

Drugs for Epilepsy





Introduction

- Epilepsy is an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons
- Can cause (for a limited duration)
 - Loss of consciousness
 - Abnormal movements
 - Atypical or odd behavior
 - Distorted perceptions



Introduction

- The site of origin of the abnormal neuronal firing determines the symptoms that are produced
- If the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion
- Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations



Introduction

- Convulsions: Involuntary violent spasm of large muscles of face, neck, arms, and legs
- Not synonymous with seizure



Introduction

- In most cases epilepsy has no identifiable cause (**Idiopathic** epilepsy)
- Symptomatic epilepsy (**secondary** to another cause)
- Activity in focal areas that are functionally abnormal may be triggered by:
 - Changes in physiologic factors such as blood gases, pH, electrolytes, and blood glucose
 - Changes in environmental factors such as sleep deprivation alcohol intake and stress



Introduction:

- **Idiopathic epilepsy (primary):**
 - When no specific anatomic cause for the seizure, such as trauma or neoplasm, is present
 - Can result from inherited abnormality in the CNS
 - Patients are treated chronically with anti-seizure drugs or vagal nerve stimulation
- **Symptomatic epilepsy**
 - Can be caused by illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol in alcoholics
 - When two or more seizures occur, the patient may be diagnosed with symptomatic (secondary) epilepsy
 - The primary cause of the seizure should be corrected if possible
 - In cases when the source of a seizure can be determined and corrected, medication may not be necessary



Introduction:

- Seizure classification determines treatment
- Seizures have been classified by:
 - Site of origin
 - Etiology
 - Electrophysiologic correlation
 - Clinical presentation



Introduction:

- Seizure classification determines treatment
- Seizures have been classified by:
 - Site of origin
 - Etiology
 - Electrophysiologic correlation
 - Clinical presentation

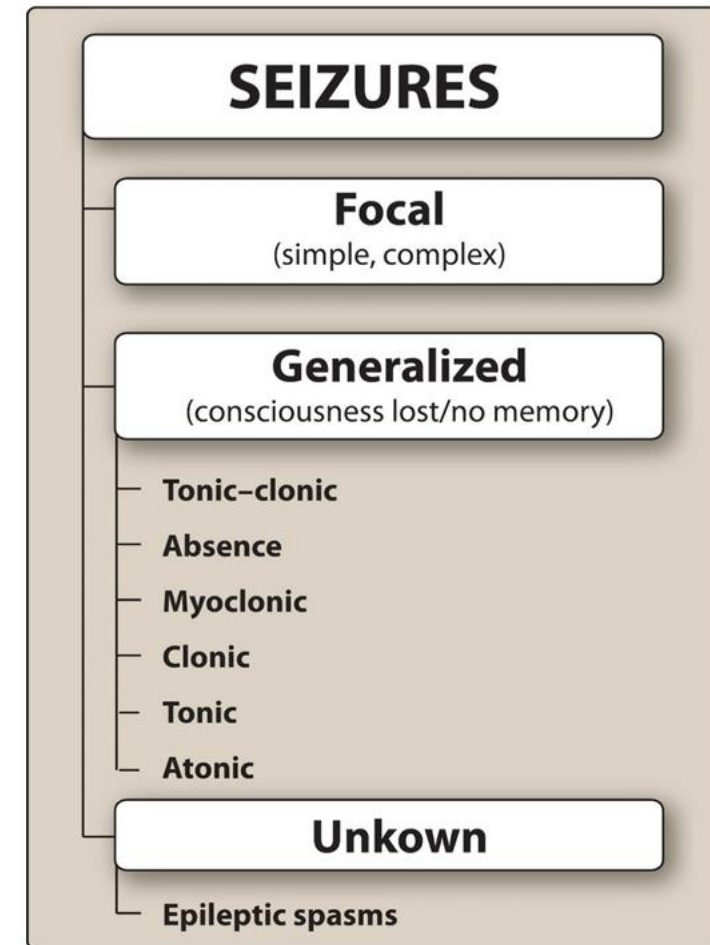


Figure 12.2 Classification of epilepsy.



