Chapter 54: Epilepsy and Status Epilepticus

INTRODUCTION

- *Epilepsy* is a common neurologic condition in which a person is prone to recurrent epileptic seizures. Epilepsies are characterized by different seizure types, ranging in severity and etiologies often with neurobiological, cognitive, psychological, and social consequences. *Status epilepticus* (SE) is a neurologic emergency associated with brain damage and death with generalized convulsive status epilepticus (GCSE) being the most common and severe form. It occurs when the length of the continuous seizure activity extends past 5 minutes or time of ongoing seizure activity extends past 30 minutes, after which there is a risk of long-term consequences.

PATHOPHYSIOLOGY

- Seizures result from excessive excitation or disordered inhibition of neurons, resulting in changes in electrical activity as measured by the electroencephalogram (EEG). Initially, a small number of neurons fire abnormally. Normal membrane conductances and inhibitory synaptic currents then break down, and excitability spreads locally (focal seizure) or more widely (generalized seizure). Epileptic seizures result only when there is also synchronization of excessive neuronal firing.
- Seizure initiation is likely caused by an imbalance between excitatory (eg, glutamate, calcium, sodium, substance P, and neurokinin B) and inhibitory (γ-aminobutyric acid [GABA], adenosine, potassium, neuropeptide Y, opioid peptides, and galanin) neurotransmission.
- GCSE is largely caused by glutamate acting on postsynaptic *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptors. Sustained depolarization can result in neuronal death.
- $GABA_A$ receptors may become less responsive to endogenous GABA and GABA agonists.
- Epilepsy etiologies can be classified into six categories: (1) genetic; (2) structural; (3) infectious; (4) metabolic; (5) immune; and (6) unknown.

CLINICAL PRESENTATION

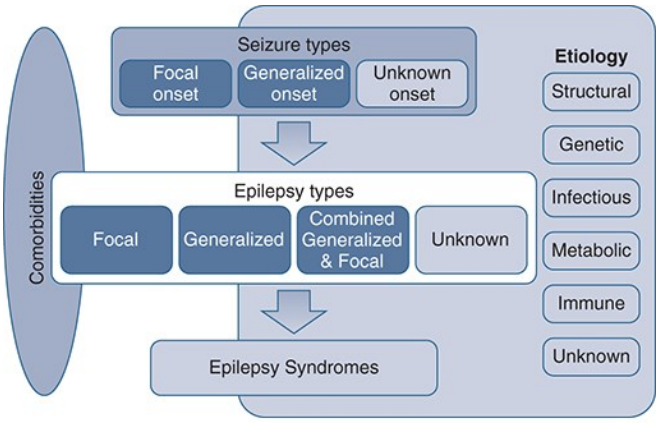
Epilepsy

- **Figure 54-1** shows the International League Against Epilepsy (ILAE) framework for the classification of seizure types.
- Many patients, particularly those with focal onset seizures with dyscognitive features or generalized tonic–clonic (GTC) seizures, are amnestic to the actual seizure event.
- Symptoms depend on seizure type and where the abnormal firing occurs. Although seizures can vary between patients, they tend to be stereotyped within an individual.
- Focal seizures (ie, partial seizures) begin in one hemisphere of the brain, and unless they become secondarily generalized (ie, evolve to a bilateral convulsive seizure), result in an asymmetric seizure. Focal seizures manifest as alterations in motor functions (eg, twitching or shaking), sensory (eg, numbness or tingling) or somatosensory symptoms, aberrations in behavior, or automatisms. Focal seizures without dyscognitive features (formerly called simple partial seizures) are associated with no impairment of consciousness. In focal seizures with dyscognitive features (formerly called complex partial seizures), there is impairment of consciousness and awareness and no memory of the event.
- Absence seizures generally occur in young children or adolescents and exhibit a sudden onset, interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes. There is only a very brief (seconds) period of altered consciousness. Absence seizures have a characteristic two to four cycles per second spike and slow-wave EEG pattern.
- GTC seizures are major convulsive episodes and are always associated with a loss of consciousness. Motor symptoms are bilateral. GTC seizures may be preceded by premonitory symptoms (ie, an aura). A tonic–clonic seizure that is preceded by an aura is likely a focal seizure that is secondarily generalized. Tonic–clonic seizures begin with a short tonic contraction of muscles followed by a period of rigidity and clonic movements. The patient may lose sphincter control, bite the tongue, or become cyanotic. The episode is frequently followed by a deep sleep.
- Interictally (between seizure episodes), there are typically no objective, pathognomonic signs of epilepsy.
- Myoclonic seizures are brief shock-like muscular contractions (jerks) of the face, trunk, and extremities. They may be isolated events or rapidly repetitive. There is no alteration of consciousness.
- In atonic seizures (the hallmark of Lennox–Gastaut syndrome), there is a sudden loss of muscle tone that may be described as a head drop, dropping of a limb, or slumping

to the ground.

FIGURE 54-1

ILAE 2017 Classification of seizure types—expanded version.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Status Epilepticus

- The four stages of GCSE are (1) stablization, (2) initial therapy, (3) secondary therapy, and (4) third therapy as indicated in **Table 54-1**.

  ✔ During first therapy phase of GCSE, each seizure produces marked increases in plasma epinephrine, norepinephrine, and steroid concentrations that may cause hypertension, tachycardia, and cardiac arrhythmias. Muscle contractions and hypoxia can cause acidosis, hypotension, shock, rhabdomyolysis, and secondary hyperkalemia, and acute tubular necrosis may ensue.

  ✔ In second therapy phase, beginning 30 minutes into the seizure, the patient begins to decompensate and may become hypotensive with compromised cerebral blood flow. Serum glucose may be normal or decreased, and hyperthermia, respiratory deterioration, hypoxia, and ventilatory failure may develop.

  ✔ The third therapy phase consists of refractory and supra-refractory GCSE where motor activity may cease, but electrical seizures may persist.

- Younger children, older persons, and those with preexisting epilepsy have a higher propensity for sequelae.
- Overall worldwide case fatality rate of 14.9%, with the highest rate in those >60 years of age (24.9%) and in those with refractory GCSE (33.3%).
- ✔ Variables affecting outcome are (1) the time between onset of GCSE and the initiation of treatment and (2) the duration of the seizure. The mortality rate is 2.6%, 19%, and 32% for those with seizures lasting 10–29 minutes, longer than 30 minutes, and longer than 60 minutes, respectively.

TABLE 54-1

Generalized Convulsive Status Epilepticus

Phase	Time	Stage	Definition
Stabilization phase	0–5 minutes		An acute condition characterized by convulsive seizures. This may include pre-hospitalization or emergency room care
Initial-therapy phase (5–20 minutes)	0–20 minutes	Impending GCSE	
Second-therapy phase (20–40 minutes)	20–40 minutes	Established GCSE	An acute condition characterized by continuous or intermittent seizures without full recovery of consciousness between events for at least 20 minutes
Third-therapy phase	40–60 minutes	Refractory GCSE	An acute condition characterized by continuous seizures despite initial treatment with 2 ASDs
	>24 hours	Supra-refractory	An acute condition characterized by seizures that continue 24 hours or longer after the administration of anesthesia, including cases in which SE recurs on reduction or withdrawal of anesthesia

ASD, antiseizure drug; GCSE, generalized convulsive status epilepticus; SE, status epilepticus.

DIAGNOSIS

- Ask the patient and family to characterize the seizure for signs/symptoms, triggers, frequency, duration, precipitating factors, time of occurrence, presence of an aura, impairment of consciousness, ictal activity, and postictal state.
- Physical, neurologic, and laboratory examination may identify an etiology.
- A person is considered to have epilepsy if they have (1) at least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart; (2) 1 unprovoked (or reflex) seizure and a probability of further seizures of at least 60% after 2 unprovoked seizures, occurring over the next 10 years; or (3) a diagnosis of an epilepsy syndrome.
- In some cases, particularly following GTC seizures, serum prolactin levels may be transiently elevated. A serum prolactin level obtained within 10–20 minutes of a tonic–clonic seizure can help differentiate seizure activity from pseudoseizure activity but not from syncope.
- Laboratory tests may rule out treatable causes of seizures (hypoglycemia, altered serum electrolyte concentrations, infections, etc.) that are not epilepsy.
- EEG is very useful in the diagnosis of various seizure disorders, but epileptiform activity is found in only about 50% of patients with epilepsy.
- Brain imaging with either a computerized tomography (CT) scan or magnetic resonance imaging (MRI) can detect structural lesions that can aid in the diagnosis of seizures and epilepsy types.

TREATMENT

Epilepsy

- Goals of Treatment: Control or reduce the frequency and severity of seizures, minimize side effects, and ensure compliance, allowing the patient to live as normal a life as possible. Complete suppression of seizures must be balanced against tolerability of side effects, and the patient should be involved in defining the balance. Side effects and comorbidities (eg, anxiety and depression) as well as social issues (eg, driving, job security, relationships, and social stigma) have significant impact on quality of life.

