36-56.

Determining the optimal therapeutic dose for an individual takes into account treatment response and adverse medication reactions. If the patient is seizure free with no adverse reactions at a minimal therapeutic dose, then an optimal dose has been achieved and no further increases is necessary. If the patient continues to have seizures at a minimal or moderate-therapeutic dose, further titration to a maximum dose may be needed for optimal seizure control. If the patient continues to have seizures at a maximum dose, or if the patient experiences intolerable adverse reactions at any dose, adding a second ASM and then tapering and discontinuing the ineffective or intolerable first ASM is appropriate. Selecting an ASM with a different mechanism of action than the first intolerable or ineffective ASM may increase the likelihood of success with the second ASM, although there is no clear evidence to support this.[57]

5 In general, ASM monotherapy is preferred. However, if the patient continues to have seizures after switching to a second ASM as monotherapy at a therapeutic dose, dual ASM therapy may be necessary, and an adjunctive ASM should be gradually added. Selection of an adjunctive ASM with a different or complementary mechanism of action is recommended and is the basis behind rational polytherapy, although there is no clear evidence in humans to support this practice.[57] For individuals who continue to have seizures on dual ASM therapy, polytherapy with three or more agents can be considered. A suggested algorithm for a general approach to the use of ASM monotherapy and polytherapy in the treatment of epilepsy is shown in Fig. 75-3.

FIGURE 75-3

An algorithm for ASM therapy. (ASM, antiseizure medication; VNS, vagal nerve stimulation.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonpharmacologic Therapy

Pharmacologic therapy with ASMs is the mainstay of treatment for patients with epilepsy. However, approximately 20% to 35% of patients will not achieve adequate seizure control and seizures may be considered medication-resistant.[34] Nonpharmacologic therapies are available for these medication-resistant seizures, as well as for individuals with medication-responsive seizures in whom the benefits of nonpharmacologic therapies outweigh its risk. Nonpharmacologic therapy for epilepsy includes diet, vagus nerve stimulation (VNS), and surgery among other modalities.

The ketogenic diet, devised in the 1920s, is high in fat and low in carbohydrates and protein, which leads to a shift in metabolism resulting in acidosis and ketosis. As protein and calorie intake are set at levels that will meet requirements for growth, most of the calories provided come in the form of heavy cream and butter, although medium-chain triglycerides can be substituted for the dietary fats. Furthermore, no sugar is allowed, the overall fluids are controlled, and vitamins and minerals are supplemented. Given these restrictions, it requires strict control and parental adherence, as this diet is often used in childhood forms of epilepsy. Although some centers find the diet useful for medically refractory patients, particularly those with certain etiologies such as glucose transporter 1 (GLUT1) deficiency, others have found that it is poorly tolerated. Long-term effects include kidney stones, increased bone fractures, and adverse growth effects.[58] An international consensus statement has offered recommendations for employing various forms of the ketogenic diet which may be more tolerable, including the use of the modified Atkins diet and the Low Glycemic Index treatment.[59]

A VNS is an Food and Drug Administration (FDA)-approved implanted medical device that is used as adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with focal seizures refractory to ASMs. It is also used off-label in the treatment of refractory primary generalized epilepsy. The mechanisms behind VNS's antiseizure actions are unknown. Human clinical studies have shown that VNS changes the cerebrospinal fluid (CSF) concentration of inhibitory and stimulatory neurotransmitters and activates specific areas of the brain that generate or regulate cortical seizure activity through increased blood flow. There is experimental evidence to suggest that the antiseizure effect of VNS is mediated by the locus coeruleus.[60]

The VNS is relatively safe and may have a positive effect on mood and behavior, often independent of seizure reduction.[61] The most common adverse reactions associated with stimulation are hoarseness, voice alteration, increased cough, pharyngitis, dyspnea, dyspepsia, and nausea. Serious adverse reactions reported include infection, nerve paralysis, hypoesthesia, facial paresis, left vocal cord paralysis, left facial paralysis, left recurrent laryngeal

nerve injury, urinary retention, and low-grade fever. In the VNS studies, the percentage of patients who achieved a 50% or greater reduction in their seizure frequency (responders) ranged from 23% to 50% at 3 months.[62,63] The effects of VNS are not noted immediately, are more long term, and are also unlikely to lead to seizure freedom but may allow for reduced seizure frequency and reduced medication burden.

6 Surgery is the treatment of choice in select patients with refractory focal epilepsy, especially those with seizures originating from the temporal lobe. A randomized controlled trial, focusing on temporal lobe epilepsy, found that 58% of patients who underwent surgery were seizure free at 1 year compared to 8% of patients who did not undergo surgery.[64] A second randomized controlled study, to evaluate the efficacy of early surgery versus continued medical management in patients who had failed two ASM trials, showed that 11 of 15 patients who had undergone surgery were seizure free at 2-year follow-up, compared to none in the medical therapy group.[65] Certain factors have been found to predict positive outcomes in surgical patients including presence of a focal brain lesion on MRI, presence of unilateral mesial temporal sclerosis, presence of a localized temporal lobe positron emission tomography (PET) abnormality (even if brain MRI is normal), concordant EEG data showing location of ictal onset and shorter preoperative seizure duration.[66-68] The last finding is important to emphasize, as it is imperative to identify patients with treatment-resistant epilepsy and to refer them to an epilepsy center as soon as possible. Epilepsy surgery is not without risk, as learning and memory can be impaired postoperatively, and general intellectual abilities have also been affected in a small number of patients.[68] Patients may need to continue ASM therapy for a period of time following successful epilepsy surgery, but dosage reduction may be achievable.

Pharmacologic Therapy

ASM Efficacy

There are more than 27 FDA-approved ASMs for the treatment of epilepsy in the United States. Only a subset of these are approved for monotherapy, and many are approved as add-on treatment only, in large part due to the difficulty in studying ASM monotherapy in randomized clinical trials. As such, many clinicians will use most ASMs off-label as monotherapy in clinical practice.

Clinical trials for ASM approval focus on their efficacy for either focal-onset epilepsies or specific epilepsy syndromes. Studies to directly compare the efficacy of individual ASMs are not practical and have not been conducted for many of these agents. All ASMs have comparable efficacy in focal-onset epilepsies, except for gabapentin, which is considered a weaker ASM and should be used as adjunctive therapy only. In generalized epilepsies and epilepsy syndromes, specific ASMs are FDA-approved (Table 75-5) or have recommendations for use in specific epilepsy types.

TABLE 75-5

Antiseizure Medications (ASMs)

ASM and Available Formulations	Postulated Mechanism of Action (MOA)/Indication	Advantages/Disadvantages	Interactions	Adverse Medication Reactions
First-Generation ASMs				
Carbamazepine (CBZ) Chewable tablet, ER tablet, liquid suspension	**MOA**: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in comorbid bipolar disorder and trigeminal neuralgia	**Effect of CBZ on ASMs**: CBZ is potent inducer of CYP3A4, CYP1A2, CYP2B6, CYP2C9/19; CBZ decreases or possibly decreases levels of brivaracetam, clonazepam, eslicarbazepine, ethosuximide,	**BOXED WARNING**: Increased risk of SJS/TEN with HLA-B*1502 allele; aplastic anemia and agranulocytosis **Common**: CNS effects including diplopia, dizziness, drowsiness; unsteadiness, lethargy; hyponatremia from SIADH

			felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol tiagabine, topiramate, valproate, zonisamide	
	Indication: Monotherapy/adjunctive therapy for focal onset, TC, and mixed seizure types except for absence seizures	**Disadvantages**: Avoid in absence epilepsy as it worsens other seizure types in those patient; screening required for those at increased risk SJS/TEN in HLA-B*1502 and HLA-A*3101 allele (eg, specific Asian groups); avoid if prior rash with other ASMs due to possible cross-reaction auto-inducer; active metabolite carbamazepine 10,11 epoxide contributes to idiosyncratic adverse reactions; avoid in patients with history of bone marrow depression or sensitivity to tricyclic compounds; cannot use within 14 days of MAO inhibitor; can cause fetal harm	**Effect of ASMs on CBZ**: Cenobamate, eslicarbazepine, felbamate, phenobarbital, phenytoin, primidone, rufinamide may decrease CBZ levels; brivaracetam, felbamate, valproate may increase carbamazepine-10,11 epoxide levels; vigabatrin may increase CBZ levels	**Serious but rare**: Other blood dyscrasias including thrombocytopenia, leukopenia; DRESS; increased intraocular pressure; cardiovascular effects including 2nd and 3rd degree AV heart block; hepatotoxicity
			Others (partial list): CYP3A4 inhibitors/inducers may increase/decrease CBZ levels; CBZ may decrease levels of hormonal contraceptives; do not administer with other liquid agents due to possibility of precipitate occurrence	**Long term**: Hyponatremia from SIADH; metabolic bone disease including osteoporosis, osteopenia, osteomalacia
Clonazepam (Schedule IV) Tablet, ODT	**MOA**: Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	**Advantages**: Useful when there is a need for a benzodiazepine with long half-life	**Effect of clonazepam on ASMs**: Clonazepam may affect levels of phenytoin	**BOXED WARNING**: Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death **Common**: CNS effects including impairment of cognitive and motor performance due to sedation and ataxia; behavior problems; paradoxical reactions such as agitation, irritability,

				aggression, anxiety, anger, nightmares, hallucinations and psychoses
	Indication: Monotherapy/adjunctive therapy for LGS (petit mal variant), akinetic, myoclonic, and absence seizures	**Disadvantages**: May increase TC seizures when used in mixed seizure types; tolerance and dependence may occur; risk of respiratory depression which is increased when used with other CNS depressants including opioids; contraindicated in acute narrow angle glaucoma and severe hepatic impairment; metabolites may accumulate with impaired renal function and may require dose adjustment; some loss of effect may occur after 3 months; withdrawal symptoms including status epilepticus may occur after discontinuation; may increase hypersalivation; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on clonazepam**: Carbamazepine, lamotrigine, phenobarbital, phenytoin may decrease clonazepam levels; vigabatrin increases clonazepam, clonazepam may be affected by other enzyme inducing or enzyme-inhibiting ASMs **Other (partial list)**: Use with opioids increases risk of respiratory depression	**Serious but rare**: Respiratory depression; hepatomegaly; muscle weakness **Long term**: Physiologic dependence; hair loss; hirsutism; ankle and facial edema
Ethosuximide (ETX) Capsule, liquid solution	**MOA**: Inhibition of T-type calcium channels	**Advantages**: Medication of choice for absence seizures	**Effect of ETX on ASMs**: ETX may affect levels of carbamazepine, phenobarbital, phenytoin, primidone, valproate	**Common**: GI distress including nausea/vomiting, cramps diarrhea; epigastric and abdominal pain; anorexia and weight loss; CNS effects including lethargy, fatigue, drowsiness, dizziness, ataxia
	Indication: Monotherapy and adjunctive therapy for absence seizures in patients ≥3 years of age	**Disadvantages**: May worsen generalized TC seizures and other seizure types when used alone in mixed types of epilepsy; contraindicated in those with allergies to succinimides; may cause fetal harm; use with caution in hepatic/renal dysfunction	**Effect of ASMs on ETX**: Valproate may increase or decrease ETX levels	**Serious but rare**: Blood dyscrasias including leukopenia, agranulocytosis, pancytopenia, eosinophilia; rash including SJS; DRESS; hepatic/renal dysfunction; lupus erythematosus; psychiatric abnormalities including night terrors and paranoid psychosis **Long-term**: Behavioral changes
Phenobarbital (PB) (Schedule III) Tablet, elixir, injectable	**MOA**: Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	**Advantages**: Easily available world-wide; extensive knowledge and experience with PHB use despite not being FDA-approved as PHB developed in early 1900s prior to	**Effect of PB on ASMs**: PB is inducer of CYP1A2, CYP2C9, CYP2C19, CYP3A4. PB may	**Common**: CNS effects including residual sedation or "hangover," impaired cognition, drowsiness,

solution		establishment of FDA and current regulatory practices	decrease levels of carbamazepine, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	dizziness, vertigo, ataxia, headache, sleep disturbance; paroxysmal effects including excitement, irritability and hyperactivity in older adults and children; GI effects including epigastric pain, nausea, vomiting, diarrhea, and constipation
	Indication: Not FDA-approved; used for focal onset and generalized seizures	**Disadvantages**: Tolerance and dependence may occur; slow taper needed when discontinuing after prolonged use; use with other CNS depressants may produce additive CNS effects; may cause respiratory depression; can cause fetal harm	**Effect of ASMs on PB**: Cenobamate, felbamate, rufinamide, valproate may increase PB levels; phenytoin may increase or decrease PB levels	**Serious but rare**: Respiratory depression and apnea; rash (SJS, TEN); cardiac effects including bradycardia, hypotension with IV administration, syncope; hepatotoxicity; megaloblastic anemia; apnea and hypoventilation
			Other (partial list): PB may decrease levels of oral contraceptives	**Long term**: Behavioral changes; connective tissue disorder; intellectual blunting; metabolic bone disease (Rickets, osteopenia, osteoporosis, osteomalacia); folate deficiency (with megaloblastic anemia)
Phenytoin (PHT) ER capsule; liquid suspension; injectable; chewable tablet (Fosphenytoin, a prodrug desterified by esterases in the blood to phenytoin, also available as injectable solution only)	**MOA**: Enhances fast inactivation of voltage-gated sodium channels; inhibits persistent sodium current (I_{NAP}) and increases threshold for action potential firing	**Advantages**: May be orally or intravenously loaded in patients who require rapid steady-state serum levels; ER formulation useful in nonadherence as dosed once daily	**Effect of PHT on ASMs**: PHT may decreases levels of brivaracetam, carbamazepine, cenobamate, clonazepam, eslicarbazepine, felbamate, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	**Common**: CNS effects including ataxia, nystagmus, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, headaches