Focal seizures

- Involve only a portion of the brain, typically part of one lobe of one hemisphere
- Symptoms depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons
- May occur at any age
- Consciousness is usually preserved
- Partial seizures may progress to become generalized tonic-clonic seizures
- Include
 - Simple partial seizures
 - Complex partial seizures



Focal seizures

- Simple focal seizures:
- Caused by a group of hyperactive neurons confined to a single locus in the brain
- The patient does not lose consciousness
- Abnormal activity of a single limb or muscle group controlled by the region of the brain experiencing the disturbance
- The patient may also show sensory distortions
- May occur at any age



Focal seizures

- Complex focal seizures:
- Complex sensory hallucinations and mental distortion
- Motor dysfunction may involve chewing movements, diarrhea, and/or urination
- Consciousness is altered



Generalized seizures

- Include abnormal electrical discharges throughout both brain hemispheres
 - May be convulsive or nonconvulsive
 - Patient usually has an immediate loss of consciousness
- Tonic-clonic seizures
- Absence seizures
- Myoclonic seizures
- Clonic seizures
- Tonic seizures
- Atonic seizures
- Febrile seizures
- Status epilepticus



Generalized seizures

- Tonic-clonic seizures:
 - Result in loss of consciousness, followed by tonic and clonic phases
 - May be followed by a period of confusion and exhaustion due to the depletion of glucose and energy
- Absence seizures:
 - Involve a brief, abrupt, and self-limiting loss of consciousness
 - Onset: 3-5 years of age and lasts until puberty or beyond
 - The patient stares and exhibits rapid eye-blinking for 3-5 seconds
- Myoclonic seizures:
 - Short episodes of muscle contractions that may recur for several minutes
 - Occur at any age but usually begin around puberty or early adulthood



Generalized seizures

- Clonic
- These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures.
- Consciousness is more impaired with clonic seizures
- Tonic
- These seizures involve increased tone in the extension muscles and are generally less than 60 seconds.
- Atonic
- These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.



Generalized seizures

- Febrile seizures
- Young children may develop seizures with illness accompanied by high fever
- Consist of generalized tonic-clonic convulsions and do not necessarily lead to a diagnosis of epilepsy
- Status epilepticus:
 - Life-threatening and requires emergency treatment
 - Two or more seizures occur without recovery of full consciousness between them



Definition of epilepsy

- Epilepsy is a disease of the brain defined by any of the following conditions:
 1. Two unprovoked (or reflex) seizures occurring more than 24 hours apart;
 2. One unprovoked (or reflex) seizure and a probability of subsequent seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
 3. Diagnosis of an epilepsy syndrome



Drugs used for epilepsy

Brivaracetam BRIVIACT
Carbamazepine TEGRETOL
Clobazam ONFI
Clonazepam KLONOPIN
Diazepam VALIUM
Divalproex DEPAKOTE
Eslicarbazepine APTIOM
Ethosuximide ZARONTIN
Felbamate FELBATOL
Fosphenytoin CEREBYX
Gabapentin NEURONTIN
Lacosamide VIMPAT
Lamotrigine LAMICTAL
Levetiracetam KEPPRA

Lorazepam ATIVAN
Oxcarbazepine TRILEPTAL
Perampanel FYCOMPA
Phenobarbital GENERIC ONLY
Phenytoin DILANTIN
Pregabalin LYRICA
Primidone MYSOLINE
Rufinamide BANZEL
Tiagabine GABITRIL
Topiramate TOPAMAX
Vigabatrin SABRIL
Zonisamide ZONEGRAN



Drugs used for epilepsy

NARROW-SPECTRUM AEDs	BROAD-SPECTRUM AEDs
<i>Phenytoin</i>	<i>Valproic acid</i>
<i>Phenobarbital</i>	<i>Lamotrigine</i>
<i>Carbamazepine</i>	<i>Topiramate</i>
<i>Oxcarbazepine</i>	<i>Zonisamide</i>
<i>Gabapentin</i>	<i>Levetiracetam</i>
<i>Pregabalin</i>	<i>Clonazepam</i>
<i>Vigabatrin</i>	<i>Clobazam</i>
<i>Tiagabine</i>	<i>Felbamate</i>

Figure 12.3

Spectrum of antiepileptic activity
of antiseizure or antiepileptic drugs
(AEDs)