Status Epilepticus

- Goals of Treatment: (1) Identify GCSE subtype and precipitating factors; (2) terminate clinical and electrical seizure activity as soon as possible, and preserve cardiorespiratory function; (3) minimize side effects; (4) prevent recurrent seizures; and (5) avoid pharmacoresistant epilepsy and/or neurologic sequelae.

Nonpharmacologic Therapy

Epilepsy

- Nonpharmacologic therapies are available for drug-resistant patients with epilepsy as well as for drug-responsive patients in which the benefits of nonpharmacologic therapies outweigh its risk (ie, ketogenic diet, vagus nerve stimulation [VNS], and surgery among other modalities).

Status Epilepticus

- Therapy starts with the stabilization phase where the time of seizure onset should be noted, vital signs should be assessed, a protected airway should be established, ventilation should be maintained, and oxygen should be administered. Intravenous access should be established and hyperthermia, if present, should be aggressively treated (eg, rectal or IV acetaminophen and cooling blanket).
- Laboratory values should be drawn, including anticonvulsant serum concentrations.
- Continuous EEG monitoring may need to occur for patients with persistent GCSE and frequent arterial blood gas determinations are necessary to assess for metabolic acidosis.

Pharmacologic Therapy

Epilepsy

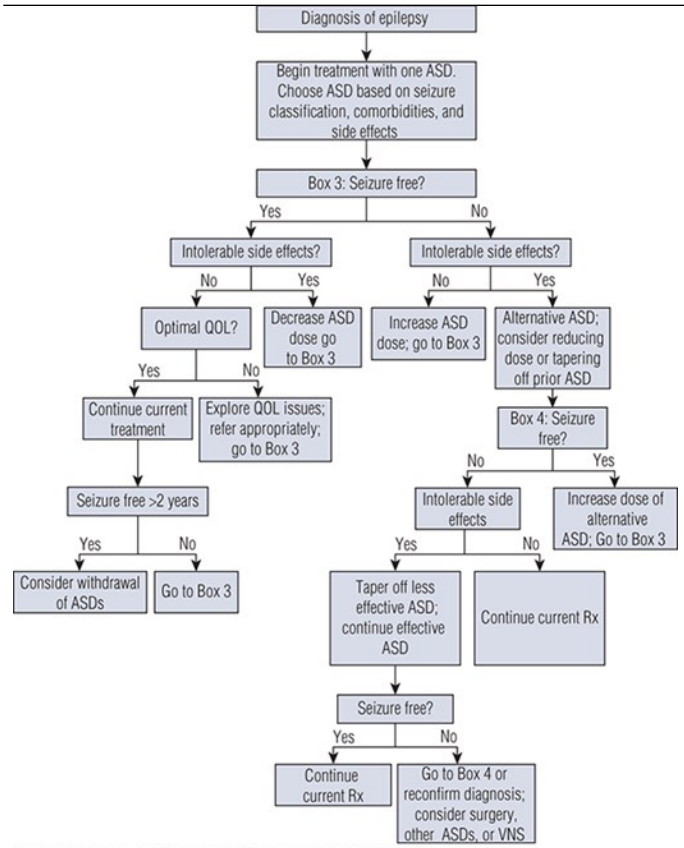
- Drug selection depends on the seizure type and epilepsy classification as well as patient-specific characteristics including age, gender, susceptibility to adverse effects, comorbid medical conditions, interactions with other medications, ability to comply with a prescribed regimen, and cost of therapy/insurance coverage. **Figure 54-2** is a suggested algorithm for treatment of epilepsy.
- Most anti-seizure drugs (ASDs) affection channel (sodium and Ca) kinetics, augmentation of inhibitory neurotransmission (increasing CNS GABA), and modulation of excitatory neurotransmission (decreasing or antagonizing glutamate and aspartate). ASDs effective against GTC and focal seizures probably work by delaying recovery of sodium channels from activation. Drugs that reduce corticothalamic T-type Ca currents are effective against generalized absence seizures.
- Begin with monotherapy. About 65% of patients can be maintained on one ASD, although not necessarily seizure free.
- Up to 60% of patients with epilepsy are nonadherent, commonly leading to treatment failure.
- Patients who have had two or more seizures should generally be started on ASDs; however, some providers start after one seizure.
- Provide the patient with a seizure and side-effect diary.
- ASD dosing is shown in **Table 54-2**.
- Many newer ASDs have been tested only as adjunctive therapy, but many providers will use them off-label as monotherapy.
- Evidence for comparable effectiveness is mostly available for older agents and for a few newer ones. In general, the newer ASDs appear to have comparable efficacy to the older drugs, and some may be better tolerated.
- **Carbamazepine**, **ethosuximide**, **gabapentin**, **levetiracetam**, **oxcarbazepine**, **phenytoin** **valproic acid**, and **zonisamide** have strong enough evidence to be labeled efficacious or effective or as probably efficacious or effective as initial monotherapy in certain seizure types.
- Some ASDs may possibly precipitate or aggravate certain seizure types, and it is suggested that they be used with caution in those patients. Examples are **carbamazepine**, **gabapentin**, **oxcarbazepine**, **phenytoin**, **tiagabine**, and **vigabatrin** in children with absence or juvenile myoclonic epilepsy.
- Initiate ASD with a low dose (ie, one-fourth to one-third of the anticipated maintenance dose), and titrated gradually over 3–4 weeks to a moderate dose. If seizures continue, titrate to a maximum dose. If the first ASD is ineffective or causes intolerable side effects, add a second ASD (preferably with a different mechanism of action), and then taper and discontinue the ineffective or intolerable drug. If the second ASD is ineffective, then polytherapy may be indicated.
- Clinicians should determine the optimal serum concentration for each patient as seizure control may occur before the “minimum” of the therapeutic serum range is reached, and some patients may need serum concentrations beyond the “maximum.”
- The therapeutic range for ASDs may be different for different seizure types (eg, higher for focal seizures with dyscognitive features than for GTC seizures).
- Serum concentration determinations can be useful to document lack of or loss of efficacy, establish noncompliance, and guide therapy in patients with renal and/or hepatic disease and patients taking multiple drugs, as well as in women who are pregnant or taking oral contraceptives.
- Lower doses of ASDs are often required in older individuals due to compromised renal or hepatic function and some patients have increased receptor sensitivity to CNS drugs, making the accepted therapeutic range invalid. Older persons often take many medications, and thus are more prone to experience neurocognitive effects and drug–drug interactions involving ASDs that affect the CPY450 system (eg, carbamazepine, phenytoin, valproic acid, and phenobarbital). Hypoalbuminemia is common in older populations, and highly bound ASDs (eg, valproic acid) can be problematic. They also experience body mass changes which can affect elimination half-life and volume of distribution. **Lamotrigine** is often considered a drug of choice for older patients with focal onset seizures because of effectiveness and tolerability.

- After 12 months of treatment, the percentage who are seizure free is highest for those with 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%).
- ASD withdrawal can be considered in a patient meeting the following profile: seizure free for 2–5 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. Factors favoring an unsuccessful withdrawal of ASDs include a history of a high frequency of seizures, repeated episodes of SE, a combination of seizure types, and development of abnormal mental functioning. Always withdraw ASDs gradually.
- Drug resistance is defined as failure of adequate trials of two tolerated and appropriately chosen and used ASD schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.
- For populations known to have altered plasma protein binding, measure free rather than total serum concentrations if the ASD is highly protein bound. Conditions altering ASD protein binding include chronic renal failure, liver disease, hypoalbuminemia, burns, pregnancy, malnutrition, displacing drugs, and age (neonates and older persons). Unbound concentration monitoring is especially useful for phenytoin.
- Neonates and infants display decreased efficiency in renal elimination and may metabolize drugs more slowly, but by age 2 or 3 years children may metabolize drugs more rapidly than adults. Thus, neonates and infants require lower doses of ASD, but children require higher doses of many ASDs than adults.
- ASD side effects and monitoring are shown in **Table 54-3**. Concentration-dependent side effects can often be alleviated by decreasing the dose or avoided by increasing the dose very slowly.
- CNS side effects are frequent and include sedation, dizziness, blurred vision, poor concentration, and ataxia.
- Barbiturates can cause more cognitive impairment than other ASDs, but in children, they can cause paradoxical excitement. In general, the newer agents have less effect on cognition, except topiramate.
- The most widely recognized idiosyncratic reactions are ASD-induced drug rashes, which can progress to Stevens–Johnson syndrome/toxic epidermal necrolysis. Variants of the HLA-B gene, HLA-B*1502, have been associated with increased risk of developing Stevens–Johnson syndrome as well as toxic epidermal necrolysis with carbamazepine (and possibly phenytoin, lamotrigine, and oxcarbazepine). This variant is found in up to 15% of individuals of Asian, southeast Asian, and south Asian origin. Patients with this variant should generally avoid these drugs. Also, the HLA genotype HLA-A*3101 is associated with carbamazepine-induced skin reactions in individuals of Chinese, Japanese, and European populations.
- Others reactions include hepatitis and blood dyscrasias. When acute organ failure occurs, it usually happens within the first 6 months of ASD therapy. Any patient taking ASDs who complains of lethargy, vomiting, fever, or rash should have a laboratory assessment, including white blood cell counts and liver function tests.
- A side effect of long-term use of ASDs is osteomalacia or osteoporosis. It is hypothesized that phenytoin, phenobarbital, carbamazepine, oxcarbazepine, felbamate, and valproic acid may interfere with vitamin D metabolism. Patients taking these drugs should receive vitamin D supplementation and calcium and bone mineral density testing if other risk factors for osteoporosis are present. Laboratory tests may reveal elevated bone-specific alkaline phosphatase and decreased serum Ca and 25-OH vitamin D, as well as intact parathyroid hormone.
- **Table 54-4** shows ASD elimination pathways and major effects on hepatic enzymes. Use caution when ASDs are added to or discontinued from a drug regimen. Pharmacokinetic interactions are common complicating factor in ASD selection.
- Phenobarbital, phenytoin, primidone, and carbamazepine are potent inducers of cytochrome P450 (CYP450), epoxide hydrolase, and uridine diphosphate glucuronosyltransferase enzyme systems. Valproic acid inhibits many hepatic enzyme systems and displaces some drugs from plasma albumin.
- Felbamate and topiramate can act as inducers with some isoforms and inhibitors with others.