	Indication: Monotherapy/adjunctive therapy for focal onset psychomotor seizures and TC seizures; prevention or treatment of seizures during or after neurosurgery, severe TBI, status epilepticus	**Disadvantages**: May aggravate seizures in patients with absence seizures; can increase blood sugar levels in diabetes; HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry; CYP2C9*3 carriers may increase development of SCARS; monitoring of free phenytoin levels required in renal, hepatic impairment, hypoalbuminemia, and pregnancy; compromised absorption with concomitant tube feeds; dose adjustments required to switch between free acid and sodium salt formulations; phenytoin dose adjustments needed in older adults due to decreased clearance; may exacerbate porphyria	**Effect of ASMs on PHT**: Carbamazepine, eslicarbazepine, vigabatrin may decrease PHT levels; brivaracetam, cenobamate, ethosuximide, felbamate, methsuximide, oxcarbazepine, rufinamide, topiramate may increase PHT levels; phenobarbital, valproate may increase or decrease PHT levels	**Serious but rare**: Blood dyscrasias including thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia; lymphadenopathy; rash (SJS/TEN/SCARS); DRESS; hepatotoxicity; angioedema; bradycardia/cardiac arrest; purple glove syndrome with IV administration
			Other (partial list): PHT can substantially reduce delavirdine concentrations and cause loss of virologic response and resistance; may decrease contraceptive levels, may increase/decrease PT/INR when given with warfarin	**Long term**: Connective tissue changes including skin thickening, gingival hyperplasia, coarsening of facial features, enlargement of lips; hirsutism; metabolic bone disease (osteoporosis, osteopenia, osteomalacia); peripheral neuropathy; cerebellar atrophy; folate deficiency (with megaloblastic anemia)
Primidone (PRM) Tablet	**MOA**: Prodrug converted to active metabolite phenylethylmalonamide-amide (PEMA) and phenobarbital with same mechanism of action	**Advantages**: Useful in patients with essential tremor	**Effect of PRM on ASMs**: PRM may decrease levels of carbamazepine, eslicarbazepine, ethosuximide, felbamate, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, stiripentol, tiagabine, topiramate, valproate, zonisamide	**Common**: CNS effects including ataxia, vertigo, nystagmus, diplopia, drowsiness, fatigue; GI effects including nausea/vomiting, anorexia, fatigue; emotional disturbances including hyperirritability **Serious but rare**: Blood dyscrasias including granulocytopenia, agranulocytosis; rash (SJS, TEN); liver dysfunction
	Indication: Monotherapy/adjunctive therapy for focal onset and TC seizures	**Disadvantages**: Contraindicated in porphyria	**Effect of ASMs on PRM**: Valproate may increase PRM levels; phenytoin may increase	**Long term**: Behavioral changes; intellectual blunting; connective tissue disorder; metabolic bone

			or decrease PRM levels; carbamazepine, eslicarbazepine may affect levels	disease (rickets, osteomalacia); folate deficiency (with megaloblastic anemia)
Valproate (VPA) Divalproex DR sprinkle capsule and tablet, Divalproex ER 24-hour tablet, valproic acid IR capsule, valproate sodium injectable solution	**MOA**: Likely potentiates GABAergic transmission among multiple other unknown mechanisms	**Advantages**: Useful in comorbid bipolar disorder and migraine; commonly used in all age groups including ages <10 years	**Effect of VPA on ASMs**: VPA may increase levels of eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, rufinamide, tiagabine, topiramate, zonisamide **Effect of ASMs on VPA**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease VPA levels; felbamate may increase VPA levels	**BOXED WARNING**: Hepatotoxicity especially for children <2 years of age and with mitochondrial disorders; fetal risk including neural tube defects, other major malformations, and decreased IQ; pancreatitis including fatal hemorrhagic pancreatitis **Common**: GI effects including abdominal pain/GI upset (worse with valproic acid IR), constipation, diarrhea, anorexia, increased appetite, weight gain, nausea/vomiting; CNS effects including blurred vision, ataxia, dizziness, headache, insomnia, nystagmus, somnolence, thinking abnormal, tremor; dose-dependent thrombocytopenia (>100 mg/mL)
	Indication: Monotherapy/adjunctive therapy for focal onset and multiple seizure types for patients ≥10 years of age; monotherapy/adjunctive therapy for absence seizures in patients ≥10 years of age	**Disadvantages**: Contraindicated in significant hepatic dysfunction, mitochondrial disorders caused by DNA polymerase γ (POLG) mutations, urea cycle disorders; use with caution in pancreatitis, bleeding and other hematopoietic disorders; risk of hyperammonemia with and without encephalopathy associated with concomitant topiramate use; pregnancy category D—contraindicated in women of childbearing potential and pregnancy category X for pregnant patients treated for migraine prophylaxis		**Serious but rare**: Hyperammonemia with and without encephalopathy; hypothermia with and without hyperammonemia; DRESS; bleeding and other hematopoietic disorders
			Other (partial list): Estrogen OCP may affect VPA levels	**Long-term**: Hair and nail changes including alopecia, hirsutism, hair texture and

				color changes, nail and nail bed disorders; irregular menses and polycystic ovary-like syndrome; weight gain; cerebral pseudoatrophy; osteoporosis and osteopenia
Second-Generation ASMs				
Felbamate (FBM) Tablet, liquid suspension	**MOA**: Antagonizes NMDA glutamate receptor; binds weakly to $GABA_A$ receptor and possibly augments GABAergic transmission	**Advantages**: May be useful in refractory epilepsy	**Effect of FBM on ASMs**: FBM may decrease carbamazepine levels; FBM may increase carbamazepine-epoxide, phenobarbital, phenytoin, valproate levels	**BOXED WARNING**: Irreversible fatal aplastic anemia aplastic anemia with greater risk in females, or history of cytopenia, ASM allergy or significant toxicity, viral infection, and/or immunologic problems with reported onset between 5-30 weeks; acute liver failure Aplastic anemia with reported onset between 5-30 weeks; acute liver failure with reported onset occurring in 5 weeks **Common**: GI effects including anorexia, vomiting, nausea; CNS effects including insomnia, headache, dizziness, somnolence
	Indication: Monotherapy/adjunctive therapy for focal onset seizures with and without TC seizures in patients ≥14 years; adjunctive therapy for focal onset and generalized seizures associated with LGS in patients aged 2-14	**Disadvantages**: For severe refractory epilepsy ONLY; contraindicated in patients with hepatic dysfunction, history of blood dyscrasias; use with caution in patients with renal dysfunction; available only through special access program; pregnancy category C	**Effect of ASMs on FBM**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease FBM levels; valproate does not affect FBM levels to a clinically significant degree	
			Other (partial list): Estrogen OCP levels not affected	
Gabapentin (GBP) Tablet, capsule, oral solution	**MOA**: Binds to presynaptic $\alpha_2\delta$ subunit of calcium channels with unknown antiseizure effect	**Advantages**: Useful in post-herpetic neuralgia, chronic pain, and neuropathy; few interactions	**Effect of GBP on ASMs**: No significant effects	**Common**: CNS effects including somnolence, dizziness, ataxia, fatigue, nystagmus; peripheral edema and weight gain; GI effects including nausea/vomiting
	Indication: Adjunctive therapy for focal onset seizures with and without TC seizures in patients ≥3 years	**Disadvantages**: Considered weakly efficacious; potential abuse when taken with opioids; withdrawal reaction characterized by anxiety, insomnia, nausea, sweating, and increased pain; absorption	**Effect of ASMs on GBP**: No significant effects	**Serious but rare**: Anaphylaxis, angioedema, DRESS; neuropsychiatric symptoms in children 3 to 12 years of age

		may be impaired for single oral doses >1,200 mg; no adequate data in pregnancy—may cause fetal harm		**Long-term**: Weight gain, peripheral edema
Lamotrigine (LTG) Tablet, chewable tablet,[a] ODT,[a] XR tablet[a]	**MOA**: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in bipolar disease; XR useful in non-adherence as dosed once daily	**Effect of LTG on ASMs**: No significant effects	**BOXED WARNING**: Rash including SJS, TEN with increased risk if given with valproate, exceeding recommended initial dose or dose escalation
	Indication: Adjunctive therapy in focal onset and TC seizures, generalized seizures of LGS in patients ≥2 years of age; monotherapy in patients with focal-onset seizures ≥16 years of age	**Disadvantages**: Slow titration required to avoid rash including SJS; rash more likely to occur if patient with prior rash to other ASM and concomitant use of valproic acid; rash incidence higher in children; may exacerbate myoclonus; dosage adjustment required in patients with moderate and severe liver impairment; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on LTG**: Carbamazepine, cenobamate, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide may decrease LTG levels; Cannabidiol increases LTG and valproate increases LTG levels by 2×	**Common**: CNS effects including dizziness, headache, diplopia, ataxia, blurred vision, somnolence, tremor; GI effects including nausea/vomiting, abdominal pain, diarrhea; other effects including rhinitis, pharyngitis, infection, fever; rash
			Other (partial list): Estrogen OCPs may decrease LTG by 50%	**Serious but rare**: DRESS; blood dyscrasias; hemophagocytic lymphohistiocytosis (HLH). Rash usually appears after 3-4 weeks of therapy and is typically generalized, erythematous, and morbilliform but can progress to SJS
Levetiracetam (LEV) Tablet, XR tablet,[a] injectable solution	**MOA**: Binds to and selectively inhibits synaptic vesicle $SV2_A$ protein thereby preventing neurotransmitter release **Indication**: Adjunctive therapy for focal onset seizures in patients >1 month, myoclonic seizures in patients with JME ≥12 years of age, and generalized TC seizures in patients ≥6 years of age	**Advantages**: Minimal interactions; XR useful in nonadherence as dosed once daily **Disadvantages**: May worsen depression, PTSD, anxiety, thought disorders; must dose adjust in dialysis/renal failure; pregnancy category C	**Effect of LEV on ASMs**: No significant effects	**Common**: CNS effects including somnolence, fatigue; behavior effects including aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability **Serious but rare**: Psychosis, hallucinations
			Effect of ASMs on LEV: No significant effects	

	with generalized epilepsy			
Oxcarbazepine (OXC) Tablet, tablet ER,[a] liquid suspension[a]	**MOA**: Enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in bipolar disorder; ER useful in nonadherence as dosed once daily	**Effects of OXC on ASMs**: OXC is inhibitor of CYP2C19 and inducer of CYP3A4/5; OXC may decrease lamotrigine levels through UGT induction and decrease perampane levels; OXC may increase phenytoin levels	**Common**: CNS effects including dizziness, somnolence, diplopia, fatigue, ataxia, abnormal vision, headache, nystagmus, tremor; GI effects including nausea, vomiting; hyponatremia due to SIADH; rash
	Indication: Monotherapy/adjunctive therapy for focal onset seizures in patients ≥4 years of age; adjunctive therapy for focal onset seizures in patients ≥2 years of age	**Disadvantages**: Higher incidence of hyponatremia, (as high as 25%); HLA-B*1502 in Asians may increase SJS or TEN risk; may require slower titration in renal impairment; active MHD metabolite may decrease in pregnancy; no adequate data in pregnant patients—may cause fetal harm	**Effect of ASMs on OXC**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease levels of OXC active metabolites; valproate may increase levels of OXC **Other (partial list)**: OXC may decrease estrogen OCP levels	**Serious but rare**: SJS, TEN; DRESS; blood dyscrasias
Tiagabine (TGB) Tablet	**MOA**: Inhibitor of GABA reuptake transporter GAT1	**Advantages**: None noted	**Effect of TGB on ASMs**: TGB may decrease VPA levels by 10%	**Common**: CNS effects including dizziness, lightheadedness, somnolence, thinking abnormal; behavior effects including asthenia, lack of energy, nervousness, irritability, difficulty with concentration or attention; GI effects including abdominal pain, nausea, and vomiting
	Indication: Adjunctive therapy for focal onset seizures in patients ≥12 years of age	**Disadvantages**: Has been associated with new onset seizure, status epilepticus, and exacerbation of EEG abnormalities in those with existing epilepsy; dosage reduction may be necessary in patients with liver disease; pregnancy category C	**Effects of ASMs on TGB**: Carbamazepine, phenobarbital, phenytoin, primidone increases TGB clearance by 60% and may decrease TGB levels; valproate may increase TGB levels by 40%	**Serious but rare**: Increase in generalized seizures and non-convulsive SE in patients with refractory epilepsy; occurrence of seizures and SE in patients without epilepsy; moderately severe to incapacitating generalized weakness; exacerbation of EEG abnormalities; rash including SJS

				Long-term: Possibility of long-term ophthalmologic effects
Topiramate (TPM) Sprinkle capsule, tablet, ER capsule	**MOA**: Antagonizes voltage-gated sodium channel; binds to $GABA_A$ receptor and augments GABAergic transmission, antagonizes AMPA/kainate glutamate receptor, weak carbonic anhydrase inhibitor	**Advantages**: Useful in comorbid migraine and obesity; ER useful in non-adherence as dosed once daily	**Effect of TPM on ASMs**: TPM is weak inhibitor of CYP2C19 and inducer of CYP3A4; TPM may increase or decrease ASMs metabolized by CYP2C19 and 3A4 including felbamate and topiramate	**Common**: CNS effects including fatigue, difficulty concentrating, confusion, language problems, tremor, paresthesias; behavioral effects including nervousness, anxiety
	Indication: Monotherapy/adjunctive therapy for focal onset seizures or primary generalized TC seizures in patients ≥2 years of age; adjunctive therapy for patients with LGS ≥2 years of age	**Disadvantages**: Avoid in patients with preexisting cognitive issues; renally dose adjust with CrCl <70 mL/min (1.17 mL/s); can cause fetal harm	**Effect of ASMs on TPM**: Carbamazepine, phenobarbital, phenytoin, primidone may decrease TPM levels; valproate may increase TPM levels **Other (partial list)**: TPM at higher doses may decrease estrogen OCP levels	**Serious but rare**: Renal stones, glaucoma, hypo/hyperthermia, oligohidrosis, metabolic acidosis, SJS, TEN, and hyperammonemia with and without encephalopathy when used with valproate **Long term**: Weight loss; renal stones; metabolic acidosis
Zonisamide (ZON) Capsule	**MOA**: Enhances fast inactivation of voltage-gated sodium channels; inhibits T-type calcium channels; weak carbonic anhydrase inhibitor	**Advantages**: Useful in tremor; useful in nonadherence as dosed once daily	**Effect of ZON on ASMs**: No significant DDIs	**Common**: CNS effects including sedation, ataxia, confusion, depression, difficulty concentrating, word-finding difficulties
	Indication: Adjunctive therapy for focal onset seizures in adults	**Disadvantages**: Contraindicated in those with sulfa allergy; dose efficacy may plateau at 400 mg; should not be used in renal failure due to increases in SCr and BUN and possible effects on GFR; pregnancy category C	**Effect of ASMs on ZON**: CYP3A4 inhibitors or inducers may alter ZON levels; carbamazepine, phenobarbital, phenytoin, valproate may decrease ZON levels	**Serious but rare**: Oligohidrosis and hyperthermia; renal stones; metabolic acidosis; rash (SJS, TEN); DRESS; fulminant hepatic necrosis; blood dyscrasias **Long term**: Weight loss; renal stones; metabolic acidosis
Third-Generation ASMs				
Brivaracetam (BRV, Schedule V) Tablet, oral	**MOA**: Binds to and selectively inhibits synaptic vesicle $SV2_A$	**Advantages**: Can consider converting well-controlled patients from levetiracetam if intolerable psychiatric adverse reactions	**Effect of BRV on ASMs**: BRV may increase carbamazepine	**Common**: CNS effects including sedation, fatigue, ataxia, nystagmus;

