

Therapeutic Class Overview

Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
 - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
 - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
 - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
 - Generalized seizures affect both sides of the brain and include:
 - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
 - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
 - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
 - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
 - Focal seizures are located in just 1 area of the brain and include:
 - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
 - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
 - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
 - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
 - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
 - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannabidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✓
Phenobarbital* (Luminal [†] , Solfoton [†])	✓
Primidone (Mysoline)	✓
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✓ ***
Clonazepam (Klonopin [§])	✓
Clorazepate (Tranxene T-Tab [§])	✓
Diazepam (Diastat [¶] , Valium [§])	✓
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✓
Phenytoin (Dilantin [§] , Phenytek)	✓
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol ^{**} , Equetro, Tegretol [§] , Tegretol-XR)	✓

Drug	Generic Availability
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✓
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✓
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✓
Gabapentin (Neurontin)	✓
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✓
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✓
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✓
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✓
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✓
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✓
Valproic acid (Depacon, Depakene)	✓
Vigabatrin (Sabril, Vigadrone**)	✓
Zonisamide (Zonegran§)	✓

* Not FDA approved

† Brand product not currently marketed; generic is available

§ Brand marketing status may vary by strength and/or formulation

|| Generic availability may vary by strength and/or formulation

¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application

** Branded generic

†† Branded generic; not currently marketed

***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✓ *		✓ *			A		✓ , A*	✓ , A*		✓ *		✓ , A*		A*	✓ *	✓ , A*	A*
Primary generalized tonic-clonic seizure (grand mal)			✓								✓			✓ *			A*	A*
Absence seizure (petit mal)					✓ *			✓ , A*		✓								
Multiple seizure types that include absence seizures								A										
Seizures of Lennox-Gastaut syndrome (LGS)		✓ *		A*	✓ , A								A*				A*	
Seizures of Dravet syndrome		✓ *																
Juvenile myoclonic epilepsy (JME)																		A*
Emergency/acute/short-term use for seizure control (see notes)							✓ *							✓ *				
Akinetic and myoclonic seizures					✓ , A													
Convulsive disorders (see notes)							A*											
Certain mixed seizure patterns or other partial or generalized seizures			✓ *															
Migraine prophylaxis								✓ *										
Trigeminal neuralgia			✓ *															
Postherpetic neuralgia															✓ *			
Bipolar disorder			✓ *					✓ *									✓ *	
Panic disorder, with or without agoraphobia					✓													
Anxiety disorder; short-term relief of anxiety symptoms						✓	✓											
Symptomatic relief of acute alcohol withdrawal						✓	✓											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome							A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)												A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓ A*		✓ *		✓ *	A*	✓ A*			A*	✓ A*	✓ A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✓ *		✓ A*				✓ A*			
Absence seizure (petit mal)		✓ *												✓ A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/short-term use for seizure control (see notes)	✓ *			✓ *			✓ *									
Infantile spasms															✓ *	
Convulsive disorders (see notes)						✓ *										
Migraine prophylaxis													✓ *	✓ *		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✓								
Bipolar disorder														✓*		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✓								
Neuropathic pain associated with spinal cord injury								✓								
Fibromyalgia								✓								

✓ = monotherapy (or not specified); A = adjunctive therapy

†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam:**
 - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- **Cannabidiol:**
 - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- **Carbamazepine:**
 - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
 - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
 - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
 - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam:**
 - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam:**
 - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam:**
 - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
 - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
 - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium:**
 - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)

- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age \geq 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use ($>$ 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
 - Treatment of the manic episodes associated with bipolar disorder (tablets)
 - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)
- **Eslicarbazepine:**
 - Treatment of partial-onset seizures in patients \geq 4 years of age
- **Ethotoin:**
 - Complex partial (psychomotor) seizures
- **Everolimus:**
 - Adjunctive treatment of adult and pediatric patients \geq 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- **Felbamate:**
 - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
 - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
 - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin:**
 - Treatment of generalized tonic-clonic status epilepticus
 - Prevention and treatment of seizures occurring during neurosurgery
 - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin:**
 - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients \geq 3 years of age with epilepsy.
 - Management of postherpetic neuralgia in adults
- **Lacosamide:**
 - Treatment of partial-onset seizures in patients \geq 4 years of age (tablet and oral solution)
 - Treatment of partial-onset seizures in patients \geq 17 years of age (injection)
- **Lamotrigine immediate-release formulations:**
 - Age \geq 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
 - Age \geq 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
 - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets:**
 - Age \geq 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age \geq 13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
 - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam:**
 - Adjunctive therapy in the treatment of partial onset seizures in adults and children \geq 1 month of age with epilepsy (age \geq 4 years and weighing $>$ 20 kg for the tablets for oral suspension [Spritam])
 - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents \geq 12 years with JME
 - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children \geq 6 years of age with idiopathic generalized epilepsy
 - The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients \geq 12 years of age with epilepsy
- **Methsuximide:**

- Control of absence (petit mal) seizures that are refractory to other drugs
- **Midazolam nasal spray:**
 - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- **Oxcarbazepine immediate-release formulations:**
 - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
 - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets:**
 - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- **Pentobarbital:**
 - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel:**
 - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
 - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved):**
 - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations:**
 - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection:**
 - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
 - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin:**
 - Adjunctive therapy for treatment of partial onset seizures in patients ≥ 1 month of age
- **Primidone:**
 - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide:**
 - Adults and pediatric patients ≥ 1 year of age
- **Stiripentol:**
 - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- **Tiagabine:**
 - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate:**
 - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
 - Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
 - Prophylaxis of migraine headache in patients ≥ 12 years of age
- **Valproic acid:**

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- **Vigabatrin:**
 - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
 - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide:**
 - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
 - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
 - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
 - Valproate is probably efficacious/effective.
 - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
 - Clonazepam and primidone are potentially efficacious/effective.
 - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
 - Oxcarbazepine is established as efficacious/effective.
 - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
 - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
 - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
 - Gabapentin and lamotrigine are established as efficacious/effective.
 - Carbamazepine is possibly efficacious/effective.
 - Topiramate and valproate are potentially efficacious/effective.
 - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
 - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
 - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
 - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
 - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
 - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.

- Oxcarbazepine is potentially efficacious/effective.
- Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- As initial monotherapy for children with newly diagnosed or untreated absence seizures:
 - Ethosuximide and valproate are established as efficacious/effective.
 - Lamotrigine is possibly efficacious/effective.
 - Gabapentin is established as inefficacious/ineffective.
 - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
- As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
 - Carbamazepine and valproate are possibly efficacious/effective.
 - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
- For patients with newly diagnosed JME:
 - Topiramate and valproate are potentially efficacious/effective.
 - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
- There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
 - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
 - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
 - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
 - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
 - For the secondary outcome, time to first seizure:
 - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
 - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
 - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
 - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
 - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.
- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically

significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.

- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
 - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
 - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
 - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
 - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
 - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018; Devinsky et al 2018; Devinsky et al 2017*). To date, no comparative trials have been published.
 - Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
 - In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018*).

- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, $p = 0.0109$) with similar tolerability (*Detyniecki et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy.** American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
 - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
 - The recommendations from the 2004 guideline include the following:
 - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
 - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
 - The 2018 recommendations include the following:
 - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
 - Lamotrigine use should be considered to decrease seizure frequency.
 - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
 - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
 - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
 - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
 - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
 - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
 - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
 - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
 - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
 - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy.** American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B, French et al 2004B*).
 - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
 - Recommendations from the 2004 guideline include the following:
 - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.

- Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
- Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
- Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
- Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
- Recommendations from the 2018 guideline include the following:
 - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
 - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
 - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
 - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
 - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
 - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
 - As monotherapy in patients with TRAFE:
 - Eslicarbazepine use may be considered to decrease seizure frequency.
 - Data are insufficient to recommend use of second- and the other third-generation AEDs.
 - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
 - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
 - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
 - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
 - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
 - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
 - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
 - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
 - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
 - Recommendations include the following:
 - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
 - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
 - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
 - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
 - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
 - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment

is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.

- It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
 - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
 - For treatment in the adult population, conclusions included the following:
 - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
 - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
 - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
 - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
 - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
 - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
 - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
 - For treatment in the pediatric population, conclusions included the following:
 - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
 - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
 - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
 - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
 - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
 - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
 - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
 - Conclusions included the following (age not specified):
 - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
 - The overall treatment algorithm directs that:
 - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
 - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
 - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).

- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
 - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
 - Recommendations include the following:
 - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotrophic hormone (ACTH) for short-term treatment of infantile spasms.
 - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
 - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
 - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
 - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
 - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
 - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2016)
 - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
 - Recommendations include the following:
 - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
 - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
 - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
 - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures.** Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
 - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
 - Recommendations/findings include the following:
 - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
 - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
 - Treatment options with established or probable efficacy include the following:
 - Focal seizures: levetiracetam
 - Epileptic spasms: High-dose or low-dose ACTH
 - Dravet syndrome: stiripentol
 - Treatment options with possible efficacy include the following:
 - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
 - Epileptic spasms: prednisone, vigabatrin
 - Benign infantile convulsions: carbamazepine, phenobarbital, valproate

- Dravet syndrome: topiramate, zonisamide, valproate
- Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
- Provoked or situational seizures: carbamazepine
- There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures.** World Health Organization (WHO) (*WHO 2011*).
 - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
 - Recommendations include the following:
 - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
 - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
 - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstated if seizures recur.
 - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
 - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
 - Recommendations include the following:
 - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
 - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
 - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
 - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
 - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
 - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
 - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
 - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
 - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
 - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
 - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
 - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
 - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
 - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.

- For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
- Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
- Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
 - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
 - Recommendations include the following:
 - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
 - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
 - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
 - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
 - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
 - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.
- Guidelines also support the use of AEDs for several common non-epilepsy indications:
 - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012*; reaffirmed in 2015; Update in progress).
 - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
 - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
 - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
 - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
 - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
 - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
 - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.

- Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder (*Post 2017, Stovall 2018*).

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
 - Systemic AEs:
 - nausea, vomiting, constipation, diarrhea, anorexia
 - rash
 - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
 - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
 - Neurologic AEs:
 - headache
 - somnolence, sedation, drowsiness, lethargy, fatigue
 - dizziness, vertigo
 - tremor, anxiety, nervousness, insomnia
 - aggression, irritability, hyperactivity
 - depression, mood alteration
 - confusion
 - ataxia
 - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
 - suicidal ideation and behavior (AEDs as a class, except everolimus)
 - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
 - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
 - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
 - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
 - hepatocellular injury (cannabidiol)
 - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, lacosamide, rufinamide)
 - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
 - multiorgan hypersensitivity (carbamazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, valproate, zonisamide)
 - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
 - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
 - Carbamazepine:
 - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
 - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
 - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
 - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Felbamate:
 - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
 - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fosphenytoin and phenytoin:
 - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
 - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
 - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
 - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
 - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
 - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
 - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
 - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program ([FDA REMS 2019](#)). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.
- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
 - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
 - More serious AEs include:

- non-infectious pneumonitis
- infections
- hypersensitivity reactions
- angioedema (when taken with an angiotensin converting enzyme inhibitor)
- renal failure
- impaired wound healing
- myelosuppression
- reduced immune response with vaccination
- hyperglycemia
- hyperlipidemia
- embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal [†] , Solfoton [†])	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	Oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (<i>Lexicomp 2019</i>)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid (Depakene, Depacon)	capsules, oral solution/syrup, injection	oral, IV	2 to 4 times per day (<i>Lexicomp 2019</i>)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved

† Brand product not currently marketed; generic is available

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoin, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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