FIGURE 54-2

An algorithm for ASD therapy.

(ASD, antiseizure drug; VNS, vagal nerve stimulation; QOL, quality of life)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 54-2

Antiseizure Drug Dosing and Target Serum Concentration Ranges

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maximum Dose	Comments Target Serum Concentration Range
First generation				
Carbamazepine	Tegretol	400 mg/day	400–1600 mg	4–12 mcg/mL[a] (17–51 µmol/L)
	Tegretol XR			
Clonazepam	Klonopin	1.5 mg/day	20 mg	20–70 ng/mL (67–233 pmol/L)
Ethosuximide	Zarontin	500 mg/day	500–1500 mg	40–100 mcg/mL (282–708 µmol/L)
Phenobarbital	Various	1–3 mg/kg/day (10–20 mg/kg LD)	180–300 mg	10–40 mcg/mL[a] (43–172 µmol/L)
Phenytoin	Dilantin	3–5 mg/kg (200–400 mg)	300–600 mg	Total: 10–20 mcg/mL (40–79 µmol/L)
		(15–20 mg/kg LD)		Unbound: 0.5–3 mcg/mL (2–12 µmol/L)
Primidone	Mysoline	100–125 mg/day	750–2000 mg	5–10 mcg/mL (23–46 µmol/L)
Valproic acid	Depakene	15 mg/kg (500–1000 mg)	60 mg/kg (3000–5000 mg)	50–100 mcg/mL (347–693 µmol/L)
	Depakote DR/ER			

	Depacon			
Second generation				
Felbamate	Felbatol	1200 mg/day	3600 mg	30–60 mcg/mL (126–252 µmol/L)
Gabapentin	Neurontin	300–900 mg/day	4800 mg	2–20 mcg/mL (12–117 µmol/L)
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25–50 mg/day if not on VPA	100–200 mg if on VPA; 300–500 mg if not on VPA	4–20 mcg/mL (16–78 µmol/L)
	Lamictal XR			
Levetiracetam	Keppra	500–1000 mg/day	3000 mg	12–46 mcg/mL (70–270 µmol/L)
	Keppra XR			
Oxcarbazepine	Trileptal	300–600 mg/day	1200–2400 mg	3–35 mcg/mL (MHD) (12–139 µmol/L)
	Oxtellar XR			
Tiagabine	Gabitril	4 mg/day	56 mg	0.02–0.2 mcg/mL (0.05–0.5 µmol/L)
Topiramate	Topamax	25–50 mg/day	200–400 mg	5–20 mcg/mL (15–59 µmol/L)
	Trokendi XR			
Zonisamide	Zonegran	100 mg/day	600 mg	10–40 mcg/mL (47–188 µmol/L)
Third generation				
Brivaracetam	Briviact	100 mg/day	200 mg/day	Not defined
Cannabadiol	Epidiolex	5 mg/kg/day	10–20 mg/kg/day	Not defined
Clobazam	Onfi	≤30 kg: 5 mg/day; >30 kg: 10 mg/day	≤30 kg up to 20 mg; >30 kg up to 40 mg	0.03–0.3 mcg/mL (0.1–1.0 µmol/L)
Eslicarbazepine	Aptiom	400 mg/day	800–1600 mg	Not defined
Lacosamide	Vimpat	100 mg/day	400 mg	Not defined
Perampanel	Fycompa	2 mg/day	8–12 mg	Not defined
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Rufinamide	Banzel	400–800 mg/day	3200 mg	Not defined
Vigabatrin	Sabril	1000 mg/day	3000 mg	0.8–36 mcg/mL (6–279 µmol/L)

[a]Units mcg/mL and mg/L are numerically equivalent, and units ng/mL and mcg/L are numerically equivalent.

LD, loading dose; MHD, 10-monohydroxycarbazepine derivative.

TABLE 54-3

Antiseizure Drugs (ASDs) (Continued)

ASD and Available Formulations	Advantages	Disadvantages	DDI: Effect of Drug on Concomitant ASD	DDIs: Effect of Concomitant ASDs on Drug	Common and Dose-Related Adverse Effects	Rare and Serious Adverse Effects[a]	Long-Term Adverse Effects

First-generation ASDs							
Carbamazepine Chewable tablet, ER tablet, liquid suspension	Useful in comorbid bipolar disorder and trigeminal neuralgia	Worsens other seizure types in patients with absence epilepsy; avoid if prior rash with other ASDs due to possible cross-reaction; increased risk of SJS/TEN in HLA-B*1502 and HLA-A*3101 allele in Asians; auto-inducer; active metabolite carbamazepine 10,11 epoxide contributes to idiosyncratic side effects; can cause fetal harm	Potent inducer of CYP3A4, CYP1A2, CYP2B6, CYP2C9/19; decreases levels of brivaracetam, clonazepam, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin, tiagabine, topiramate, valproate	Phenobarbital, phenytoin, primidone decrease levels; valproate increases carbamazepine-10,11 epoxide	CNS effects including diplopia, dizziness, drowsiness, unsteadiness, lethargy	Boxed warning: Increased risk of SJS/TEN and HLA-B*1502 allele; aplastic anemia and agranulocytosis Other blood dycrasias including thrombocytopenia, leukopenia; DRESS; hyponatremia; increased intraocular pressure; cardiovascular effects including second- and third-degree AV heart block; hepatotoxicity; genitourinary effect; nephrotoxicity	Hyponatremia (periodically monitor sodium); metabolic bone disease including osteoporosis, osteopenia, osteomalacia
Clonazepam (Schedule IV) Tablet, ODT	Useful in patients with panic disorder, myoclonic seizures, and subcortical myoclonus	May increase TC seizures when used in mixed seizure types; tolerance and dependence may occur; use with other CNS depressant may produce additive effects; may cause respiratory depression; contraindicated in acute narrow angle glaucoma and severe liver impairment; withdrawal symptoms may occur after discontinuation; no adequate data in pregnancy—may cause fetal harm	May affect levels of phenytoin	May be affected by enzyme-inducing or enzyme-inhibiting ASDs	CNS effects including sedation, ataxia; paradoxical reactions such as agitation, irritability, aggression, anxiety, anger, nightmares, hallucinations and psychoses	Boxed warning: Concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death Blood dyscrasias including leukopenia, thrombocytopenia, eosinophilia; rash; cardiovascular or respiratory depression; hepatotoxicity; muscle weakness	Physiologic dependence; loss of effect; hair loss; hirsutism; ankle and facial edema
Ethosuximide Capsule, liquid solution	Drug of choice for absence seizures	Worsens generalized TC seizures and other seizure types; contraindicated in	May affect levels of phenytoin, carbamazepine, phenobarbital,	Valproate may increase or decrease levels	GI distress including nausea/vomiting, cramps diarrhea; anorexia and	Blood dyscrasias including leukopenia, agranulocytosis, pancytopenia; rash	Behavioral changes