solution, injectable solution	protein thereby preventing neurotransmitter release		metabolite; BRV may increase phenytoin levels; no added therapeutic benefit when given with levetiracetam	behavioral effects including irritability, aggressive behavior, anxiety, agitation, restlessness, tearfulness, apathy, altered mood, mood swings, hyperactivity, adjustment disorder; GI effects including nausea, vomiting
	Indication: Monotherapy/adjunctive therapy for focal onset seizures in patients ≥1 month of age; injection solution approved for ≥16 years of age	**Disadvantages**: Dosage adjustments required in hepatic impairment; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on BRV**: CYP2C19 inhibitors may alter BRV levels **Other (partial list)**: rifampin will reduce BRV levels	**Serious but rare**: Angioedema; bronchospasm; decreased neutrophils; psychosis and depression; hematologic abnormalities including leukopenia and neutropenia
Cenobamate (CBM, Schedule V) Tablet	**MOA**: Inhibition of voltage-gated sodium channels; positive allosteric modulator of $GABA_A$ ion channel	**Advantages**: None	**Effect of CBM on ASMs**: CBM is a CYP2C19, CYP2B6, CYP3A inhibitor and may increase substrate levels; CBM is a CY2B6, CYPC8, CYP3A4 inducer and may decrease substrate levels; CBM may increase phenytoin, phenobarbital, clobazam concentrations; CBM may decrease lamotrigine, carbamazepine concentrations; CBM does not affect valproic acid, levetiracetam, or lacosamide	**Common**: CNS effects including somnolence, dizziness, fatigue, diplopia, headache; dizziness and disturbance in gait and coordination; cognitive dysfunction including memory impairment, disturbance in attention, confusional state, slowness of thought; vision changes including diplopia, blurred vision, and impaired vision; laboratory abnormalities including hepatic transaminases, potassium elevation
	Indication: Monotherapy/adjunctive therapy for focal-onset seizures in adults	**Disadvantages**: Must be slowly titrated q2weeks to avoid DRESS; contraindicated in Familial Short QT syndrome; caution when administering with other medications that shorten QT interval; use with caution and dose reduce in hepatic and renal impairment; use not recommended in end-stage hepatic or renal disease; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on CBM**: Phenytoin may decrease CBM; valproate, phenobarbital, carbamazepine do not significantly impact CBM **Other (partial list)**: CBM may decrease estrogen OCP levels; additive risk with other	**Serious but rare**: DRESS with fast titration (weekly intervals); QT interval shortening; appendicitis

			medications that shorten the QT interval; use with CNS depressants increases CNS toxicity	
Eslicarbazepine (ESL) Tablet	**MOA**: Selectively enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful in non-adherence as dosed once daily	**Effect of ESL on ASMs**: Inhibitor of CYP2C19; ESL may affect carbamazepine, perampanel, phenytoin, phenobarbital, primidone levels	**Common**: CNS effects including dizziness, somnolence, nausea, headache, diplopia, fatigue, vertigo, ataxia, blurred vision, tremor; hyponatremia due to SIADH; rash
	Indication: Monotherapy or adjunctive therapy for focal onset seizures in patients ≥4 years of age	**Disadvantages**: Avoid in severe hepatic impairment; dose adjustment in renal failure; avoid concomitant use with carbamazepine and oxcarbazepine; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on ESL**: Carbamazepine, phenobarbital, primidone, and phenytoin may decrease ESL levels **Other (partial list)**: ESL decreases estrogen OCP levels	**Serious but rare**: SJS; anaphylaxis, angioedema, DRESS; cardiac effects including prolonged PR interval, AV block; hepatotoxicity; blood dyscrasias **Long-term**: Hyponatremia
Lacosamide (LCM) (Schedule V) Tablet, oral solution, injectable solution	**MOA**: Selectively enhances slow inactivation of voltage-gated sodium channels	**Advantages**: Minimal interactions	**Effect of LCM on ASMs**: LCM is a potential CYP2C19 inhibitor but no clinically significant effects of LCM on other ASMs have been observed **Effect of ASMs on LCM**: LCM is a substrate of CYP3A4, CYP2C9, and CYP2C19; carbamazepine, phenytoin, phenobarbital, primidone may decrease LCM levels by 15-20% **Other (partial list)**: LCM may increase levels of strong CYP3A4 or CYP2C9 inhibitors in renal or hepatically impaired patients; risk of cardiac abnormalities increased with concomitant	**Common**: CNS effects including diplopia, headache, nausea, somnolence, dizziness, ataxia; GI effects including constipation, diarrhea, nausea, vomiting, dyspepsia, dry mouth, oral hypoesthesia/paresthesia; laboratory abnormalities including LFT elevations
	Indication: Monotherapy/adjunctive therapy for focal onset seizures in patients ≥4 years of age	**Disadvantages**: Avoid in 3rd degree heart block; must obtain ECG prior to intravenous infusion; use with caution in patients with underlying proarrhythmic conditions or on concomitant medications that affect cardiac conduction; not recommended in severe hepatic impairment; requires dose adjustment in renal impairment; oral solution contains phenylalanine and is a risk in patients with phenylketonuria no adequate data in pregnancy—may cause fetal harm		**Serious but rare**: Cardiac effects including AV conduction abnormalities, prolonged PR interval, atrial arrhythmias, syncope (especially in patients with diabetes); DRESS and hypersensitivity reactions; blood abnormalities including neutropenia and anemia

			medications that affect cardiac conduction	
Perampanel (PER) (Schedule III) Tablet, oral suspension	**MOA**: Selectively and noncompetitively antagonizes AMPA glutamate receptor on post-synaptic neuron	**Advantages**: Useful in mixed seizure types; useful in non-adherence as dosed once daily	**Effect of PER on ASMs**: PER is a modest enzyme inducer at high doses	**BOXED WARNING**: Aggression, hostility, irritability, anger, and homicidal ideation
	Indication: Monotherapy for focal onset seizures in patients ≥4 years of age; adjunctive therapy for TC seizures in patients ≥12 years of age	**Disadvantages**: Avoid in active psychosis or unstable recurrent affective disorders with significant hostility or aggressive behavior; avoid in severe hepatic/renal impairment or hemodialysis; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on PER**: Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate decrease PER levels; valproate has no effect on PER levels **Other (partial list)**: PER decreases estrogen OCP levels	**Common**: CNS effects including dizziness, somnolence, fatigue, falls, vertigo, ataxia, headache, confusion; GI effects including nausea, weight gain, vomiting, abdominal pain; behavioral effects including irritability anxiety; weight gain; falls sometimes leading to serious head injuries **Serious but rare**: DRESS
Pregabalin (PGB) (Schedule V) Capsule, tablet CR, oral solution	**MOA**: Binds to presynaptic $\alpha_2\delta$ subunit of calcium channels	**Advantages**: Useful in patients with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, neuropathic pain with spinal cord injury; minimal DDIs due to renal excretion	**Effect of PGB on ASMs**: No significant effects	**Common**: CNS effects including dizziness, somnolence, blurred vision, difficulty with concentration and attention; dry mouth; edema and weight gain
	Indication: Adjunctive therapy for focal onset seizures in patients ≥4 years of age	**Disadvantages**: Caution in preexisting cognitive disorders; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on PGB**: No significant effects	**Serious**: Potential for misuse when taken with opiates **Long term**: Weight gain
Third-Generation ASMs with FDA Approval for Specific Epilepsy Syndrome Indications				
Cannabidiol (CBD, Schedule V) Oral solution	**MOA**: Unknown, does not act on cannabinoid receptors	**Advantages**: Useful for refractory seizures in LGS and Dravet Syndrome	**Effect of CBD on ASMs**: CBD increases lamotrigine levels; CBD increase levels of clobazam active metabolite by 3×	**Common**: CNS effects including somnolence, fatigue, malaise, asthenia; sleep disorders including insomnia, poor quality sleep; GI effects including decreased appetite; diarrhea; transaminase elevations
	Indication: Monotherapy/adjunctive therapy for patients with	**Disadvantages**: Avoid in patients with hypersensitivity reactions to cannabis, THC; liver function and bilirubin monitoring	**Effect of ASMs on CBD**: CYP3A4 and CYP2C19 inhibitors will	**Serious but rare**: Hepatotoxicity; hypoxia; respiratory failure

	LGS and Dravet Syndrome, ≥2 years of age	before and at 1, 3, and 6 months of treatment specially if given with valproate; no adequate data in pregnant woman—may cause fetal harm	increase CBD levels; CYP3A4 and CYP2C19 inducers will decrease CBD levels	
Clobazam (CLB, Schedule IV) Tablet, oral suspension	**MOA**: Binds $GABA_A$ receptor and potentiates GABA by modulating chloride conductance	**Advantages**: Despite FDA approval for LGS only, may be useful in all types of epilepsy; less sedating benzodiazepine	**Effect of CLB on ASMs**: CLB is inhibitor of CYP2C9 and inducer of CYP3A4; CLB may affect levels of CYP2C9, CYP3A4 substrates	**BOXED WARNING**: Concomitant use with opioids increases risk of death **Common**: CNS effects including somnolence, sedation, lethargy; pyrexia; constipation; drooling
	Indication: Adjunctive therapy for patients with LGS ≥2 years of age	**Disadvantages**: Monitor patients with history of substance use; use with other CNS depressant may produce additive CNS effects; may cause respiratory depression, coma, and death; no adequate data in pregnant patients—may cause fetal harm	**Effect of ASMs on CLB**: Carbamazepine, felbamate, phenobarbital, phenytoin, primidone may decrease CLB levels; cannabidiol, cenobamate, stiripentol increase CLB levels **Other (partial list)**: CLB decreases estrogen OCP levels	**Rare but serious**: Rash (SJS, TEN); anemia; liver enzyme elevations; respiratory depression
Fenfluramine (FEN, Schedule IV) Oral solution	**MOA**: Increases extracellular serotonin through actions on serotonin transporter protein, agonist at serotonin $5HT_2$ receptors	**Advantages**: Useful for refractory seizures in Dravet Syndrome	**Effect of FEN on ASMs**: No significant effects **Effect of ASMs on FEN**: CYP1A2, 2B6 inducers will decrease FEN; stiripentol + clobazam will increase FEN concentrations (max daily dose of FEN is reduced to 17 mg); cyproheptadine and potent 5-HT serotonin receptor binding agents may decrease efficacy of FEN **Other (partial list)**: Rifampin will decrease FEN, strong CYP1A2 and CYP2B6 inducers will decrease FEN	**BOXED WARNING**: Risk of valvular heart disease and pulmonary arterial hypertension; echocardiograms required before, during, and after treatment **Common**: GI effects like decreased appetite/weight, vomiting, diarrhea, constipation; CNS effects like somnolence, sedation, lethargy; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increase; salivary effects like drooling, hypersecretion; pyrexia; falls; status epilepticus; abnormal echocardiogram **Rare but serious**: increased blood pressure
	Indication: Treatment of seizures associated with Dravet Syndrome in patients ≥2 of age	**Disadvantages**: Contraindicated within 13 days of MAO inhibitors due to risk of serotonin syndrome; may increase blood pressure; not recommended in severe hepatic or renal impairment; available only through FINETPLA REMS; no adequate data in pregnancy—may cause fetal harm		

				including hypertensive crisis; risk of valvular disease and pulmonary arterial hypertension; mydriasis precipitating acute angle closure glaucoma
Rufinamide (RFN) Tablet, oral suspension	**MOA**: Selectively enhances fast inactivation of voltage-gated sodium channels	**Advantages**: Useful for refractory seizures in LGS	**Effect of RFN on ASMs**: RFN is weak inhibitor of CYP2E1 and weak inducer of CYP3A4; RFN modestly decreases levels of carbamazepine, lamotrigine; RFN increases levels of phenobarbital, phenytoin	**Common**: CNS effects including somnolence, fatigue, coordination abnormalities, dizziness, gait disturbances, ataxia; GI effects including nausea **Rare but serious**: DRESS; rash (SJS); status epilepticus; leukopenia; QT interval shortening
	Indication: Adjunctive therapy for patients with LGS ≥1 year of age	**Disadvantages**: Contraindicated in severe liver impairment or in familial short QT syndrome; use caution with other drugs that shorten QT interval; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on RFN**: Carbamazepine, phenobarbital, phenytoin decrease RFN levels by 19%-46%; valproate increases RFN levels up to 70%	
			Other (partial list): RFN decreases estrogen OCP levels	
Stiripentol (STP), capsule	**MOA**: Possibly acts on $GABA_A$ receptor and may also inhibit CYP450 to increase blood levels of clobazam and its active metabolite	**Advantages**: Useful for refractory seizures in Dravet Syndrome	**Effect of STP on ASMs**: STP is inhibitor and inducer of CYP1A2, 2B6, 3A4 and possible inhibitor of CYP2C8, 2C19, P-gp transporter, BCRP transporter; STP increases clobazam concentration 2-fold and clobazam active metabolite 5-fold (must decrease clobazam dosage when used together)	**Common**: Somnolence, decreased appetite/weight, agitation, ataxia, hypotonia, nausea, tremor, dysarthria, insomnia
	Indication: Adjunctive therapy with clobazam for seizure associated with Dravet Syndrome in	**Disadvantages**: Must be used as adjunctive therapy with clobazam; hematologic testing is required prior to first dose and q6months after due to risk of	**Effect of ASMs on STP**: STP is substrate of CYP1A2, CYP2C19, CYP3A4 and phenytoin,	**Rare but serious**: Neutropenia and thrombocytopenia; monitor

	patients ≥2 (no evidence for monotherapy)	neutropenia and thrombocytopenia; powder formulation contains phenylalanine and is a risk in patients with phenylketonuria; not recommended in moderate or severe hepatic or renal impairment; no adequate data in pregnancy—may cause fetal harm	phenobarbital, carbamazepine may decrease stiripentol levels	
Vigabatrin (VGB) Tablet, powder packet	**MOA**: Binds to and irreversibly inhibits GABA transaminase	**Advantages**: Useful in infantile spasms for whom potential benefit outweighs risk of vision loss; renally cleared and has less DDIs than other ASMs	**Effect of VGB on ASMs**: VGB is inducer of CYP2C9; VGB decreases levels of phenytoin by 20%; VGB possibly increases levels of carbamazepine by 10%; VGB increases C_{max} of clonazepam	**BOXED WARNING**: Progressive and permanent bilateral peripheral visual loss including tunnel vision and decrease in visual acuity **Common**: CNS effects including fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, abnormal coordination, confusion; weight gain; edema; peripheral neuropathy; laboratory abnormalities including decreases in ALT/AST in pediatric patients; aggression; infection including upper respiratory tract infection, bronchitis, ear infection, and acute otitis media constriction; vision loss
	Indication: Adjunctive therapy for refractory focal onset seizures in patients ≥2 years of age (not indicated as first-line); monotherapy for infantile spasms in patients 1 month to 2 years of age	**Disadvantages**: Permanent vision loss in most patients after a certain duration of exposure requiring eye exams Q3 months; requires REMS program registration; no adequate data in pregnancy—may cause fetal harm	**Effect of ASMs on VGB**: Carbamazepine, primidone, valproate have no effect on VGB **Other (partial list)**: Unlikely to affect estrogen OCP levels	**Serious but rare**: Seizure exacerbation, particularly absence and myoclonic seizures in patients with generalized epilepsies; anemia; onset of vision loss is unpredictable and can occur after weeks, months, or years with risk increasing in a dose-related and life exposure–related manner; abnormal MRI signal changes in infants treated for infantile spasms strongly suggestive of intramyelinic edema in

				select brain areas

[a]All ASMs may increase the risk of suicidal thoughts or behavior and patients treated with an ASM should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