		those with allergies to succinimides; may cause fetal harm; use with caution in hepatic/renal dysfunction	phenytoin, primidone, valproate		weight loss; CNS effects including drowsiness, dizziness, hiccoughs	including SJS; DRESS; hepatic/renal dysfunction; lupus erythematosus	
Phenobarbital (Schedule III) Tablet, elixir, injectable solution		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	May decrease levels of carbamazepine, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, tiagabine, topiramate, valproate	Valproate increases levels; phenytoin increases or decreases levels	CNS effects including residual sedation, drowsiness, lethargy, confusion, ataxia, vertigo; paroxysmal excitement, irritability and hyperactivity in older persons and children; GI effects including nausea, vomiting	Respiratory depression and apnea; rash (SJS, TEN); cardiac effects including bradycardia, hypotension, syncope; hepatotoxicity	Behavioral changes; connective tissue disorder; intellectual blunting; metabolic bone disease (osteoporosis, osteopenia, osteomalacia); folate deficiency (with megaloblastic anemia)
Phenytoin ER capsule; liquid suspension; injectable; chewable tablet (Fosphenytoin, a prodrug desterified by esterases in the blood to phenytoin, also available as injectable solution only)	Useful in nonadherence as dosed once daily	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; monitoring of free phenytoin levels required in pregnancy, older persons or low albumin; compromised absorption with concomitant tube feeds	May decrease levels of brivaracetam, carbamazepine, clonazepam, eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, perampanel, tiagabine, topiramate, valproate	Ethosuximide, felbamate, oxcarbazepine, methsuximide, topiramate may increase levels; carbamazepine, vigabatrin may decrease levels; phenobarbital, valproate may increase or decrease levels	CNS effects including ataxia, nystagums, slurred speech, decreased coordination, mental confusion, dizziness, insomnia, transient nervousness, headaches	Blood dyscrasias including thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia; rash (SJS/TEN); DRESS; hepatotoxicity, cardiac effects; purple glove syndrome with IV administration	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 Tablet	Useful in essential tremor	Contraindicated in patients with porphyria	May decrease levels of carbamazepine, eslicarbazepine, ethosuximide, lamotrigine, oxcarbazepine, perampanel, phenytoin,	Valproate may increase levels; phenytoin may increase or decrease levels	CNS effects including ataxia, vertigo, nystagmus, diplopia, drowsiness, fatigue; GI effect including nausea/vomiting,	Blood dyscrasias including granulocytopenia, agranulocytosis; rash (SJS, TEN); liver dysfunction	Behavioral changes; intellectual blunting; connective tissue disorder; metabolic bone disease (rickets, osteomalacia); folate deficiency (with megaloblastic anemia)

			rufinamide, tiagabine, topiramate, valproate		anorexia, fatigue; emotional disturbances including hyperirritability		
Valproate Divalproex DR sprinkle capsule, Divalproex DR tablet, Divalproex ER 24-hour tablet, valproic acid IR capsule, valproate sodium injectable solution	Useful in comorbid bipolar disorder and migraine	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; 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	May increase levels of eslicarbazepine, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, rufinamide, topiramate	Carbamazepine, phenobarbital, phenytoin, primidone decrease levels; felbamate can increase levels; estrogen OCPs may affect levels	GI effects including abdominal pain/GI upset (worse with 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 (associated with valproate concentrations >100 mg/mL; 693 umol/L).	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 Hyperammonemia with and without encephalopathy; hypothermia with and without hyperammonemia; DRESS; bleeding and other hematopoietic disorders	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 ASDs							
Gabapentin Tablet, capsule, oral solution	Useful in postherpetic neuralgia, chronic pain, and neuropathy; few drug–drug interactions	Considered weakly efficacious; potential abuse when taken with opioids; withdrawal reaction characterized by anxiety, insomnia, nausea, sweating, and increased pain; absorption may be impaired for doses >1,200					

		mg; no adequate data in pregnancy—may cause fetal harm					
Lamotrigine Tablet, chewable tablet[a], ODT[a], XR tablet[a]	Useful in bipolar disease; XR useful in nonadherence as dosed once daily	Slow titration required to avoid rash including SJS; increased risk if patient with prior rash to other ASD 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	Does not inhibit liver enzymes	Valproate increases lamotrigine levels by 2x; carbamazepine, phenytoin, phenobarbital, primidone decrease levels by 40%; estrogen OCPs decrease lamotrigine by 50%	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	Boxed warning: Rash including SJS, TEN with increased risk if given with valproate, exceeding recommended initial dose or dose escalation 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 Tablet, XR tablet[a], injectable solution	Minimal drug–drug interactions; XR useful in nonadherence as dosed once daily	May worsen depression, PTSD, anxiety, thought disorders; dose adjustment in dialysis/renal failure is necessary; pregnancy category C			CNS effects including somnolence, fatigue; behavior effects including aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability	Psychosis, hallucinations	
Oxcarbazepine Tablet, tablet ER[a], liquid suspension[a]	Useful in bipolar disorder; ER useful in nonadherence as dosed once daily	Higher incidence of hyponatremia (as high as 25%); must check HLA-B*1502 in Asians to predict SJS or TEN; active MHD metabolite may decrease in pregnancy; no adequate data in pregnant women—may cause fetal harm	Inhibitor of CYP2C19 and inducer of CYP3A4/5; increases phenytoin levels; decreases lamotrigine levels through UGT induction; decreases estrogen OCP levels	Carbamazepine, phenytoin and phenobarbital decreases active metabolite levels	CNS effects including dizziness, somnolence, diplopia, fatigue, ataxia, abnormal vision, headache, nystagmus, tremor; GI effects including nausea, vomiting	Hyponatremia; rash (SJS, TEN); DRESS; blood dyscrasias	Hyponatremia

Tiagabine Tablet		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		Carbamazepine, phenytoin, primidone, phenobarbital decrease levels; valproate increases levels by 40%	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 and nausea	Increase in generalized seizures and nonconvulsive 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	Possibility of long-term ophthalmologic effects
Topiramate Sprinkle capsule, tablet, XR tablet, capsule, capsule ER	Useful in comorbid migraine and obesity; XR useful in nonadherence as dosed once daily	Avoid in patients with preexisting cognitive issues; renally dose adjust with CrCl <70 mL/min; can cause fetal harm	Weak inhibitor of CYP2C19 and inducer of CYP3A4; decreases estrogen OCP levels	Phenytoin carbamazepine decreases levels	CNS effects including fatigue, difficulty concentrating, confusion, language problems, tremor paresthesias; behavioral effects including nervousness, anxiety	Renal stones; glaucoma; oligohidrosis and hyperthermia; metabolic acidosis; rash (SJS, TEN); hypothermia and hyperammonemia with and without encephalopathy when used with valproate	Weight loss, renal stones, metabolic acidosis
Zonisamide Capsule	Useful in tremor; useful in nonadherence as dosed once daily	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		CYP3A4 inhibitors or inducers may alter levels; carbamazepine, phenobarbital, phenytoin, valproate decrease levels	CNS effects including sedation, ataxia, confusion, depression, difficulty concentrating, word-finding difficulties	Oligohidrosis and hyperthermia; renal stones; metabolic acidosis; rash (SJS, TEN); DRESS; fulminant hepatic necrosis; blood dyscrasias	Weight loss, renal stones, metabolic acidosis
Third-generation ASDs							
Brivaracetam (Schedule V) Tablet, oral solution, injection solution	Consider converting well-controlled patients from levetiracetam if intolerable psychiatric side effects	Dosage adjustments required in hepatic impairment; no adequate data in pregnancy—may cause fetal harm	Increases carbamazepine metabolite; increases phenytoin levels	CYP2C19 inhibitors may alter levels	CNS effects including sedation, fatigue, ataxia, nystagums; behavioral effects including irritability, aggressive behavior, anxiety;	Angioedema; bronchospasm; decreased neutrophils; psychosis	

					GI effects including nausea, vomiting		
Cannabidiol (Schedule V) Oral solution	Useful for refractory seizures in LGS and Dravet syndrome	Avoid in patients with hypersensitivity reactions to cannabis, THC; liver function and bilirubin monitoring 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	Increases lamotrigine levels; increase levels of clobazam active metabolite by 3 times	CYP3A4 and CYP2C19 inhibitors will increase levels; CYP3A4 and CYP2C19 inducers will decrease levels	CNS effects including somnolence, fatigue, malaise, asthenia; sleep disorders including insomnia, poor quality sleep; GI effects including decreased appetite; diarrhea; transaminase elevations	Hepatotoxicity; hypoxia; respiratory failure	
Clobazam (Schedule IV) Tablet, oral suspension		Monitor patients with history of substance abuse; use with other CNS depressant may produce additive CNS effects; may cause respiratory depression, coma, and death; no adequate data in pregnant women—may cause fetal harm	Inhibitor of CYP2C9 and inducer of CYP3A4; affects levels of CYP2C9, CYP3A4 substrates; decreases estrogen OCP levels	Carbamazepine, felbamate, phenobarbital, phenytoin, primidone decrease levels	CNS effects including somnolence, sedation, lethargy; pyrexia; constipation; drooling	Boxed warning: Concomitant use with opioids increases risk of death Rash (SJS, TEN); anemia; liver enzyme elevations; respiratory depression	
Eslicarbazepine Tablet	Useful in nonadherence as dosed once daily	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	Inhibitor of CYP2C19; affects carbamazepine, phenytoin, phenobarbital, primidone levels; decreases estrogen OCP levels	Carbamazepine, phenobarbital, primidone, and phenytoin decrease levels	CNS effects including dizziness, somnolence, nausea, headache, diplopia, fatigue, vertigo, ataxia, blurred vision, tremor	Hyponatremia; rash (SJS); anaphylaxis, angioedema, DRESS; cardiac effects including prolonged PR interval, AV block; hepatotoxicity; blood dyscrasias	Hyponatremia
Lacosamide (Schedule V) Tablet, oral solution, Injectable solution	Minimal drug–drug interactions	Avoid in third-degree heart block; use with caution in patients with underlying proarrhythmic	Substrate of CYP3A4, CYP2C9, and CYP2C19; carbamazepine, phenytoin,	CYP2C19 inhibitor but no clinically significant effects	CNS effects including ataxia, dizziness, diplopia, headache, tremor; GI effects including nausea, vomiting	Cardiac effects including AV conduction abnormalities, prolonged PR interval, atrial	

		conditions or on concomitant medications that affect cardiac conduction; no adequate data in pregnancy—may cause fetal harm	phenobarbital, primdone, decrease levels by 15%–20%			arrhythmias, syncope (especially in patients with diabetes)	
Perampanel (Schedule III) Tablet, oral suspension	Useful in mixed seizure types; useful in nonadherence as dosed once daily	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	Modest enzyme inducer at high doses; carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, topiramate decrease levels; valproate has no effect on levels; decreases estrogen OCP levels		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	Boxed warning: Aggression, hostility, irritability, anger, and homicidal ideation	Weight gain
Pregabalin (Schedule V) Capsule, tablet CR, oral solution	Useful in patients with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, neuropathic pain with spinal cord injury; minimal DDIs due to renal excretion	Preexisting cognitive disorders; no adequate data in pregnancy—may cause fetal harm			CNS effects including dizziness, somnolence, blurred vision, difficulty with concentration and attention; dry mouth; edema and weight gain	Potential for abuse when taken with opiates	Weight gain
Rufinamide Tablet, oral suspension		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	Weak inhibitor of CYP2E1; weak inducer of CYP3A4; modestly decreases levels of carbamazepine, lamotrigine; increases levels of phenobarbital, phenytoin; decreases estrogen OCP	Carbamazepine, phenobarbital, phenytoin decrease levels by 19%–46%; valproate increases levels up to 70%	CNS effects including somnolence, fatigue, coordination abnormalities, dizziness, gait disturbances, ataxia; GI effects including nausea	DRESS; rash (SJS); status epilepticus; leukopenia; QT interval shortening	

			levels				
Vigabatrin Tablet, powder packet	Useful in infantile spasms for whom potential benefit outweighs risk of vision loss	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	Inducer of CYP2C9; decreases levels of phenytoin by 20%; possibly increases levels of carbamazepine by 10%; increases C_{max} of clonazepam		CNS effects including fatigue, somnolence, nystagmus, tremor, blurred vision, memory impairment, abnormal coordination, confusion; weight gain; edema; peripheral neuropathy In pediatric patients: aggression; infection including upper respiratory tract infection, bronchitis, ear infection, and acute otitis media	Boxed warning: Progressive and permanent bilateral peripheral visual constriction including tunnel vision; reduced visual acuity Seizure exacerbation, particularly absence and myoclonic seizures in patients with generalized epilepsies; anemia	Onset of vision loss is unpredictable 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 ASDs may increase the risk of suicidal thoughts or behavior and patients treated with an ASD 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; ASD, antiseizure drug; 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.

TABLE 54-4

Antiseizure Drug Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Drugs	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 active oxcarbazepine 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
Cannabadiol	CYP2C19; CYP3A4; GT	Minor	CYP1A2; CYP2B6; GT	CYP2C8/9 and 19
Clobazam	CYP3A4; CYP2C19; CYP2B6	2	CYP3A4 (weak)	CYP2C9
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
Rufinamide	Hydrolysis	2	CYP3A4 (weak)	CYP2E1 (weak)
Vigabatrin	None	Almost completely	CYP2C9	None

CYP, cytochrome P450 isoenzyme system; GT, glucuronyltransferase.

First-Generation ASDs

Carbamazepine

- Food, especially fat, may enhance the bioavailability of carbamazepine.
- Controlled- and sustained-release preparations dosed every 12 hours are bioequivalent to immediate-release preparations dosed every 6 hours. The sustained-release capsule can be opened and sprinkled on food.
- Carbamazepine may be continued unless the white blood cell count drops to less than 2500/mm^3 (2.5 × 10^9/L) and the absolute neutrophil count drops to less than 1000/mm^3 (1 × 10^9/L).
- Carbamazepine may interact with other drugs by inducing their metabolism. The interaction of erythromycin and clarithromycin (CYP3A4 inhibition) with carbamazepine is particularly significant. Autoinduction of its own metabolism starts 3–5 days after initiating and is complete in 21–28 days. Reversal of autoinduction is rapid after discontinuation.

Ethosuximide

- Titration over 1–2 weeks to maintenance doses of 20 mg/kg/day usually produces therapeutic serum concentrations. It is usually given in two equal doses daily.
- There is some evidence for nonlinear metabolism at higher serum concentrations.

Phenobarbital

- Phenobarbital, a potent enzyme inducer, interacts with many drugs.

Phenytoin

- Phenytoin is a first-line ASD for many seizure types (see Table 54-3).
- Absorption may be saturable at higher doses (above 400 mg). Do not change brands without careful monitoring. The IM route is best avoided, as absorption is erratic. Fosphenytoin can safely be administered IV and intramuscularly (IM). Equations are available to normalize the phenytoin concentration in patients with hypoalbuminemia or renal failure.
- Zero-order kinetics occurs within the usual therapeutic range, so any change in dose may produce disproportional changes in serum concentrations.
- Most adult patients can be maintained on a single-daily dose, but children often require more frequent administration. Only extended-release preparations should be used for single-daily dosing.
- For phenytoin serum concentration less than 7 mcg/mL (28 µmol/L), the daily dose should be increased by 100 mg; if the concentration is 7–12 mcg/mL (28–48 µmol/L), the daily dose can be increased by 50 mg; and if the concentration is greater than 12 mcg/mL (48 µmol/L), the daily dose can be increased by 30 mg or less. At concentrations greater than 50 mcg/mL (200 µmol/L), phenytoin can exacerbate seizures.
- If protein-binding interactions are suspected, free rather than total phenytoin serum concentrations are a better therapeutic guide.
- Folic acid replacement enhances phenytoin clearance and can result in loss of efficacy. Phenytoin tablets and suspension contain phenytoin acid, whereas the capsules and parenteral solution are phenytoin sodium. Ninety-two milligrams of phenytoin acid is approximately equal to 100 mg of phenytoin sodium.

Valproic acid and divalproex sodium

- The free fraction may increase as the total serum concentration increases, and monitoring free concentrations may be more useful than total concentrations, especially at higher serum concentrations and in patients with hypoalbuminemia.
- At least 10 metabolites have been identified, and some may be active.
- It is first-line therapy for primary generalized seizures, such as absence, myoclonic, and atonic seizures, and is approved for adjunctive and monotherapy treatment of focal onset seizures. It can also be useful in mixed seizure disorders.
- GI complaints may be minimized with the enteric-coated formulation or by giving with food.
- Although carnitine supplementation may partially ameliorate hyperammonemia, it is expensive and is not generally supported.
- Valproic acid is an enzyme inhibitor. Carbapenems and combination oral contraceptives may lower serum levels of valproic acid.
- Once-daily dosing is possible with the extended-release divalproex, but more frequent dosing is the norm due to reports of breakthrough seizures.
- The enteric-coated tablet divalproex sodium causes fewer GI side effects. It is metabolized in the gut to valproic acid. When switching from Depakote to Depakote-ER, the dose should be increased by 14%–20%.

Second-Generation ASDs

Felbamate

- Felbamate is approved as adjunctive treatment for seizures of Lennox–Gastaut syndrome and is effective as monotherapy or adjunctive therapy for focal onset seizures as well. Because of reports of aplastic anemia (1 in 3000 patients) and hepatitis (1 in 10,000 patients), felbamate is recommended only for patients refractory to other ASDs. Risk factors for aplastic anemia may include a history of cytopenia, ASD allergy or toxicity, viral infection, and/or immunologic problems.

Gabapentin

- Gabapentin is a second-line agent for patients with focal onset seizures.

- Binding is saturable, causing dose-dependent bioavailability. It is eliminated exclusively renally, and dosage adjustment is necessary in patients with impaired renal function.
- Dosing is initiated at 300 mg at bedtime and increased to 300 mg twice daily on the second day and 300 mg three times daily on the third day. Further titrations are then made. When the total daily dose is 3600 mg/day or greater, divide the daily dose into at least four doses.