AMPA, A-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid; ASM, antiseizure medication; AV, atrioventricular; BUN, blood urea nitrogen; C_{max}, maximum concentration; CNS, central nervous system; CR, controlled-release; CrCl, creatinine clearance; CYP, cytochrome p450 isoenzyme system; DDI, drug-drug interaction; DR, delayed-release; DRESS, drug rash with eosinophilia and systemic symptoms; EEG, electroencephalogram; FDA, Food and Drug Administration; ER, extended-release; GABA, gamma-aminobutyric acid; GAT1, GABA transporter type 1; GI, gastrointestinal; GFR, glomerular filtration rate; HLA, human leukocyte antigen; IQ, intelligence quotient; IR, immediate release; IV, intravenous; LGS, Lennox–Gastaut syndrome; OCP, oral contraceptives; ODT, orally dissolving tablet; PTSD, posttraumatic stress disorder; SJS, Steven–Johnson syndrome; TEN, toxic epidermal necrolysis; TBI, traumatic brain injury; TC, tonic–clonic; UGT, UDP-glucuronosyltransferase; XR, extended-release.

Data from References 17-20, 23, 36-56, 69, and 88-90.

The evidence for ASM long-term efficacy in new-onset or untreated epilepsy was reviewed by the ILAE in 2013 and the AAN in 2018. Based on evidence, ASMs were labeled as “established as efficacious,” “probably efficacious,” “possibly efficacious,” or “potentially efficacious” for new-onset epilepsy of various types including focal epilepsies in children, adults, and older individuals; focal, generalized, or unclassified epilepsy with tonic–clonic seizures in children and adults; and epilepsy syndromes like CAE, JME, and benign epilepsy with centro-temporal spikes (BECT).[27] Additionally, the ILAE and AAN identified limited evidence that some ASMs may possibly precipitate or aggravate certain seizure types, and, therefore, it is suggested that they should be used with caution in those patients (eg, carbamazepine and phenytoin in generalized onset tonic–clonic seizure types or carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin among others in patients with CAE or JME).[27] Despite the availability of ILAE and AAN recommendations summarizing ASM efficacy, based on the best available evidence in both new-onset and refractory epilepsy, there continues to be limited evidence to definitively guide pharmacotherapy decisions for refractory epilepsy.[73,74] Therefore, after assessing the evidence for ASM efficacy for a particular epilepsy or seizure type, pharmacotherapy decisions are guided by patient-specific factors, tolerability, risk for medication adverse reactions, and medication interactions (Tables 75-1 to 75-4).

ASM Effectiveness

In general, ASM “efficacy” is a measure of the ability of an ASM to prevent seizures or reduce their frequency in “ideal” circumstances. In contrast, ASM “effectiveness” is a more pragmatic measure of ASM benefit in “real-world” clinical setting and takes into account tolerability and their adverse reaction profiles. While ASM “efficacy” is generally considered similar in focal-onset epilepsies, ASM “effectiveness” varies and may be dependent on individual patient characteristics. Therefore, knowledge of individual ASM adverse reactions is important in determining ASM effectiveness and plays a significant role in their selection and optimization.

Adverse medication reactions can be categorized into two categories, dose-related (eg, concentration dependent) and idiosyncratic. As ASMs are often used life-long, adverse reactions associated with chronic long-term use and related to overall cumulative exposure should also be recognized. A general approach to understanding these different categories of ASM adverse reactions is reviewed in the following sections. For specific adverse reactions associated with each individual ASM, please refer to Table 75-5.

ASM Concentration-Dependent Adverse Medication Reactions

All ASMs have some common dose-related adverse reactions that they share as a class, as well as their own unique dose-related profile, often related to medication mechanism of action. As all ASMs act on the CNS to exert antiseizure effects, they all commonly cause dose-related CNS adverse reactions including sedation, dizziness, blurred or double vision, difficulty with concentration, ataxia, and impaired cognition which is of particular concern. Barbiturates and sodium channel inhibitors in particular cause more sedation and cognitive impairment than other commonly used ASMs (although in children, barbiturates may paradoxically cause hyperactivity). While newer agents have been associated with a lower incidence of CNS adverse effects, topiramate, in particular, is known to cause substantial cognitive impairment.[75]

Concentration-dependent adverse reactions are common and troublesome but not usually life-threatening, as they can be avoided by titrating the

dose upward very slowly in many cases or can be alleviated by decreasing the dose.[76] Although they are more likely to occur at higher doses and higher concentration ranges, it is important to note that patients dosed and maintained below or within "therapeutic concentration ranges" may still experience these reactions.[77] Patients who change from polytherapy with multiple agents to dual therapy or monotherapy may also demonstrate improvement in CNS adverse reactions, especially if principles of rational polytherapy are used.

ASM Idiosyncratic Adverse Medication Reactions

More uncommon are idiosyncratic adverse reactions, which are generally related to chemical characteristics of the ASM and individual patient susceptibility, rather than the ASM's pharmacology. While most idiosyncratic reactions are mild, they can be serious, potentially life threatening, and can affect virtually any organ, although the skin, liver, and blood cells are most commonly affected. The most widely recognized idiosyncratic reactions associated with ASMs are rashes, which are more common with particular ASMs (eg, carbamazepine, phenytoin, phenobarbital, and lamotrigine) but may occur with any. While these rashes are often mild, some can progress to severe life-threatening rashes including Steven–Johnsons syndrome (SJS) or toxic epidermal necrolysis (TEN). Hepatitis or blood dyscrasias have also occurred with many ASMs and can progress to acute hepatic failure or fatal aplastic anemia such as those rare cases reported with felbamate. Additionally, ASM treatment itself may sometimes worsen seizures as a paradoxical toxic effect of the medication.[75,76]

A warning on suicidal behavior and ideation also accompanies all ASMs. This is based on pooled analyses of almost 200 placebo-controlled trials of 11 different ASMs showing that patients randomized to an ASM had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. While the estimated incidence of suicidal ideation was low, less than 0.5% of patients on ASMs, this was greater than the 0.24% of patients on placebo. While some believed that this risk is nonsignificant, responsible providers must carefully assess this risk when evaluating their patients for ASM therapy, especially as depression and anxiety are common comorbid conditions in epilepsy. Patients and caregivers should be informed that ASMs may increase the risk of suicidal thoughts and should be advised to be on the alert for any unusual changes in mood or behavior.[76]

Adverse ASM Reactions Associated with Chronic Therapy

Antiseizure medications are often used life-long and one adverse reaction of chronic ASM therapy is osteomalacia and osteoporosis.[78,79] The effects on bone can range from asymptomatic high-turnover disease with findings of normal bone mineral density, to markedly decreased bone mineral density sufficient to warrant the diagnosis of osteoporosis. It has been hypothesized that mechanistically certain ASMs, including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, felbamate, and valproate, may interfere with vitamin D metabolism to cause this adverse reaction.[80] It is unknown whether other ASMs also cause osteomalacia and/or osteoporosis, but patients receiving chronic therapy should receive supplemental vitamin D and calcium, as well as bone mineral density testing if other risk factors for osteoporosis are present.

Antiseizure Medications

Of the ASMs available, their mechanisms of action fall into five broad categories: (1) modification of ionic conductance (eg, sodium channel inhibition, calcium channel inhibition); (2) enhancement of GABAergic (inhibitory) neurotransmission (eg, $GABA_A$-receptor agonism, inhibition of GABA metabolism/reuptake); (3) suppression of excitatory (usually glutamergic) excitatory neurotransmission (eg, inhibition of kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid [AMPA] receptor, inhibition of *N*-methyl D-aspartate [NMDA] receptor; (4) modulation of neurotransmitter release (eg, SV2A binding); and lastly (5) other unique or unknown mechanisms.[69] While it is useful to know mechanism of action for rational therapy and polytherapy, it is easiest to organize the ASMs into three generations which are not determined by structure or mechanism of action but by the time period in which they were FDA-approved. Each of the three generations of ASMs has specific characteristics that should be considered during selection of initial and subsequent ASM therapy. The following section is meant to highlight these major characteristics. Certain unique characteristics of specific medications within each class are also highlighted. For more specific information on pharmacokinetics, dosing, FDA-approved indication, preferred use in therapy, medication interactions, and adverse medication effects, see Tables 75-2 to 75-5. For additional detailed information on each ASM, the reader is referred to the individual FDA-approved ASM package inserts.

First-Generation ASMs

The first-generation ASMs, approved by the FDA from 1908 to 1978, are (1) carbamazepine, (2) clonazepam, (3) ethosuximide, (4) phenobarbital, (5)

phenytoin (and its esterified prodrug fosphenytoin), (6) primidone, and (7) valproate. Valproate is available as valproic acid and divalproex, which is a specific formulation of valproate composed of sodium valproate and valproic acid in a 1:1 molar relationship. Within the gastrointestinal track, divalproex dissociates to valproate as the active form.[69] The ASMs within this class, while considered to be among the most efficacious in controlling seizures, have complex pharmacokinetics, multiple interactions, and an increased incidence of adverse reactions that, in general, make them more complicated to manage than either the second- or third-generation ASMs.

Mechanisms of Action

With the exception of ethosuximide, all the first-generation ASMs have mechanisms of action that act either to primarily promote GABAergic activity or to inhibit sodium channels. The GABAergic first-generation ASMs include the barbiturate phenobarbital, primidone which is a prodrug metabolized to phenobarbital, and the benzodiazepine clonazepam which is a full $GABA_A$-receptor agonist.[20,37,69] Pharmacologically, these GABAerigic ASMs bind to sites at the $GABA_A$ receptor as agonists, increasing chloride channel opening and promoting hyperpolarization, which results in cells that are less susceptible to electrical impuses.[20,37,69] In contrast, phenytoin and carbamazepine bind to voltage-gated sodium channels in their inactive form preventing repetitive and sustained firing of sodium-dependent action potentials and stabilizing the threshold against hyperexcitability.[18,19,69] Because they bind the inactive form of the sodium channel, these agents cause a voltage-dependent and use-dependent block, which may preferentially target hyperexcitable areas that fire frequently.[18,19,69] Lastly, ethosuximide has a unique mechanism of action within this class and inhibits t-type calcium channels in cells of the thalamus and the cortex, preventing the abnormal firing of these cells that occur in absence epilepsies.[38,69]

Pharmacokinetics

First-generation ASMs have complex pharmacokinetics, especially phenytoin, with 90% of total phenytoin being protein bound in individuals with normal protein status and 10% being unbound as free phenytoin. Only unbound free phenytoin is pharmacologically active.[19] Reference ranges for total and free phenytoin levels were created with this ratio in mind, with a total phenytoin level in the therapeutic range of 10 to 20 mg/L (mcg/mL; 40-79 µmol/L) corresponding to a pharmacologically active free phenytoin level of 1 to 2 mg/L (mcg/mL; 4-8 µmol/L). Both total phenytoin and free phenytoin levels are routinely used in practice to guide therapy and it is important to understand what phenytoin level is being used to accurately interpret the true level of pharmacologically active medication. In patients with low protein status (eg, hypoalbuminemia, end-stage renal disease, critically ill patients), total serum phenytoin levels in the 10 to 20 mg/L (mcg/mL; 40-79 µmol/L) range no longer correspond to an active free phenytoin level of 1 to 2 mg/L (mcg/mL; 4-8 µmol/L) and does not reflect the true level of pharmacologically active phenytoin.[81] Monitoring of free phenytoin levels better reflect the true therapeutic levels in patients with hypoalbuminemia. However, free phenytoin levels, while commonly ordered, are not rapidly available through many laboratories (eg, results may take days to weeks). Valproate is also extensively bound to albumin, and due to saturable binding, the valproate free fraction will increase as the total serum concentration increases.[39] Similar to phenytoin therapeutic monitoring, the total valproate levels may not represent the amount of free medication available to exert a pharmacologic effect. However, free valproate levels are not commonly ordered, and only total valproate levels are generally available. Therefore, it is also important to know the patient's serum albumin level and protein status to aid in interpretation of total phenytoin and valproate serum levels.[39,81] This is especially true with phenytoin as various correction equations can be used to aid in interpreting total serum phenytoin levels in patients with low protein status, including the Winter–Tozer equation.[81] Valproate levels are not routinely corrected for low protein status in clinical practice, although it is still important to be aware of its possible effect. Carbamazepine, ethosuximide, and phenobarbital are also highly protein bound, but this has less of a clinically meaningful impact in practice.[18,37,38]

Phenytoin is metabolized in the liver by CYP450 enzymes and displays Michaelis–Menten pharmacokinetics.[36] At daily doses ≤300 mg, phenytoin's metabolism is generally linear in most patients. However, at doses ≥300 mg daily, it may saturate its metabolizing enzymes and a small change in dose can result in a disproportionally large increase in serum concentrations, potentially leading to toxicity.[19,36] This can also occur at low serum concentrations in some patients. Therefore, at phenytoin doses ≥300 mg, it is recommended to increase by 30-mg increments instead of 100-mg increments.

Carbamazepine, ethosuximide, phenobarbital, and valproate are also hepatically metabolized by CYP450 enzymes but in general display linear pharmacokinetics at clinically relevant doses.[18,37-39] An exception to this is ethosuximide which displays some evidence of nonlinear kinetics at higher

concentrations.[38] Carbamazepine is a particularly strong inducer of CYP metabolism and induces its own metabolism in a process known as autoinduction, where its half-life starts decreasing 3 to 5 days after therapy initiation with autoinduction being complete within 21 to 28 days.[18,36] Importantly, the reversal of autoinduction is rapid upon carbamazepine discontinuation.

Carbamazepine, ethosuximide, phenobarbital, phenytoin, and valproate all have narrow therapeutic ranges and require monitoring of serum concentrations (see Table 75-4 for target therapeutic ranges of specific ASMs and section "Evaluation of Therapeutic Outcomes" for role of serum concentration monitoring).[36]

Medication Interactions

As all of the first-generation ASMs undergo CYP450 hepatic metabolism, they also have significant interactions. In particular, carbamazepine, phenobarbital, and phenytoin are substrates and inducers of many CYP enzymes. As such, they will affect each other's metabolism if used in combination and may result in decreased levels of one or the other medication. They also affect metabolism of all other ASMs and medications that go through similar CYP450 pathways (Table 75-4) and vice versa.[18,19,36,37]

Enzyme-inducing ASMs may also induce uridine 5′-diphospho-glucuronosyltransferase (UGT) metabolism and have significant interactions with medications that undergo UGT metabolism, like lamotrigine, a second-generation ASM that undergoes UGT1A4 metabolism.[18,19,36,37]

Valproate on the other hand is an inhibitor of CYP450 and UGT metabolism and inhibits the metabolism of the first-generation ASMs as well as other ASMs and medications that go through similar CYP450 and UGT pathways. In particular, valproate decreases the clearance of phenobarbital and lamotrigine by 30% to 50% and can lead to phenobarbital and lamotrigine toxicity.[36,39]

First-generation enzyme-inducing ASMs may cause increased clearance of oral contraceptives (OCs) compromising their efficacy. The enzyme inhibitor, valproate, does not cause OC failure but OCs may cause increased valproate metabolism and subsequent increased risk in seizures. Therefore, in a patient of childbearing age with epilepsy, education around these interactions is a must.[18,19,37,39]

Adverse Medication Reactions

The first-generation ASMs are, in general, associated with a higher incidence of dose-related and idiosyncratic adverse reactions including neurotoxic effects, hepatotoxicity, and SJS/TEN. There are also a number of unique adverse effects associated with first-generation ASMs that are of particular note such as hyponatremia with carbamazepine, hyperactivity with phenobarbital in children, and gingival hyperplasia and osteoporosis with chronic use of phenytoin.[18,40,49] Valproate especially has a number of unique adverse effects including concentration-dependent thrombocytopenia at serum levels above 100 mg/L (mcg/mL; 693 µmol/L), hyperammonemia related to carnitine deficiency that may or may not lead to encephalopathy, idiosyncratic pancreatitis, and well-known teratogenicity.[39,82] Adverse effects of first-generation ASMs are listed in Table 75-5.

Advantages and Disadvantages

First-generation ASMs are very efficacious in epilepsy. Valproate, in particular, is considered a broad-spectrum ASM and is useful in both focal-onset and generalized-onset seizures as well as various epilepsy syndromes.[27,73,74] Phenobarbital has been in use for the longest period of time and is readily available worldwide. Carbamazepine and phenytoin are very efficacious in focal-onset seizures and have known efficacy in controlling tonic–clonic seizures but may exacerbate other generalized seizures and should be used with caution in generalized-onset epilepsy, especially generalized atypical absence.[18,19,27,73,74] Valproate and carbamazepine are also useful in multiple other comorbid conditions including migraine and bipolar disorder.[18,39] Despite their known advantages, however, first-generation ASMs should generally be considered after second-generation ASMs have failed, due to the greater tolerability, fewer medication interactions, and generic availability of the second-generation ASMs. The exception to this rule is ethosuximide, which is the medication of first choice for treatment of absence seizures but has limited use in other epilepsies.[36,83]

Second-Generation ASMs

The second-generation ASMs were developed with knowledge regarding the limitations of the first-generation ASMs and were FDA-approved from

1993 to 2000. Included in this class are (1) felbamate, (2) gabapentin, (3) lamotrigine, (4) levetiracetam, (5) oxcarbazepine, (6) tiagabine, (7) topiramate, and (8) zonisamide. In general, these medications are considered to have similar efficacy in controlling seizures as first-generation ASMs, have relatively simple pharmacokinetics with fewer interactions, and have an overall lower incidence of adverse effects.

Mechanisms of Action

The second-generation ASMs have mechanisms of action that include enhancement of GABAergic activity (eg, tiagabine) and sodium channel inhibition (eg, lamotrigine, oxcarbazepine, zonisamide) but also expand beyond that.[69] Notably, ASMs with novel mechanisms of action that were introduced within this generation include felbamate that modulates neurotransmission via inhibition of the *N*-methyl D-aspartate (NMDA) glutamate receptor, topiramate that inhibits the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor,[40,50] and levetiracetam that may modulate both glutamergic and GABAergic neurotransmission through modulation of presynaptic neurotransmitter release via inhibition of SV2A protein, considered the master regulator molecule of neurotransmitter release.[49,69] For the other medications in this class, their therapeutic effects are seen through novel mechanisms that have not been fully elucidated (eg, gabapentin that binds to presynaptic $\alpha_2\delta$ subunit of calcium channels, possibly resulting in decreased release of the excitatory neurotransmitters glutamate, noradrenaline, substance P, and calcitonin gene-related peptide).[41] Furthermore, topiramate and zonisamide are also carbonic anhydrase inhibitors, which can modulate the bicarbonate gradient in the brain and possibly affects GABAA receptor function, although whether or not this impacts antiseizure activity is unknown.[42,50] Additionally, during this time period, a second-generation structurally related derivative of carbamazepine, oxcarbazepine, was also introduced that exhibits a similar mechanism of action, but with an improved pharmacokinetic and adverse reaction profile.[43]

Pharmacokinetics

The second-generation ASMs also have pharmacokinetics that are less complex than first-generation ASMs. In general, they are not significantly protein bound and are well absorbed with good bioavailability, although of note, gabapentin relies on the L-amino acid carrier protein in the gut and the CNS to be actively transported across those membranes. As binding is saturable, this causes a dose-dependent bioavailability, with decreasing bioavailability with increasing dose, as the transporter is believed to be saturated at doses ≤1,200 mg per single dose.[41,84]

Unlike the first-generation ASMs which are all hepatically metabolized, two second-generation ASMs, gabapentin and levetiracetam, are primarily renally eliminated and dosage adjustments may be necessary in patients with significantly impaired renal function.[41,49] Additionally, topiramate is approximately 60% renally eliminated and should be dose adjusted in patients with renal impairment, although topiramate also undergoes CYP3A4 metabolism.[50] As for the remaining second-generation ASMs, felbamate, lamotrigine, oxcarbazepine, tiagabine, and zonisamide are all hepatically metabolized.[40,42-45] In contrast to carbamazepine, oxcarbazepine does not undergo autoinduction and also has an active metabolite (a monohydroxy derivative [MHD], 10-OH-carbazepine) that is inactivated by glucuronidation and eliminated by the kidneys. As such, oxcarbazepine may also require dosage reduction with significant renal impairment.[43]

Medication Interactions

Since gabapentin and levetiracetam do not undergo any appreciable hepatic metabolism, they display minimal medication interactions.[41,49] Felbamate, oxcarbazepine, tiagabine, zonisamide, and topiramate at higher doses are all hepatically metabolized and while there are some pharmacokinetic effects on the CYP450 pathways,[40,42,43,45,50] these effects are generally much less significant than those of the first-generation ASMs. Specifically, felbamate may induce or inhibit the metabolism of first-generation ASMs (or vice versa).[36,40] Oxcarbazepine inhibits CYP2C19 and induces CYP3A4/5, therefore, causing interactions with first-generation ASMs metabolized by these pathways, although to a lesser extent than its precursor carbamazepine. Additionally, oxcarbazepine may also reduce lamotrigine levels through a suggested induction of UGT enzymes, again to a lesser extent than its precursor carbamazepine.[36,43] Similarly topiramate is a weak inhibitor of CYP2C19 and an inducer of CYP3A4, therefore interacting with the first-generation ASMs as well as other medications that are metabolized by these pathways.[36,50]

Of the second-generation ASMs, lamotrigine has the most substantial interactions, which in some cases can be rather significant. Given valproate's enzyme-inhibiting properties, valproate can substantially inhibit the metabolism of lamotrigine, while carbamazepine, phenobarbital, phenytoin can substantially increase the metabolism of lamotrigine due to enzyme induction. As such, detailed dose and titration recommendations are available in

the situation for when lamotrigine is used in combination with these ASMs. It is important to follow dose titration recommendations for lamotrigine carefully, as too rapid dose titrations increase the risk for rash including SJS. Of note, lamotrigine itself does not inhibit liver enzymes and, therefore, has a low potential for pharmacokinetic interactions with other medications.[36,44]

Oxcarbazepine and topiramate both can interact with ethinyl estradiol and cause contraceptive failure, although topiramate doses ≤200 mg/day are unlikely to alter oral contraceptive pharmacokinetics.[43,50] The potential of lamotrigine to affect OC metabolism is minimal, but OCs can affect lamotrigine metabolism[44] as concomitant OCs lead to induction of lamotrigine glucuronidation by ethinyl estradiol. Once the OCs are withdrawn, significant increases in lamotrigine levels can be seen, including during the week of hormone withdrawal as part of various cyclic oral contraceptive treatments.[85]

In contrast to the first-generation ASMs, the second-generation ASMs have wide therapeutic ranges. While serum levels of second-generation ASMs are available through most laboratories, they are not routinely monitored, and levels may take many weeks to come back (see Table 75-3 for target therapeutic ranges of specific ASMs). One may monitor plasma levels of oxcarbazepine's active metabolite (MHD), which is more clinically significant than measuring oxcarbazepine levels directly. The therapeutic range for MHD is between 15 and 35 mcg/mL (mg/L; 59 to 138 µmol/L).[36]

Adverse Medication Reactions

The second-generation ASMs are associated with a lower incidence of dose-related CNS adverse reactions and are considered to be better tolerated than the first-generation ASMs. The exceptions are topiramate, which is associated with word-finding difficulties and cognitive slowing, and zonisamide which is a sodium channel inhibitor and associated with increased sedation and cognitive slowing. These neurotoxic effects are more common with rapid titration and high doses.[86,87]

Despite being better tolerated overall, there are a number of unique and severe adverse reactions associated with individual second-generation ASMs that must be considered when selecting therapy. The most severe of these is associated with felbamate which may potentially cause fatal idiosyncratic reactions including acute liver failure (1 in 10,000 patients), with reported onset between 68 and 354 days of therapy, and aplastic anemia (1 in 3,000 patients), with greater risk being seen in females, those with a history of cytopenia, prior ASM allergy or significant ASM toxicity, viral infection, and/or immunologic problems.[40] Tiagabine has been associated with new-onset seizures and status epilepticus.[45] Lamotrigine can cause rash, usually appearing after 3 to 4 weeks of therapy, and is typically generalized, erythematous, and morbilliform, but can progress to SJS. Rashes are more likely to occur if the patient has had a prior rash to another ASM[88] and risk factors for more serious rashes include concomitant use of valproic acid and situations where high initial doses or rapid dosage escalation is used. When dosed appropriately, the incidence of rash is similar to that of carbamazepine and phenytoin. The incidence of lamotrigine rash is higher in children than in adults.[89]

Of more moderate severity, topiramate and zonisamide are uniquely associated with kidney stones which can occur in 1.5% to 4% of patients who should be encouraged to maintain adequate fluid intake for the prevention of this adverse effect. Topiramate and zonisamide can also cause metabolic acidosis especially in patients with renal disease, severe respiratory disorders, diarrhea, surgery, and in patients on the ketogenic diet.[42,50]

Levetiracetam is well-recognized for causing irritability in many patients, which may be lessened with dose reduction.[49] Similarly, in patients receiving gabapentin for pain, abrupt discontinuation is associated with a withdrawal reaction characterized by anxiety, insomnia, nausea, sweating, and increased pain.[41]

Oxcarbazepine generally causes fewer adverse effects than the first-generation carbamazepine, but may have a higher incidence of hyponatremia, reported in as high as 25% of patients.[83] This adverse event occurs more often in older adult patients and in patients receiving concomitant sodium-depleting medications such as diuretics and is not very common in children. The incidence of rash with oxcarbazepine is less compared to carbamazepine, although approximately 25% to 30% of patients who develop a rash with carbamazepine also experience a similar reaction with oxcarbazepine.[43]

Advantages and Disadvantages

As previously stated, the second-generation ASMs are considered to be similar in efficacy to first-generation ASMs, but with better tolerability and

fewer medication interactions. Levetiracetam, in particular, is considered a useful broad-spectrum ASM with little, if any, CNS adverse effects besides irritability. It is routinely used as first-line monotherapy to treat focal-onset epilepsy and to a lesser extent myoclonic seizures of JME and primary generalized seizures.[36,49] However, increasing recognition of the unusually high prevalence of irritability and impact on QOL is limiting more widespread use of levetiracetam.

Lamotrigine is also efficacious in many epilepsy types, and, besides rash, is generally well tolerated with minimal CNS adverse effects, especially in older adults patients who may experience less cognitive adverse effects with lamotrigine than with other ASMs.[90] However, its use is mainly limited by the need for slow titration to avoid rash (especially if the patient is on valproate) and it is not a good agent for patients who need to reach therapeutic ASM levels quickly.[44] Both lamotrigine and oxcarbazepine may be a good ASM for patients with comorbid bipolar disorder, with oxcarbazepine not requiring very slow dose titration.[36,43,44] (See Chapter 89 for more information on the role of these ASMs for bipolar disorder.)