Lamotrigine

- Lamotrigine is useful as both adjunctive therapy and monotherapy for partial seizures and can be considered first- or second-line therapy. It is also approved for primary GTC seizures, and for primary generalized seizure of Lennox–Gastaut syndrome.

Levetiracetam

- Renal elimination of unchanged drug accounts for 66% of levetiracetam clearance, and the dose should be adjusted for impaired renal function. It is metabolized in blood by nonhepatic enzymatic hydrolysis.
- It is effective in the adjunctive treatment of focal onset seizures in patients 1 month of age and older, myoclonic seizures in patients 12 years and older, and primary GTC seizures in patients 6 years and older.
- The recommended initial adult dose is 500 mg orally twice daily. In some intractable seizure patients, the oral dose has been titrated rapidly over 3 days up to 3000 mg/day (1500 mg twice daily). It can be loaded orally or intravenously.

Oxcarbazepine

- The relationship between dose and serum concentration is linear. It does not autoinduce its own metabolism.
- It is indicated for use as adjunctive therapy for partial seizures in patients 6 years and older.
- Concurrent use of oxcarbazepine with ethinyl estradiol and levonorgestrel-containing contraceptives may render these agents less effective.
- In patients converted from carbamazepine, the typical maintenance doses of oxcarbazepine are 1.5 times the carbamazepine dose or less if patients are on larger carbamazepine doses. See manufacturer's recommendations for dosing by weight.

Tiagabine

- Tiagabine is adjunctive therapy for patients 12 years and older with focal onset seizures who have failed initial therapy.
- Tiagabine is displaced from protein by naproxen, salicylates, and valproate.

Topiramate

- Topiramate is a first-line ASD for patients with partial seizures as an adjunct or for monotherapy. It is also approved for tonic–clonic seizures in primary generalized epilepsy and for generalized seizures in Lennox–Gastaut syndrome.
- The dose should be adjusted in renally impaired patients.
- It increases the clearance of ethinyl estradiol.
- Dose increments may occur every 1 or 2 weeks. For patients on other ASDs, doses greater than 400 mg/day do not appear to lead to improved efficacy and may increase side effects.

Zonisamide

- Zonisamide, a broad-spectrum sulfonamide ASD, is approved as adjunctive therapy for partial seizures in adults.
- Start dosing in adults at 100 mg/day and increase by 100 mg/day every 2 weeks. It is suitable for once- or twice-daily dosing, but once-daily dosing may cause more side effects.

Third-Generation ASDs

Brivaracetam

- Dosage adjustment is required in all stages of hepatic impairment.

Cannabadiol

- Cannabadiol is a purified drug derived from marijuana whose exact antiseizure mechanism is unknown.
- It is FDA approved for Dravet syndrome and LGS.

Clobazam

- Abrupt discontinuation can cause a withdrawal syndrome (eg, behavioral disorder, tremor, anxiety, dysphoria, insomnia, convulsions, and psychosis).
- As an inducer of CYP3A4, clobazam may lower serum levels of some oral contraceptives. It is an inhibitor of CYP2D6. In older persons and poor metabolizers of CYP2C19, initiate dosing as in patients weighing less than 30 kg.
- It is more effective than clonazepam for Lennox–Gastaut syndrome but less effective than clonazepam for myoclonic jerks and absence seizures. It is adjunctive treatment for seizures of Lennox–Gastaut syndrome.

Eslicarbazepine

- Eslicarbazepine acetate is a prodrug that undergoes hydrolysis to S-licarbazepine, the major active metabolite of oxcarbazepine. It is FDA approved for monotherapy or adjunctive therapy of focal onset seizures.
- It is mostly renally excreted, and dosage adjustment is needed when creatinine clearance is less than 50 mL/min (0.8 mL/sec). It may increase the PR interval on the ECG. It causes less hyponatremia than oxcarbazepine.

Ezogabine

- Ezogabine is approved for adjunctive treatment of focal onset seizures, and is recommended only after several alternative drugs have been tried.
- Lower doses are recommended in older persons.
- It can cause urinary retention and QT prolongation.
- Alcohol may increase systemic exposure to **ezogabine** with an increase in side effects. It can increase lamotrigine clearance and reduce digoxin clearance.
- It may cause falsely elevated results on urine and serum bilirubin laboratory tests.
- It must be taken three times daily.

Lacosamide

- Lacosamide is approved as adjunctive therapy in patients 17 years old or greater with focal onset seizures.
- There is a linear relationship between daily doses and serum concentrations up to 800 mg/day. Moderate hepatic and renal impairment both increase systemic drug exposure by up to 40%.
- The starting dose is 100 mg/day in two divided doses, with dose increase by 100 mg/day every week until a daily dose of 200–400 mg has been reached.

Perampanel

- Perampanel has a half-life of approximately 100 hours, and its clearance in increased two- to threefold by enzyme-inducing ASDs.
- It is FDA approved for adjunctive therapy of focal onset seizures in patients 12 years and older and as adjunctive therapy for primary GTC in patients 12 years and older.

Pregabalin

- Pregabalin is FDA approved as adjunctive therapy for adults with focal onset seizures. It is considered a second-line agent for those who have failed initial treatment.
- It is eliminated unchanged primarily by renal excretion; dosage adjustment is required in patients with significant renal dysfunction.

Rufinamide

- Rufinamide is an adjunctive agent used for seizures of LGS in patients 1 year and older and in adults. Reserve rufinamide for patients who have failed other ASDs.
- Children may have a higher clearance of rufinamide than adults.

- It is dosed twice daily because of slow absorption and a short half-life. Drug interactions are common.
- Multiorgan hypersensitivity has occurred within 4 weeks of dose initiation in children younger than 12 years.

Vigabatrin

- Vigabatrin is monotherapy for infantile spasms in infants 1 month–2 years of age, and a third-line adjunctive agent for refractory complex partial seizures in patients 10 years and older.
- It is excreted unchanged in the urine. Dosage adjustment is necessary in pediatric and renally impaired patients.
- Access to vigabatrin is restricted as all providers must be certified in the Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program.

Special Considerations in Patients of Reproductive Age

- Estrogen has a seizure-activating effect, and progesterone has a seizure-protective effect. Enzyme-inducing ASDs (eg, phenobarbital, phenytoin, carbamazepine, topiramate, oxcarbazepine, and perhaps rufinamide, lamotrigine, clobazam, and felbamate) may cause oral contraceptive failures; supplemental birth control is advised if breakthrough bleeding occurs. Women taking these ASDs should take twice the usual dose of emergency contraception.
- For catamenial epilepsy (seizures just before or during menses) or seizures that occurring during ovulation, conventional ASDs should be tried first, but intermittent supplementation with higher-dose ASDs or benzodiazepines should be considered. Acetazolamide has been used with limited success. Progestational agents may also be effective.
- Seizures often improve in frequency at menopause.
- Women with epilepsy who are seizure free for 9–12 months before becoming pregnant, have an 84%–92% chance of being seizure free during pregnancy. Fluctuations in ASD serum concentrations during pregnancy may be due to reduced gastric motility, nausea and vomiting, increased drug distribution, increased renal elimination, altered hepatic enzyme activity, or changes in protein binding.
- ASD monotherapy is preferred in pregnancy. Clearance of phenytoin, carbamazepine, lamotrigine, oxcarbazepine, and levetiracetam increases during pregnancy, and protein binding may be reduced. Serum concentrations of phenobarbital, primidone, ethosuximide, and valproic acid may also fluctuate during pregnancy. Serum concentrations of ASDs should be monitored closely durng pregnancy. There is a higher incidence of adverse pregnancy outcomes in women taking ASDs, including an increased risk of major congenital malformations (MCMs).
- Valproic acid is associated with a risk of MCMs 3.5–4 times that of offspring of nonepileptic women. There is also an increased risk of neurodevelopmental effects including effects on cognition in children. **Valproic** acid should not be used in pregnancy, but when it is used, doses should not exceed 500–600 mg/day.
- Topiramate use during pregnancy has been associated with cleft palate and possibly low birth weight and hypospadias.
- Teratogenic effects may possibly be prevented by adequate folate intake, although strong evidence is lacking. Prenatal vitamins with folic acid (0.4–5 mg/day) are recommended for women of childbearing potential taking ASDs. Higher folate doses should be used in women who have previously delivered a child with a neural tube defect and women who are taking valproic acid.
- ASDs with low protein binding will accumulate in breast milk.
- Other adverse outcomes of maternal seizures are growth, psychomotor, and mental retardation. Vitamin K, 10 mg/day orally, given to the woman during the last month of pregnancy may prevent neonatal hemorrhagic disorder. Alternatively, parenteral vitamin K can be given to the newborn at delivery.
- Data suggest that men with epilepsy have reduced fertility, and that carbamazepine, oxcarbazepine, and valproic acid are associated with sperm abnormalities. Valproic acid seems to cause testicular atrophy resulting in reduced testosterone volume, whereas levetiracetam appears to slightly increase serum testosterone.

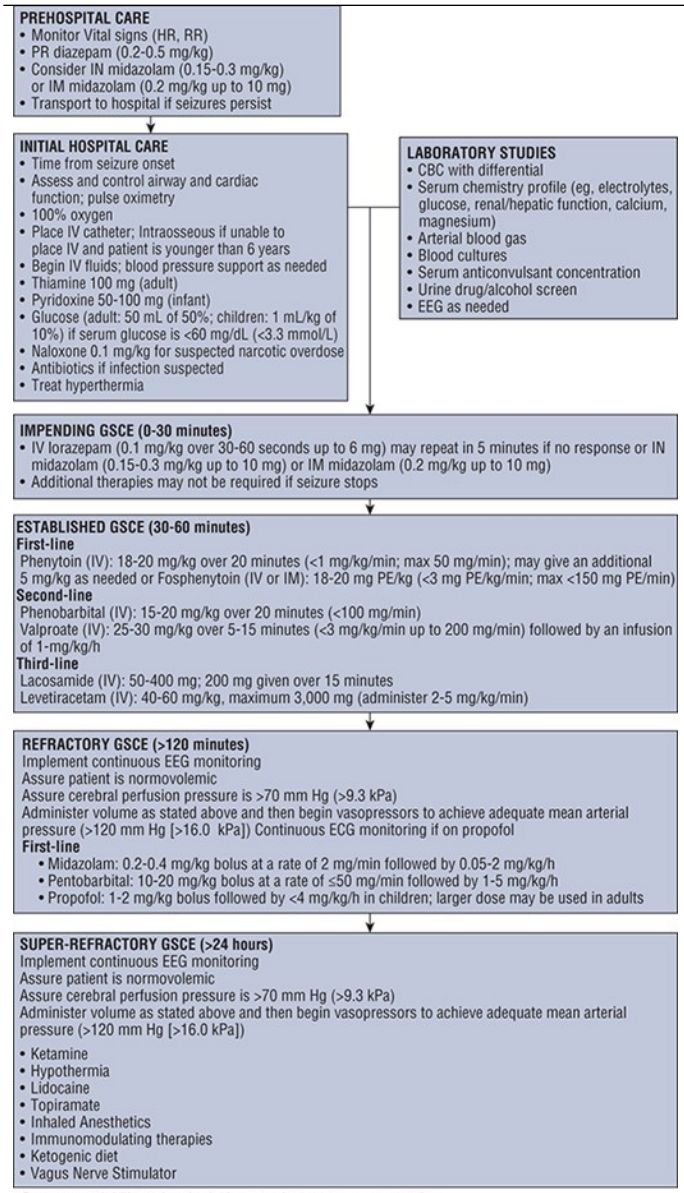
Status Epilepticus

- For any tonic–clonic seizure that does not stop automatically or when doubt exists regarding the diagnosis, treatment of GCSE should begin during the diagnostic workup. **Figure 54-3** is an algorithm for treatment of GCSE. **Table 54-5** includes doses of medication for GCSE, and **Table 54-6** has adverse drug reactions and monitoring of parameters.

FIGURE 54-3

Algorithm for the treatment of GCSE.

(BP, blood pressure; CBC, complete blood count; CI, continuous infusion; D12.5W, 12.5% dextrose in water; D25W, 25% dextrose in water; D50W, 50% dextrose in water; EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; HR, heart rate; IN, intranasal; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate.)



[a]Because variability exists in dosing, monitor serum concentration

Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 54-5

Dosing of Medications Used in the Initial and Established Treatment of GCSE

Drug (Route)	Brand Name	Initial Dose (Maximum Dose)	Maintenance Dose
Diazepam (IV)	Valium plus generic		
Adult		0.25 mg/kg[a,b,c] (20 mg)	Not used
Pediatric		0.25–0.5 mg/kg[a,c] (20 mg)	Not used
Fosphenytoin (IV)	Cerebyx plus generic		
Adult Pediatric		20–25 mg PE/kg 20–25 mg PE/kg	4–5 mg PE/kg/day 5–10 mg PE/kg/day
Levetiracetam (IV)	Keppra plus generics		
Adult Pediatric		2000–3000 mg 40–60 mg/kg (3000 mg)	1000 mg thrice a day 40–60 mg/kg/day, given twice or thrice a day
Lorazepam (IV)	Ativan plus generic		
Adult Pediatric		4 mg[b,c] (6 mg) 0.1 mg/kg[a,c] (6 mg)	Not used Not used
Midazolam (IV, IM)	Versed plus generic		
Adult Pediatric		200 mcg/kg[a,d] (10 mg) 150 mcg/kg[a,d] (10 mg)	50–500 mcg/kg/hr[e] 60–120 mcg/kg/hr[e]
Phenobarbital (IV)	Generic		
Adult Pediatric		10–20 mg/kg[e] 15–20 mg/kg[e]	1–4 mg/kg/day[e] 3–5 mg/kg/day[e]
Phenytoin (IV)	Dilantin plus generic		
Adult Pediatric		20–25 mg/kg[f] 20–25 mg/kg[f]	4–5 mg/kg/day[e] 5–10 mg/kg/day[e]
Valproate (IV)	Depacon plus generic		
Adult Pediatric		15–30 mg/kg (3000 mg) 20–25 mg/kg (3000 mg)	1–4 mg/kg/hr[e] 1–4 mg/kg/hr[e], or give every 4–6 hours

[a]Doses can be repeated every 10–15 minutes until the maximum dosage is given.

[b]Initial doses in the older persons are 2–5 mg.

[c]Larger doses can be required if patients chronically on a benzodiazepine (eg, clonazepam).

[d]Can be given by the intramuscular, rectal, or buccal routes.

[e]Titrate dose as needed.

[f]Administer additional loading dose based on serum concentration.

[g]The rate should not exceed 25 mg/min in older patients and those with known atherosclerotic cardiovascular disease.

GCSE, generalized convulsive status epilepticus; PE, phenytoin equivalents.

TABLE 54-6

Adverse Drug Reactions and Monitoring of Patients Receiving Drugs for GCSE

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Diazepam	Hypotension and cardiac arrhythmias	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly; hypotension may occur with large doses
Fosphenytoin	Hypotension and cardiac arrhythmias; paresthesia, pruritus	Vital signs and ECG during administration	Hypotension is less than phenytoin, as product does not contain propylene glycol; pruritus generally involves the face and groin areas, is dose and rate related, and subsides 5–10 minutes after infusion
Lidocaine	Fasciculations, visual disturbances, tinnitus, seizures		Occur at serum concentrations between 6 and 8 mg/L (25.6–34.1 µmol/L); seizures >8 mg/L (34.1 µmol/L)
Lorazepam	Apnea, hypotension, bradycardia, cardiac arrest, respiratory depression, metabolic acidosis, and renal toxicity	Vital signs and ECG during administration; HCO_3 and serum creatinine; cumulative dose of propylene glycol	Accumulation of propylene glycol during prolong continuous infusions may cause acidosis
Pentobarbital	Hypotension	Vital signs and ECG during administration	Rate of infusion should be slower or dopamine should be added if hypotension occurs
Phenytoin	Hypotension and cardiac arrhythmia; nystagmus	Vital signs and ECG during administration	Contains propylene glycol. Large loading doses are generally not given to older individuals with preexisting cardiac disease or in critically ill patients with marginal blood pressure. The infusion rate should be slowed if the QT interval widens or if hypotension or arrhythmias develop; horizontal nystagmus suggests toxicity
Phenobarbital	Hypotension, respiratory, and CNS depression	Vital signs and mental status; EEG if used in anesthesia doses	Contains propylene glycol; if hypotension occurs, slow the rate of administration or begin dopamine; apnea and hypopnea can be more profound in patients treated initially with benzodiazepines
Propofol	Progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias	Vital signs, ECG, osmolar gap; EEG if used in anesthesia doses	Referred to as propofol-related infusion syndrome, which can be fatal
Topiramate	Metabolic acidosis	Acid base status (serum bicarbonate)	Extremely rare

CNS, central nervous system; ECG, electrocardiogram; EEG, electroencephalogram.

Stabilization Phase

- Thiamine (100 mg IV) should be given prior to IV glucose (see **Figure 54-3**).