Topiramate and zonisamide are efficacious agents but due to their effects on cognition are sometimes considered after other ASMs. Topiramate additionally requires a very slow titration due to its CNS adverse reactions, further limiting its use. On the other hand, topiramate is usually considered earlier in therapy for those patients with epilepsy who also have comorbid migraines or those who have a wish to lose weight as it has some efficacy in this regard. Similarly, zonisamide is considered earlier in therapy for those patients who have issues with medication adherence as it is dosed once daily and has one of the longest half-lives of all the ASMs.[36,42,50]

Gabapentin is oftentimes considered a poorly efficacious ASM that may even exacerbate generalized-onset seizures and should be avoided in generalized-onset epilepsies.[27,73,74] However, it is well tolerated and widely used as adjunctive therapy in focal-onset epilepsy mostly for its benefit in comorbid conditions such as neuropathic pain and not necessarily for its efficacy in controlling seizures.[41] Tiagabine and felbamate have serious adverse reactions and are generally reserved for use only after failure of other ASMs, which is unfortunate as felbamate is broad spectrum (eg, can be used in focal-onset epilepsies and generalized-onset epilepsy syndromes like Lennox–Gastaut syndrome [LGS]) and is an effective ASM.[40] Furthermore, because of the risk of fatal aplastic anemia and liver failure, the use of felbamate requires signed written consent.[40]

Third-Generation ASMs

The third-generation ASMs were FDA-approved from 2004 to 2020 and agents in this generation can be further subcategorized into those that are approved for typical seizure indications and ASMs that are approved for specific epilepsy syndromes. The third-generation ASMs approved for typical seizure indications include (1) brivaracetam, (2) cenobamate, (3) eslicarbazepine, (4) lacosamide, (5) perampanel, and (7) pregabalin. The ASMs that are approved for specific epilepsy syndromes include (1) cannabidiol for LGS and Dravet Syndrome, (2) clobazam for LGS, (3) rufinamide for LGS, (4) stiripentol for Dravet Syndrome, and (5) vigabatrin for focal onset seizures as well as infantile spasms. (Note, topiramate, a second-generation ASM is also approved for LGS as well as focal onset or primary generalized seizures.) While many of the ASMs were approved for very specific indications only, they are often used off-label in refractory epilepsy after failure of other first-line ASMs.

Mechanisms of Action

Similar to the first-generation ASMs, many of the medications within this classification pharmacologically exert their effects through sodium channel inhibition and GABAergic mechanisms, as these continue to be proven to be efficacious in preventing seizures. Of the third-generation ASMs noted above, eslicarbazepine, lacosamide, and rufinamide are third-generation sodium channel inhibitors.[46,53,56] Eslicarbazepine is a derivative of carbamazepine that has a 5- to 15-fold lower affinity for the resting state of sodium channels than that of carbamazepine or oxcarbazepine, leading to a selectivity for neurons that are firing (typically seen in epilepsy).[46,69] Eslicarbazepine is postulated to inhibit sodium channels, through enhancement of slow inactivation, similar to lacosamide, another third-generation sodium channel inhibitor. Rufinamide, on the other hand, prolongs the inactivation phase of sodium channels similar to phenytoin and carbamazepine.[53,56,69]

Third-generation GABAergic ASMs also include vigabatrin, clobazam, and stiripentol. Vigabatrin is an amino acid that is a structural analog of GABA and is a selective, irreversible inhibitor of GABA-transaminase, the enzyme that degrades GABA.[23] Clobazam is a 1,5-chlorinated benzodiazepine derivative (structurally different from the 1,4 benzodiazepine clonazepam) that binds the $GABA_A$ receptor at the benzodiazepine site as an agonist and enhances inhibitory chloride ion transmission promoting hyperpolarization of the neuron. However, it demonstrates lower affinity for the $GABA_A$ subunits that

facilitate sedation, thereby reducing the incidence of this particular adverse effect.[52] Additionally, unlike traditional benzodiazepines which are nonselective full receptor agonists, clobazam is believed to be only a partial agonist.[52,69] Stirpipentol is believed to possibly act on $GABA_A$ receptors and may also inhibit CYP450 enzymes to increase blood levels of clobazam and its active metabolite.[70] Cenobamate is one of the newest ASMs and combines the two most common mechanisms of ASMs as it is believed to inhibit volgatge-gated sodium channels as well as being an allosteric modulator of the $GABA_A$ ion channel.[71]

In addition to these, two other derivatives of second-generation ASMs have also been introduced. The first agent is pregabalin, a derivative of gabapentin which pharmacologically works in a similar fashion by binding to presynaptic $\alpha_2\delta$ subunit of calcium channels.[55] The second agent is brivaracetam, a more selective derivative of levetiracetam that has a 15- to 30-fold higher affinity for SV2A, and binds SV2A to modulate neurotransmitter release and glutamergic and GABAergic transmission.[51,69]

Three new third-generation ASMs with novel mechanisms of action have also been introduced. Perampanel is a highly selective noncompetitive AMPA-type glutamate receptor antagonist,[54] and cannabadiol is purified derivative of cannabis whose exact antiseizure mechanism is unknown.[47] Fenfluramine's exact antiseizure mechanism is also unknown but it is known to increase extracellular serotonin through actions on serotonin transporter protein, and is an agonist at serotonin 5HT receptors and has efficacy in Dravet Syndrome.[72]

Pharmacokinetics

The third-generation ASMs have variable pharmacokinetic profiles which are unique to the individual agent and while some have simple pharmacokinetics, others have more complex pharmacokinetics almost similar to that of the first-generation ASMs.

Pregabalin and vigabatrin are the third-generation ASMs with the simplest pharmacokinetics (ie, good absorption, low protein binding, uncomplicated metabolism, linear elimination kinetics) and are the only two in this generation that are renally cleared.[23,36,55] Rufinamide, while hepatically metabolized, also displays simple pharmacokinetics, undergoing biotransformation via a carboxylesterase-mediated hydrolysis with no involvement of the CYP450 and UGT system.[36,56] Eslicarbazepine, despite being a prodrug that requires hydrolytic first-pass metabolism in the liver to form its active metabolite S-licarbazepine, also has relatively simple pharmacokinetics. After first-pass, eslicarbazepine is subsequently glucuronidated and renally excreted, requiring dosage adjustment in renal impairment but surprisingly not requiring adjustment in hepatic impairment.[36,46] Lacosamide is 40% renally eliminated and 60% hepatically metabolized by CYP3A4, CYP2C9, and CYP2C19, requiring dose adjustment in renal and hepatic impairment, but otherwise displays relatively simple pharmacokinetics.[36,53]

The third-generation agents with more complex pharmacokinetic profiles are brivaracetam, clobazam, and perampanel. Brivaracetam is metabolized by CYP2C19, and CYP2C19 poor and fast metabolizers may display altered brivaracetam pharmacokinetics. Brivaracetam dosage adjustment is required in all stages of hepatic impairment.[36,51] Clobazam is metabolized in the liver by CYP3A4 and CYP2C19 to a primary active metabolite *N*-desmethylclobazam which is then metabolized by CYP2C19. As such, its pharmacokinetics are also affected by CYP2C19 polymorphic variants and it also requires dosage adjustment in hepatic impairment.[36,52] Perampanel is highly protein bound (96%-96%) and eliminated primarily via CYP3A4 metabolism to an inactive metabolite with an elimination half-life of about 100 hours. Its use is not recommended in severe renal or hepatic impairment.[36,54]

Fenfluramine is complicated because it goes through hepatic metabolism by CYP1A2, CYP2B6, CYP2D6 with minor involvement of a few other CYPs to an active metabolite norfenfluramine which is then inactivated. Similarily stiripentol is also metabolized by CYP1A2, CYP2C19, and 3A4.[70,72] Of note, eslicarbazepine and perampanel are the two ASMs in this generation that have long half-lives and are dosed once-a-day. Monitoring of third-generation ASM serum concentrations is not routinely done and therapeutic ranges have not been clearly identified for some of these agents.[36]

Medication Interactions

As previously stated pregabalin does not undergo hepatic metabolism and, similar to its precursor gabapentin, has little to no interactions.[36,55] Vigabatrin, while not hepatically metabolized, is an inducer of CYP2C9 and has been noted to have slight effects on CYP2C9 substrates (eg, decreases phenytoin plasma levels by approximately 20% and possibly increases serum carbamazepine by 10%).[23,36]

Third-generation ASMs with fewer interactions are lacosamide, rufinamide, and fenfluramine. Lacosamide levels may be increased if used in combination with strong inhibitors of CYP3A4, CYP2C9, but most of these interactions are clinically insignificant.[36,53] Lacosamide is also a substrate of CYP2C19 and its blood levels can be modestly decreased (~15%-20%) by enzyme-inducing ASMs.[36,53] Rufinamide, a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4, may modestly affect the clearance of carbamazepine, lamotrigine, phenobarbital, and phenytoin and vice versa.[36,56] Additionally, concurrent use of rufinamide and OCs may result in reduced OCs efficacy while lacosamide does not reduce OC levels.[53,56] In regards to fenfluramine, stiripentol and clobazam combination act upon fenfluramine to increase its levels and other potent serotonin receptor binding agents may decrease its efficacy. However, fenfluramine does not generally act upon other ASMs and therefore has fewer interactions.[72]

Third-generation ASMs with more significant interactions include brivaracetam, clobazam, eslicarbazepine, and perampanel. Brivaracetam is a CYP2C19 substrate, and carbamazepine, phenobarbital, and phenytoin decrease its levels. Brivaracetam in turn may increase levels of the carbamazepine-epoxide metabolite and phenytoin levels but does not interact with lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproate, or OCs to a significant extent.[51] Clobazam is a CYP3A4 and CYP2C19 substrate and its levels may be affected by CYP3A4- and CYP2C19-inducing and -inhibiting medications such as felbamate and the first-generation ASMs, respectively.[36,52] Additionally, clobazam inhibits CYP2D6 and may affect the metabolism of other medications that use this pathway as well as lowering the serum levels of some OCs due to its weak induction effect on CYP3A4.[52] Like carbamazepine, eslicarbazepine is affected by CYP2C19 inducers and can itself inhibit CYP2C19 and affect plasma concentration of medications metabolized by this enzyme. However, similar to oxcarbazepine, the effects of eslicarbazepine are less significant than carbamazepine. Eslicarbazepine can also induce CYP3A4 affecting medications that are metabolized by this isoenzyme and may also lower OC levels.[36,46] Stiripentol is an inducer and inhibitor of multiple CYP enzymes and may also possibly be an inhibitor of the P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) transporters.[70] Of the third-generation ASMs, perampanel has the most potential for interactions as its serum levels are decreased by enzyme-inducing ASMs, it displays modest enzyme-inducing properties of its own at the high end of its dose range (12 mg/day), and it may lower OC levels.[36,54]

Adverse Medication Reactions

Third-generation ASMs have adverse reactions which are unique to the individual ASM, with some having minimal adverse effects, while others are known for specific serious effects. As the third-generation agents are the most recently FDA-approved ASMs, we have the least long-term experience with their use clinically; therefore, long-term and rare adverse effects may emerge as we gain more experience with them in a large population.

Among this generation, brivaracetam, lacosamide, and pregabalin are generally well tolerated, although we have the least experience with brivaracetam. In general, lacosamide's primary adverse reactions are CNS; however, these occur at a lower incidence than other ASMs and are more common in patients receiving concomitant treatment with other sodium channel inhibitors. Additionally, lacosamide is also associated with a lengthening of the PR interval which is not clinically significant unless used in combination with another ASM that lengthens the PR interval.[53] Pregabalin has an adverse effect profile that is notable for sedation and weight gain.[55]

Similarly, clobazam also is not commonly associated with any serious adverse reactions beyond CNS effects, but as a benzodiazepine, abrupt discontinuation may cause a withdrawal syndrome which could include seizures, psychosis, hallucinations, behavioral disorder, tremor, anxiety, dysphoria, and insomnia.[52]

In contrast, eslicarbazepine, rufinamide, and perampanel have more serious adverse reactions. Eslicarbazepine as a sodium channel inhibitor is associated with CNS effects and hyponatremia, although the occurrence of hyponatremia with this agent is less common than with carbamazepine and oxcarbazepine.[46] Eslicarbazepine like its earlier counterparts may still be associated with rash including SJS and TEN, hepatotoxicity, and hematologic adverse reactions. As rufinamide is also a sodium channel inhibitor, it is also associated with increased CNS effects as well as some rare and serious adverse reactions including an increased incidence of seizures and precipitation of status epilepticus. Additionally, multiorgan hypersensitivity has occurred within 4 weeks of starting treatment with rufinamide in patients younger than 12 years of age.[56] Aggression is a major common adverse reaction with perampanel and there is a FDA-boxed warning pertaining to monitoring of psychiatric, behavioral, mood, or personality changes which may be life-threatening.[54] Cenobamate mostly has CNS adverse reactions but there is also a risk of drug reactions with eosinophilia and systemic symptoms (DRESS) with fast titration; therefore, the dosage should be increased no faster than every two weeks. Additionally cenobamate is associated with QT interval shortening and a rate of appendicitis which was higher than in the normal population. Stiripentol may cause neutropenia

and thrombocytopenia which necessitates frequent monitoring of blood counts including prior to the first dose and every 6 months during and 6 months after discontinuing. Fenfluramine which was previously used as a weight-loss medication has known cardiac effects at higher doses and has a boxed warning regarding risk of valvular heart disease and pulmonary arterial hypertension, which requires echocardiograms before, during, and after treatment.[70-72]

Vigabatrin has the most serious adverse effects in this generation, as it may cause progressive, irreversible, bilateral concentric visual field constriction in a high percentage of patients. It may also reduce visual acuity in a dose-related and life exposure–related manner. Vigabatrin also may aggravate seizures, particularly absence and myoclonic seizures in patients with generalized epilepsies, and patients with history of depression, psychosis, or behavioral disturbances may be at greater risk to develop psychiatric effects with vigabatrin use.[23,91] Furthermore, in up to 11% of patients (up to age 3 years) treated with high doses of this medication for infantile spasms, MRI findings have been strongly suggestive of intramyelinic edema in select brain areas. While these findings appear to be reversible, their significance is unclear.[23,91]

Advantages and Disadvantages

Cannabadiol, fenfluramine, rufinamide, stiripentol, and vigabatrin have all been approved for specific epilepsy syndromes (Dravet syndrome and LGS, LGS, and infantile spasms, respectively) and in general should be considered for those indications.[23,47,56]

9 In regards to focal-onset epilepsies, third-generation ASMs have been used in clinical practice for the treatment of these epilepsies and probably have similar efficacy to the first- or second-generation ASMs. However, most third generations are not available in generic form now (except for pregabalin) and are less cost-effective than other ASMs. Therefore, third-generation ASMs should be reserved for use after failure of other agents.

Of the third-generation ASMs, lacosamide has become an ASM of choice among many providers, due to its ease of use, including the availability of intravenous loading and lack of medication interactions. However, there is no strong evidence to support this practice and lacosamide is only available as a brand product. Therefore, due to its cost, lacosamide should be reserved as second-line or third-line therapy after failure of other equally efficacious, less expensive ASMs.

Among the third-generation ASMs, clobazam may have the broadest use, as clobazam is believed to be efficacious in a wide variety of epilepsies including focal-onset and primary generalized epilepsies (despite having FDA approval only for LGS seizures) and perampanel is broadly approved for focal-onset seizure with or without secondary generalization as well as for primary GTC seizures.[52,54] Perampanel use, however, is somewhat limited by the appearance of aggression in some patients.[54]

Lastly, all ASMs in this generation except for eslicarbazepine, rufinamide, and vigabatrin are controlled substances making prescribing and access more difficult for these ASMs.[46,47,51-56] While vigabatrin is not a controlled substance, access is still restricted as all providers must be certified in the Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program in order to prescribe it.[23]

Therapeutic Considerations in Older Adults and Young

The most important aspect of ASM therapy is tailoring the choice of medication to the individual patient using knowledge of an individual ASM's pharmacodynamic and pharmacokinetic profile and its known advantages and disadvantages combined with knowledge of patient-specific factors including seizure type(s), age, sex, concomitant medical problems (including hepatic function, renal function), and interactions with concurrent medications.

In general, older adults are more often on many different medications which may contribute to increased sensitivity to neurocognitive effects. Additionally, this population may be more prone to the increased possibility of interactions with ASMs that affect the CYP450 system (eg, carbamazepine, phenytoin, and valproate); therefore, a thorough review of all medications is necessary prior to starting or modifying treatment. Hypoalbuminemia is also common in older adults, and highly albumin-bound ASMs (eg, phenytoin and valproate) should be closely monitored.[77] As patients age, they can also experience changes in body mass, such as an increase in fat to lean body mass or decrease in body water, which can affect volume of distribution and elimination half-life.[77] In addition, the older adults may have compromised renal or hepatic function that require ASM dosage adjustment.[77] Lamotrigine is often considered the medication of choice in older adults with focal-onset seizures, as results from a Department of Veterans Affairs cooperative trial found that it had equal efficacy to carbamazepine and gabapentin and was better tolerated than carbamazepine.[90]

For neonates and infants, an increase in the total body water to fat ratio and a decrease in serum albumin and α-acid glycoprotein can result in volume of distribution changes that affect ASM elimination half-life. Additionally, infants up to the age of 3 years have decreased renal elimination of ASMs, with neonates being the most affected. Hepatic activity is also reduced in neonates and infants, but by age 2 to 3 years, hepatic activity becomes more robust than that seen in adults. Therefore, whereas neonates and infants require lower doses of ASMs, children require higher doses than that seen in adults. Therapeutic medication monitoring becomes especially important in the young, even though the definitions of therapeutic blood levels are less certain in these patients than in adults.[77]

Therapeutic Considerations in Females (and Males)

Estrogen and progesterone are among the many hormones that can influence brain electrical excitability, as estrogen has a slight proconvulsant effect, whereas progesterone exerts a mild antiseizure effect.[15] In some individuals, vulnerability to seizures is highest just before and during the menstrual flow (catamenial seizures) and at the time of ovulation, which is believed to be due to a slight increase in estrogen relative to progesterone, or due to progesterone withdrawal and changes in the estrogen-to-progesterone ratio.[15] The risk of catamenial seizures is estimated be anywhere from 10% to 70% in females with epilepsy.[15] In these individuals, conventional ASMs should be used as primary agents, but intermittent supplementation with higher dose of ASM or benzodiazepines should be considered. Acetazolamide has also been used during catamenial periods, but with variable and limited success, and hormonal therapy with progestational agents, particularly cyclic natural progesterone therapy, may be effective in certain subsets of patients.[92]

At menopause, seizures often improve in frequency, particularly in individuals with a catamenial seizure pattern. However, for patients requiring hormone replacement therapy, it has been reported that conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate may increase the frequency of epileptic seizures. Therefore, a hormone replacement therapy that consists of just a single estrogenic compound, such as 17-β-estradiol, along with a natural progesterone, may be recommended for individuals with disruptive menopausal symptoms.[93]

Antiseizure medications may also have an effect on endogenous and exogenous hormones. As previously stated, enzyme-inducing ASMs increase the metabolism of estrogen, progesterone, and testosterone and increase production of sex hormone-binding globulin, leading to decreases in the free fraction of these hormones endogenously. These alterations lead to disturbances in the regulation of the hypothalamic–pituitary–adrenal axis and contribute to reproductive endocrine disorders including menstrual irregularity, infertility, sexual dysfunction, and in some patients polycystic ovary syndrome (PCOS).[94] Valproate, in particular, may affect sex hormone concentrations causing hyperandrogenism and polycystic changes, especially in individuals who have gained weight or those who start valproic acid prior to age 20.[94] Exogenously, enzyme-inducing ASMs can cause treatment failures in individuals taking OCs, as discussed in the prior sections, due to increased metabolism of ethinyl estradiol and progestin. Medroxyprogesterone depot injections and hormone-releasing intrauterine systems, on the other hand, are not similarly affected by ASMs, and it is unclear if there is an effect of ASMs on the transdermal contraceptive patch or the emergency contraceptive pill. A supplemental or alternative form of birth control (eg, IUD) is advised if breakthrough bleeding occurs in individuals taking certain types of ASMs (eg, enzyme-inducing ASMs) and OCs, and it has been suggested that they use twice the normal dose of emergency contraception.[95]

Data suggests that males with epilepsy have reduced fertility, and that carbamazepine, oxcarbazepine, and valproic acid are associated with sperm abnormalities. In addition, valproic acid seems to cause testicular atrophy resulting in reduced testosterone volume, whereas levetiracetam slightly increases serum testosterone. Various ASMs have also been anecdotally reported to affect libido and sexual function in both males and females.[95]

Therapeutic Considerations for Pregnancy and Lactation

Pregnancy and epilepsy is a particularly complex topic. The goal of treatment in pregnant patients with epilepsy is to achieve the best possible control of seizure with minimal adverse effects for the pregnant individual and the child. Epilepsy-related complications during pregnancy include possible changes in seizure frequency, fluctuating ASM plasma levels, and possible teratogenic effects of ASMs.[96,97]

Despite multiple reports of both increased and decreased seizure frequency during pregnancy, a recent practice parameter update issued by the American Academy of Neurology (AAN) found that there was inconclusive evidence to support that pregnancy was associated with changes in seizure frequency. What was concluded, however, was that patients with epilepsy who were seizure free for at least 9 months to 1 year prior to pregnancy had a very high probability (84%-92%) of remaining seizure free during pregnancy.[96] However, if seizures are increasing during pregnancy, it is important to

inquire about nonadherence in a normally adherent patient, as they may be concerned about the potential adverse medication effects on the developing fetus.[98]

Fluctuations in ASM concentration may be caused by physiologic changes that occur during pregnancy including reduced gastric motility, nausea and vomiting, increased medication distribution, increased renal elimination, altered hepatic enzyme activity as well as changes in protein binding.[95] Physiologic changes, such as changes in protein binding, can begin as early as the first 10 weeks of pregnancy, and may not normalize until 4 weeks postpartum (eg, protein binding of carbamazepine, phenobarbital, and phenytoin). Fluctuations in ASM plasma concentrations due to increased ASM clearance have been found to be true for lamotrigine, carbamazepine, phenytoin, oxcarbazepine, and levetiracetam.[96] Clinical consequences of ASM fluctuations are variable and some patients will not experience increased seizure frequency despite fluctuating levels. Patients on lamotrigine, however, have been found to undergo a 40% decrease in the ratio of plasma lamotrigine concentration to dose, resulting in deterioration of seizure control in approximately 75% of pregnant patients.[95] It is therefore recommended that ASM levels, particularly lamotrigine levels, be monitored closely during pregnancy, and that dosage increases occur over the course of the pregnancy if needed. This should be followed up with a rapid decrease in the postpartum period. Fluctuations have also been reported for phenobarbital, valproic acid, primidone, and ethosuximide, although strong evidence for this is lacking.[96]

Adverse pregnancy outcomes associated with ASM use include an increased risk of major congenital malformations (MCMs) compared to pregnant persons without epilepsy.[97] This risk is believed to be due to ASM exposure and not seizures, as infants born to patients with epilepsy who do not take ASMs have the same risk of birth defects as infants born to seizure-free individuals (2%-3%).[98] The most concerning effects are found with the use of valproic acid which is associated with a risk of MCMs that is 3.5 to 4 times that of offspring from patients without epilepsy, especially if taken during the first trimester of pregnancy.[97,99] Furthermore there is an increased risk of neurodevelopmental deficits, including effects on cognition, in children exposed to valproic acid *in utero.*[97,99] These effects are dose-dependent, and the risk of MCM significantly increases at 600 mg/day, with the greatest risk observed at doses that exceed 1,000 mg/day.[99] However, individual susceptibility is genetically determined, and teratogenicity can occur at much lower doses in some persons. Due to these findings, it is recommended that valproate should not be used in pregnant individuals or in female patients of childbearing potential with epilepsy and that withdrawal of valproate or switching to an alternative treatment should be considered.

Data on teratogenic risk with the newer agents are limited, although topiramate was reclassified from pregnancy category C to D due to an increased association with cleft palate (it may also have a negative effect on birth weight and cause increases in hypospadias).[50] In general, higher ASM doses, higher ASM serum concentrations, polytherapy (especially polytherapy with valproate), and a family history of birth defects increase the teratogenic risk of ASMs.[97] As such, the risk of birth defects is believed to have gone down with decreasing doses and decreasing use of polytherapy.

Deciding on the most effective single-medication treatment prior to conception is vitally important. Teratogenic effects of ASM must always be considered when choosing ASMs for patients of reproductive age, even when the plans are not to become pregnant, as many unplanned pregnancies occur and MCMs generally occur early in pregnancy before the patient is aware of their pregnancy. With proper counseling and management, more than 90% of these pregnancies will still have satisfactory outcomes. Updated practice parameters are available to aid in the selection of ASMs in pregnancy and the counseling and management of pregnant patients with epilepsy.[96,97,99]

Teratogenic effects may possibly be prevented by adequate folate intake. Although data are insufficient to show that folate is effective in preventing MCM in patients with epilepsy, there is no evidence of harm. Therefore, the AAN recommends that all females of childbearing potential, take folic acid prior to conception and during pregnancy. The AAN cites insufficient data to support a specific dose but prenatal vitamins containing folic acid 0.4 to 5 mg/day can be recommended.[100] Folate doses in the high range should be used in individuals with a history of a previous pregnancy with a neural tube defect or in those taking valproic acid. Additionally, some ASMs may possibly cause neonatal hemorrhagic disorder and there is a lack of strong evidence to determine if prenatal vitamin K supplementation can reduce this complication. However, vitamin K 10 mg/day is often administered orally to the pregnant person during the last month of pregnancy and/or administered parenterally to the newborn at delivery.[101]

Some ASMs pass into human milk and those with less protein binding will accumulate more. Treatment with ASMs is not necessarily a reason to discourage breastfeeding, although ASM concentrations are measurable in infants fed human milk. In fact, an argument could be made that since ASMs should rarely be discontinued abruptly, providing human milk after birth allows for a downward titration of a medication that the baby was exposed to for the past 9 months. Infants born to patients taking any ASM (particularly barbiturates or benzodiazepines) should be closely observed

for signs of excess sedation, irritability, or poor feeding.[101,102] In general, FDA labeling of ASMs including valproate state that the developmental and health benefits of human milk should be considered along with the patient's underlying seizure disorder, their clinical need for that ASM, and any potential adverse effects from the ASM on the infant fed human milk. Additionally, FDA labeling states caution should be exercised when an ASM is administered to an individual providing human milk to an infant.

Therapeutic Considerations in Patients of Asian and South Asian Decent

A common idiosyncratic effect of ASMs is rash. However, in some cases, the rash can quickly progress to SJS, TEN, or DRESS, which are severe and life-threatening conditions. There is a strong association between the presence of an inherited variant of the *HLA-B* gene, *HLA-B*1502*, in these populations, and the risk of developing SJS/TEN with carbamazepine phenytoin, and oxcarbazepine.[18,19,43] The frequency of HLA-B*15:02 is highest in East Asian (6.9%), Oceanian (5.4%), and South/Central Asian (4.6%) populations, although of note, while it is present, it is less frequent in Japan (<1%) and Korea (<2.5%). The variant is largely absent in individuals not of Asian origin. Testing for HLA B*1502 is recommended for patients with ancestry from genetically at-risk. If the genetic testing is positive, these ASMs should generally be avoided. In addition, the *HLA* genotype *HLA-A*3101* is associated with multiple carbamazepine-induced cutaneous reactions in Chinese, Japanese, and European populations and carbamazepine should be avoided in patients with that genotype.[18] Many *HLA-B*1502*-positive and *HLA-A*3101*-positive patients treated with ASMs will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in *HLA-B*1502*-negative and *HLA-A*3101*-negative patients of any ethnicity. Of those who do experience SJS/TEN with carbamazepine, 90% will have this reaction within the first few months of treatment.[18]

EVALUATION OF THERAPEUTIC OUTCOMES

The goal of therapy for all ASMs is seizure freedom or reduction in seizure frequency, while minimizing adverse medication reactions. Determining clinical response to treatment involves identifying the number and type of seizures and adverse medication reactions during the monitoring and follow-up phase of treatment. Providing the patient with a seizure and adverse reactions diary will assist in this effort as the severity and frequency of seizures should be monitored by the patient and the family and recorded in the seizure diary. External factors such as seizure triggers can also influence seizure frequency. Therefore, patients should be educated that seizure triggers should be identified and documented because avoiding them may have a significant impact on seizure control. Additionally, although seizures tend to be stereotyped within an individual, the clinical presentation of the seizure may change over time or with treatment and this should be documented. During all follow-up visits, the seizure diary should be reviewed with both patients and family to determine whether patients are truly seizure free.

Patients should also be monitored for all ASM adverse reactions and assessed for dose-related CNS effects (eg, drowsiness, fatigue, dizziness, blurry vision, and incoordination). Such adverse reactions are common, especially when initiating ASM therapy as well as with polytherapy. If possible, CNS adverse reactions should be avoided, either by dose reduction of monotherapy, reduction or elimination of polytherapy, or substituting for a better tolerated ASM.