Initial Therapy Phase (5–20 Minutes)

- Benzodiazepines are effective initial therapy in most patients. Benzodiazepine preference is based on pharmacokinetics, route of administration, pharmacoeconomics, adverse-effect profile, and current availability. Evidence-based guidelines recommend the initial use of IM midazolam, IV lorazepam, or IV diazepam (see **Figure 54-3**) in adults and the use of IV lorazepam or IV diazepam in children.
- IV **diazepam** is extremely lipophilic and quickly distributed into the brain, but it redistributes rapidly into body fat, causing a very short duration of effect (<0.5 hour). Therefore, give a longer-acting anticonvulsant (eg, phenytoin or phenobarbital) immediately after the diazepam.
- IV **lorazepam** is currently considered the benzodiazepine of choice by most practitioners. It takes longer to reach peak brain levels than diazepam but has a longer duration of action (12–24 hours).
- IV **midazolam** is water soluble and diffuses rapidly into the CNS but has a very short half-life. Maintenance doses must be given by continuous infusion. Midazolam has a more reliable IM absorption than either diazepam or lorazepam. There is increasing interest in giving it buccally, IM, and intranasally when IV access cannot be obtained readily. Buccal midazolam may be more effective than rectal diazepam in children.
- Guidelines also recommend the use of IV phenobarbital as an alternative first-line agent in adults during the initial therapy stage.

  ✔ If the initial loading dose does not stop the seizures within 20–30 minutes, an additional dose (10–20 mg/kg) can be given, before moving to anesthetic agents. When necessary, larger loading doses (eg, 30 mg/kg) have been used in neonates.
- Once GCSE is controlled, the maintenance dose should be started within 12–24 hours.

Second-Therapy Phase: Established GCSE (20–40 Minutes)

- Phenytoin is second-line for GCSE unresponsive to the benzodiazepines or in seizures that recur after successful benzodiazepine treatment.
- Phenytoin has a 20–36 hour half-life, but it cannot be delivered fast enough to be a first-line agent.
- Phenytoin should be diluted to 5 mg/mL or greater in normal saline. Maintenance doses should be started within 12–24 hours of the loading dose.
- In determining a loading dose, consider whether the patient was taking phenytoin prior to admission and the phenytoin serum concentration if known. A larger loading dose is required in obese patients.
- Fosphenytoin, the water-soluble phosphate ester of phenytoin, is a phenytoin prodrug.
- Do not give the loading dose IM unless IV access is impossible.
- Serum phenytoin concentrations should not be obtained for at least 2 hours after IV and 4 hours after IM administration.
- IV valproate or levetiracetam are acceptable first-line agents if a benzodiazepine fails to control seizures after 20 minutes, or if seizures recur following a benzodiazepine and/or a hydantoin. Dosing for these agents is outlined in **Table 54-5**.

Third-Phase Therapies: Refractory GCSE (40–60 Minutes)

- When adequate doses of a benzodiazepine, and a single dose of a second anticonvulsant (hydantoin, valproate, levetiracetam, and/or barbiturate) have failed, the condition is termed refractory. Approximately 10%–15% of patients will develop refractory GCSE. Doses of agents used to treat refractory GCSE are given in **Table 54-7**.
- There is no consensus regarding the agent of choice, sequencing of therapy, or treatment of refractory GCSE.
- ✔ Some clinicians recommend anesthetic doses of midazolam as the first-line treatment for refractory GCSE (see **Table 54-7**) in combination with another drugs that are mechanistically different. Most patients respond within an hour.

  ✔ Successful benzodiazepine discontinuation is enhanced by serum phenytoin concentrations >20 mg/L (79 µmol/L) and phenobarbital concentrations >40 mg/L (172 µmol/L).
- A short-acting barbiturate (eg, pentobarbital or thiopental) (see **Figure 54-3**) may require intubation and respiratory support as well as continuous EEG and monitoring of vital signs.

  ✔ Give a loading dose of pentobarbital to provide serum concentration (40 mg/L; 177 µmol/L) sufficient to induce an isoelectric EEG. Usual duration of coma is 2–3 days, aiming to discontinue use as soon as possible.
- Propofol is very lipid soluble and has a large volume of distribution and a rapid onset of action. It has comparable efficacy to midazolam for refractory GCSE. Adverse effects and monitoring are shown in **Table 54-6** and dosing is shown in **Table 54-7**. Once EEG burst suppression is achieved, the dose should be reduced.

- Topiramate tablets can be crushed, dissolved in a small amount of water, and given orally or nasogastrically. Response tends to be delayed hours to days. If metabolic acidosis occurs, it can be treated with citrates, with a goal of maintaining a serum bicarbonate level of at least 20 mEq/L (mmol/L).

Super-Refractory GCSE (>24 Hours)

- **Ketamine** appears to be a reasonable option to consider in refractory GCSE that has failed inhaled analgesics (**Figure 54-3**). Advantages include maintenance of arterial blood pressure, pulse, and cardiac output, but it may cause hallucinations upon awakening, increased salivation, and increased intraocular and intracranial pressures.
- IV **lidocaine** is not recommended unless other agents have failed. Serum concentrations should be monitored to avoid drug accumulation and toxicity (**Table 54-6**).
- **Inhaled anesthetics** are used once other approaches fail. **Halothane**, **isoflurane**, are difficult to administer outside the operating room, and an anesthesiologist is required. They have no proven advantages over traditional anticonvulsants, and they can increase intracranial pressure.
- In the absence of contraindications, a trial of large doses of steroids (eg, 1 g/day of IV **prednisolone** for 3 days, followed by 1 mg/kg/day in four divided doses) should be used in patients with unidentified etiology for super-refractory GCSE. Responders should continue long-term steroids, IV immunoglobulins, and other immunomodulatory agents, such as **cyclophosphamide** or **rituximab**.

TABLE 54-7

Dosing of Medications Used to Treat Refractory or Super-Refractory GCSE

Drug (Brand Name)	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Ketamine (generics)			
Adult	1–4 mg	1–5 mg/kg/hr	
Pediatric	0.5–2 mg/kg	1–10 mg/kg/hr	
Lacosamide (Vimpat)			
Adult	200–400 mg	200 mg bid	Administer IV over 15 minutes, monitor serum concentrations
Pediatric	6–10 mg/kg (400 mg)	6–12 mg/kg/day, given twice a day	
Lidocaine (generics)			
Adult	50–100 mg	1.5–3.5 mg/kg/hr	Administer IV in ≤2 minutes
Pediatric	1 mg/kg (maximum 3–5 mg/kg in the first	1.2–3 mg/kg/hr	

	hour)		
Midazolam (Versed plus generic)			
Adult pediatric	200 mcg/kg[a] 150 mcg/kg[a]	50–500 mcg/kg/hr[b] 60–120 mcg/kg/hr[b]	Initial dose may be given IM; administer IV over 0.5–1 mg/min; continuous-infusion rate should be increased every 15 minutes in those who do not respond and should be guided by EEG response; development of tachyphylaxis can require frequent increases in dose; decrease dose by 1 mcg/kg/min every 2 hours once GCSE is controlled
Pentobarbital (generics)			
Adult Pediatric	10–20 mg/kg 15–20 mg/kg	1–5 mg/kg/hr[b] 1–5 mg/kg/hr[b]	Over 1–2 hours, the rate of infusion should be slowed or dopamine should be added if hypotension occurs; gradually titrate dose upward until there is evidence of burst suppression on EEG (ie, isoelectric EEG) or prohibitive adverse effects occur. Twelve hours after a burst suppression is obtained, the rate should be titrated downward every 2–4 hours
Propofol (Diprivan plus generic)			
Adult	2 mg/kg	5–10 mg/kg/hr[b]	Over 10 seconds in adults and 20–30 seconds in pediatric patients
Pediatric	3 mg/kg	2–4 mg/kg/hr[c]	
Topiramate (Topamax plus generic)			
Adult Pediatric	300–500 mg 5–15 mg/kg (400 mg)	400–1600 mg/day 5–10 mg/kg/day, given thrice a day	Given orally in divided dose every 12 hours. Doses as large as 25 mg/kg/day for 2–5 days have been used in children. Monitor serum bicarbonate levels and serum concentrations

[a]Doses can be repeated twice at 10–15 minute intervals until the maximum dosage is given.

[b]Titrate dose as needed.

[c]Generally recommended not to exceed a dose of 4 mg/kg/hr and a duration of 48 hours.

EVALUATION OF THERAPEUTIC OUTCOMES

- The goal therapeutic outcome for all ASDs is seizure freedom or reduction in seizure frequency, while minimizing adverse effects.
- Monitor long term for seizure control, side effects, social adjustment including quality of life, drug interactions, compliance, and side effects. Clinical response is more

important than serum drug concentrations.

- Screen periodically for psychiatric disorders (eg, anxiety and depression).
- Ask patients and caregivers to record severity and frequency of seizures. Medication adherence should be assessed continually.
- The morbidity and mortality associated with GCSE can be minimized by the rapid implementation of a rational therapeutic plan.
- An EEG is an extremely important tool used to determine when abnormal electrical activity has been aborted, but also can assist in determining which anticonvulsant was effective.

See Chapter 73, Epilepsy, authored by Viet-Huong V. Nguyen, Sunita Dergalust, and Edward Chang and Chapter 74, Status Epilepticus, authored by Stephanie J. Phelps and James W. Wheless, for a more detailed discussion of these topics.