Patients should also be assessed for idiosyncratic adverse reactions which usually require withdrawal in an affected patient, including serious rash (ie, SJS, TEN), hematologic dyscrasias, electrolyte abnormalities (eg, hyponatremia), and hepatotoxicity. Laboratory assessment, including complete blood cell (CBC) counts, chemistries, and liver function tests, should be performed at baseline and after initiation of ASMs to monitor for idiosyncratic adverse reactions. Other specific laboratory tests can be performed if there is clinical suspicion of adverse reactions (eg, measuring ammonia levels in a patient with suspected hyperammonemic encephalopathy from valproic acid). Acute organ failure due to an idiosyncratic reaction, when it occurs, generally occurs within the first 6 months of ASM therapy,[103] although there is a delay between treatment initiation and the onset of symptoms. There is also a more rapid onset if a patient who has had an idiosyncratic reaction to a specific ASM is rechallenged.[103]

Patients on chronic ASM therapy should be monitored for long-term medication adverse effects. Specifically, for those patients on chronic ASMs known to cause osteoporosis (eg, phenytoin and phenobarbital), bone density loss can be measured via bone-density scanning (eg, DEXA) after many years of treatment. Gums should be visually inspected for gingival hyperplasia at follow-up (eg, phenytoin) and patients should also be instructed to have regular and thorough dental care.

Medication adherence should also be monitored and when seizures are not controlled, medication nonadherence must always be considered, as it is the single most common reason for treatment failure. It is estimated that up to 60% of patients with epilepsy are nonadherent.[104] The rate of nonadherence is increased by the complexity of the regimen and by doses taken three and four times a day.[104] Frequent uncontrolled seizures can also

predispose a patient to nonadherence secondary to confusion over whether the medication was taken. Nonadherence is not influenced by age, sex, psychomotor development, or seizure type.[104]

Obtaining serum concentrations of ASMs is a method by which to optimize therapy for an individual patient, but is not a therapeutic end point in itself. A patient's clinical response is more important than the actual serum medication concentration as seizure control can occur before the "minimum" of the published therapeutic range is achieved, and adverse medication effects can appear before the "maximum" of the range is achieved. Some patients may need and tolerate concentrations beyond the maximum. Clinicians should define a therapeutic range for an individual patient as the concentration below which there are adverse effects and above which the patient experiences seizures. Then serum levels can be useful to document lack of efficacy, loss of efficacy, and to determine how much room there is to increase a dose based on expected toxicity. Serum levels can also be particularly useful to determine nonadherence and should be checked if there are questions. Depending on the ASM, serum levels can also be useful in patients with significant renal and/or hepatic disease, patients taking multiple agents, and individuals who are pregnant or taking OCs.[36,77]

Patients should also be monitored long term for comorbid conditions, social adjustment (including QOL assessments), and medication interactions. Periodic screening for comorbid neuropsychiatric disorders, such as depression, suicidal ideation, and anxiety, is also important. Screening for learning and development issues in children is also imperative as neurodevelopmental comorbidities commonly coexist with epilepsy and may be associated with use of ASMs.[2]

Overall treatment outcomes are increasingly focusing on obtaining an optimal QOL for the patient and the AAN has developed quality performance measures for the clinician that define a high quality of care of these patients. Among those performance measures, it is important to remember to counsel patients about ASM adverse reactions and initiate a discussion about depression. Additionally, factors that can impact QOL in patients with epilepsy which should be addressed include issues about driving, economic security, forming relationships, and epilepsy safety such as precautions when swimming, social isolation, and social stigma.[2,32]

10 After the initiation of treatment, approximately 65% of patients treated for new-onset epilepsy can be expected to be maintained on one ASM and may be seizure free.[34] The percentage of patients who are seizure free on one ASM varies by seizure type. After 12 months of treatment, the percentage who are seizure free is highest for those who have only GTC seizures (48%-55%), lowest for those who have only focal seizures (23%-26%), and intermediate for those with mixed seizure types (25%-32%).[102,105]

Polytherapy with two or more ASMs is appropriate for patients who cannot achieve seizure freedom on ASM monotherapy. Of the 35% of patients with unsatisfactory control on monotherapy, 10% will be well controlled with a two-ASM treatment. Of the remaining patients, 20% will continue to have unsatisfactory control despite greater than two-ASM treatment and are deemed to be medication resistant.[34] The ILAE consensus definition for medication-resistant epilepsy includes lack of seizure freedom from at least two adequate trials of an ASM as monotherapy or polytherapy, which were appropriately chosen and used.[103] Those who have unsatisfactory control despite multiple ASM treatment may be candidates for the ketogenic diet, a vagal nerve stimulator, and/or surgery, which is especially encouraged for those who are good surgical candidates. In fact, the AAN has included assessment about patient knowledge and referral to surgery in their quality performance measures.[32]

For a patient with long-standing epilepsy, adequacy of their current medication regimen, whether they are seizure free or not, should be routinely evaluated. Reevaluate goals when necessary, especially in those 20% to 35% of patients where seizure freedom cannot be achieved, as obtainable goals which balance seizure control with patient-specific QOL factors[2,32] and wishes (eg, decrease in the number of seizures with minimized medication adverse effects) should be established. Patient education and assurance of patient understanding of the goals is also an essential part of the care plan.

For some patients who have not experienced seizures for many years and who are deemed to have a low risk of recurrence, ASM withdrawal may be considered. The AAN has issued guidelines for discontinuing ASMs in seizure-free patients.[106] After assessing the risks and benefits to both the patient and society, ASM withdrawal can be considered in a patient meeting the following profile: seizure free for 2 to 5 years, a history of a single type of focal seizure or primary generalized seizures, a normal neurologic exam and normal IQ, and an EEG that has normalized with treatment.[107,108] When these factors are present, the relapse rate at 1 year is expected to be 35% and 29% at 2 years.[109] For those patients who relapse after withdrawal, ASMs can be restarted; while seizure freedom can be regained for most patients who restart ASMs, it does not happen for all.[110] Factors associated with a poor prognosis in discontinuing ASMs, despite a seizure-free interval, include a history of a high frequency of seizures, repeated episodes of status

epilepticus, a combination of seizure types, and development of abnormal mental functioning.[107,108]

CONCLUSION

Epilepsy is a group of diseases that present with variable signs and symptoms and is a major burden in terms of QOL, morbidity, and risk of premature mortality from SUDEP, especially in those who continue to have seizures. Pharmacologic management of epilepsy consists of symptomatic treatment only. The mainstay of pharmacologic therapy is ASMs, with a goal of suppression of seizure occurrence. Over the years, over two dozen ASMs with various mechanisms of action, pharmacokinetics, adverse effect profiles, and interaction profiles have become available for the treatment of epilepsy. When selecting ASM therapy, efficacy must be balanced with ASM adverse effects and cost and take into consideration patient-specific factors including age, sex, susceptibility to adverse effects, concomitant medications, and ability to adhere with selected regimen. Suppression of seizures can be achieved with ASM monotherapy or polytherapy in up to two-thirds of all patients with epilepsy but do not alter long-term prognosis. In patients with medication-resistant epilepsy, nonpharmacologic options such as ketogenic diet, vagal nerve stimulation, and epilepsy surgery should be considered. Epilepsy surgery is the most effective way to achieve long-term seizure freedom, but is an option for only a few people with medication-resistant epilepsy. With improved understanding of epilepsy pathophysiology and pathogenesis, better, disease modifying, and curative pharmacological treatments may become available.

ABBREVIATIONS

AAN	American Academy of Neurology
AES	American Epilepsy Society
AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ASM	antiseizure medication
AUC	area under the medication concentration time curve
BECT	benign epilepsy with centro-temporal spikes
CAE	childhood absence epilepsy
C_{max}	maximal blood medication concentration
CT	computed tomography
DEXA	dual energy x-ray absorptiometry
DRESS	drug reactions with eosinophilia and systemic symptoms
EEG	electroencephalogram
EFHC1	EF-hand containing protein-1
GABA	γ-aminobutyric acid
GTC	generalized tonic–clonic
IGE	idiopathic generalized epilepsy

ILAE	International League Against Epilepsy
LGS	Lennox–Gastaut syndrome
JME	juvenile myoclonic epilepsy
MCMs	major congenital malformations
MRI	magnetic resonance imaging
NMDA	*N*-methyl-D-aspartate
OC	oral contraceptive
PCOS	polycystic ovary syndrome
QOL	quality of life
REMS	risk evaluation and mitigation strategy
SCARs	severe cutaneous adverse reactions
SE	status epilepticus
SJS	Steven–Johnsons syndrome
SP	simple partial
SUDEP	sudden unexplained death in epilepsy
TEN	toxic epidermal necrolysis
T_{max}	time to maximal blood medication concentration
VNS	vagus nerve stimulation
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. At what age is the incidence of epilepsy the highest?
   A. Childhood
   B. Adolescence
   C. Older adult
   D. Both A and C
2. The key feature of generalized-onset seizures is
   A. Onset encompassing the entire brain.
   B. Onset in a network of cells in one hemisphere.
   C. Onset in a network of cells distributed bilaterally.
   D. Spread to both hemispheres.
3. The key feature of focal unaware seizures is
   A. Onset in one hemisphere.
   B. Impaired awareness.
   C. Retained awareness.
   D. Evolution to bilateral convulsions.
4. Nonpharmacologic therapy of the epilepsy patient can involve all of the following in the appropriate patient *except*
   A. Temporal lobe surgery

B. Low glycemic index diet treatment

C. Acupuncture

D. Vagal nerve stimulator

5. Which ASM is *most* associated with major congenital malformations?

A. Lamotrigine

B. Topiramate

C. Levetiracetam

D. Valproic acid/divalproex

6. Which ASM may aggravate other seizure types in childhood absence epilepsy, a generalized-onset epilepsy?

A. Phenytoin

B. Valproate/divalproex

C. Ethosuximide

D. Levetiracetam

7. Which ASM is a CYP450 inhibitor?

A. Carbamazepine

B. Phenytoin

C. Phenobarbital

D. Valproic acid/divalproex

8. Which ASM has saturable GI absorption at large doses?

A. Gabapentin

B. Tiagabine

C. Levetiracetam

D. Lacosamide

9. Which ASM is often associated with increased irritability?

A. Felbamate

B. Clobazam

C. Levetiracetam

D. Lamotrigine

10. Patient H has a history of calcium phosphate kidney stones and is allergic to sulfa. Which is the *worst* choice of ASM to use in the treatment of this patient's partial seizures?

A. Lacosamide

B. Zonisamide

C. Carbamazepine

D. Oxcarbazepine

11. Which ASM is more likely to cause word-finding problems?

A. Valproic acid/divalproex

B. Tiagabine

C. Phenytoin

D. Topiramate

12. Which ASM is associated with an increased risk of rash including SJS if the recommended dose escalation is exceeded?

A. Peramapnel

B. Lamotrigine

C. Eslicarbazepine

D. Clobazam

13. Which ASM is associated with irreversible vision loss after long-term use?

A. Vigabatrin

B. Lacosamide

C. Valproic acid/divalproex

D. Rufinamide

14. In a patient taking an enzyme-inducing ASM, which form of birth-control does *not* need a back-up method to avoid pregnancy?

A. Transdermal contraceptive patch

B. Emergency contraceptive pill

C. Oral contraceptive pills

D. Hormone-releasing intrauterine device system

15. A drug-resistant epilepsy patient is one who has failed:

A. One drug

B. Two drugs

C. Three drugs

D. More than three drugs

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** While epilepsy is a chronic disease that can present at all ages, the highest number of new epilepsy cases will present in childhood and the older population. New epilepsy cases presenting in childhood are often of genetic origin and epilepsy cases presenting in the older population are usually acquired due to brain injury (eg, stroke).

2. **C.** Generalized-onset seizures start in bilaterally distributed networks (eg, a network encompassing both sides of the brain) and not necessarily everywhere in the brain (see Fig. 75-1).

3. **B.** A focal unaware seizure corresponds to the prior term "complex partial seizure" and its distinguishing feature is impaired awareness at any time during a focal seizure (Fig. 75-1). The distinguishing feature of focal seizures (both unaware and aware) is its onset in one hemisphere.

4. **C.** Epilepsy surgery, including temporal lobe surgery, ketogenic diet which is a low glycemic index diet treatment, and vagal nerve stimulation are all nonpharmacologic therapies that have benefit in decreasing seizure frequency in epilepsy. Acupuncture does not have benefit in epilepsy.

5. **D.** Valproic acid/divalproex especially has a number of unique adverse effects including a well-known teratogenicity and is pregnancy category D in epilepsy and pregnancy category X for migraine prevention (Table 75-5).

6. **A.** Both phenytoin and carbamazepine are very efficacious in focal-onset seizures and have known efficacy in controlling tonic–clonic seizures but may exacerbate other generalized seizures and should be used with caution in generalized-onset epilepsy, especially generalized atypical absence (Table 75-5).

7. **D.** Valproic acid/divalproex is an inhibitor of CYP450 and UGT metabolism and inhibits the metabolism of the first-generation ASMs as well as other ASMs and drugs that go through similar CYP450 and UGT pathways (Tables 75-3 and 75-5).

8. **A.** Gabapentin relies on the L-amino acid carrier protein in the gut and the CNS to be actively transported across those membranes. As binding is saturable this causes a dose-dependent bioavailability, with decreasing bioavailability with increasing dose as the transporter is believed to be saturated at doses ≤ 1,200 mg per single dose.

9. **C.** Levetiracetam is well-recognized for causing irritability in many patients, an effect which may be lessened with dose reduction (Table 75-5). There is increasing recognition of the unusually high prevalence of irritability and its impact on QOL with levetiracetam.

10. **B.** Zonisamide is contraindicated in those with sulfa allergy and is associated with a rare risk of renal stones (Table 75-5).

11. **D.** Word-finding difficulties and cognitive slowing have been commonly reported to occur (Table 75-5) especially during rapid titration and with high doses of topiramate.

12. **B.** Lamotrigine can cause rash (Table 75-5), usually appearing after 3 to 4 weeks of therapy, and is typically generalized, erythematous, and morbilliform, but can progress to Steven–Johnson syndrome. Rashes are more likely to occur if the patient has had a prior rash to another ASM and risk factors for more serious rashes include concomitant use of valproic acid and situations where high initial doses or rapid dosage escalation is used.

13. **A.** Vigabatrin may cause progressive, irreversible, bilateral concentric visual field constriction in a high percentage of patients and may also reduce visual acuity in a dose-related and life exposure–related manner (Table 75-5).

14. **D.** Enzyme-inducing ASMs can cause treatment failures in patient's taking oral OCPs due to increased metabolism of ethinyl estradiol and progestin. It is unclear if there is an effect of ASMs on the transdermal contraceptive patch or the emergency contraceptive pill but it has been suggested that individuals use twice the normal dose of emergency contraception. Medroxyprogesterone depot injections and hormone-releasing intrauterine systems, on the other hand, are not similarly affected by ASMs.

15. **B.** The ILAE consensus definition for drug-resistant epilepsy includes lack of seizure freedom from at least two adequate trials of ASM monotherapy or polytherapy, which were appropriately chosen and used.