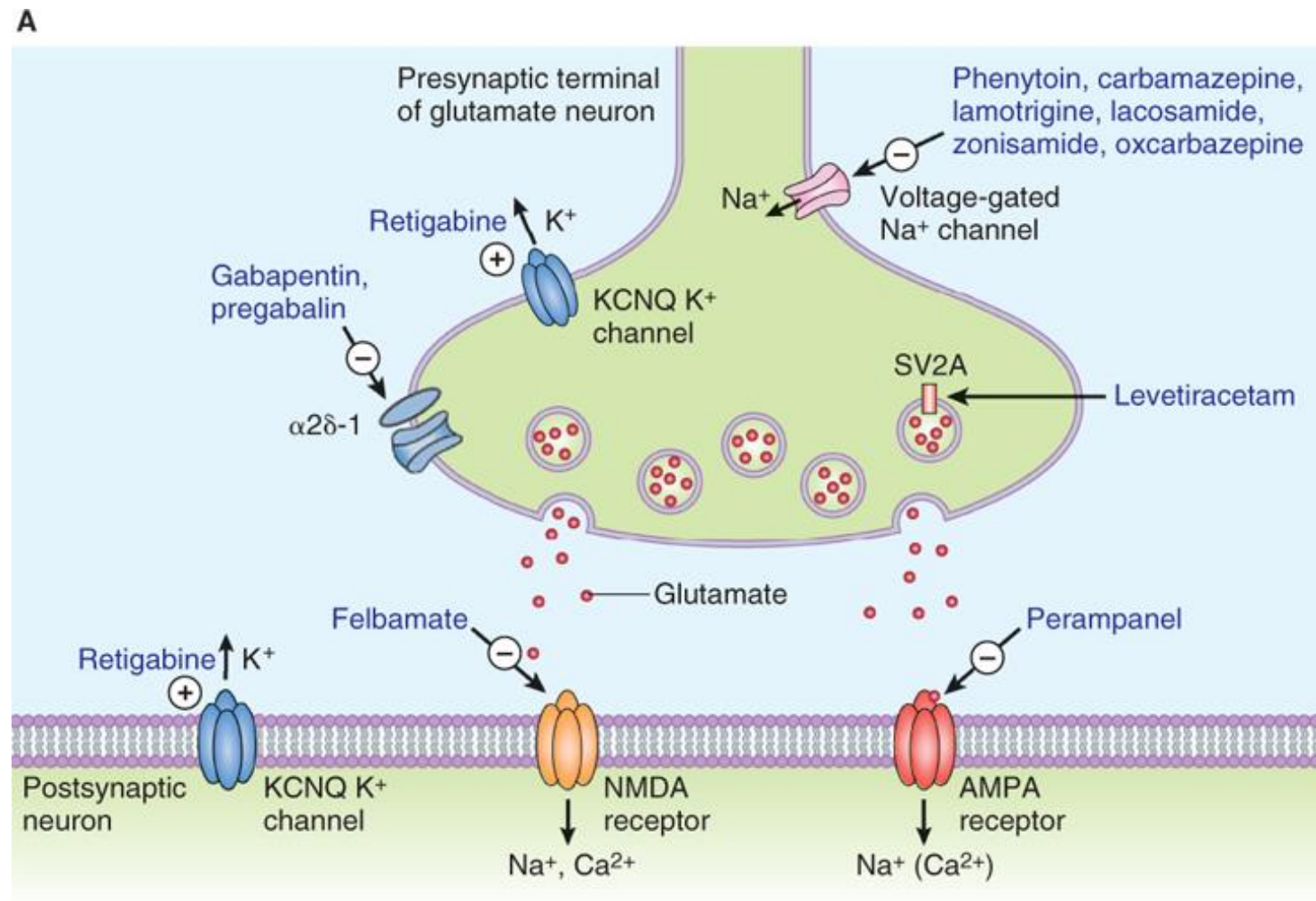
Mechanism of action of antiepileptics

- Blocking voltage gated channels (Na^+ or Ca^{2+})
- Enhancing inhibitory GABA impulses
- Interfering with excitatory glutamate transmission

- Some antiepileptic drugs appear to have multiple targets in CNS
- Antiepilepsy drugs suppress seizures but do not “cure” or “prevent” epilepsy



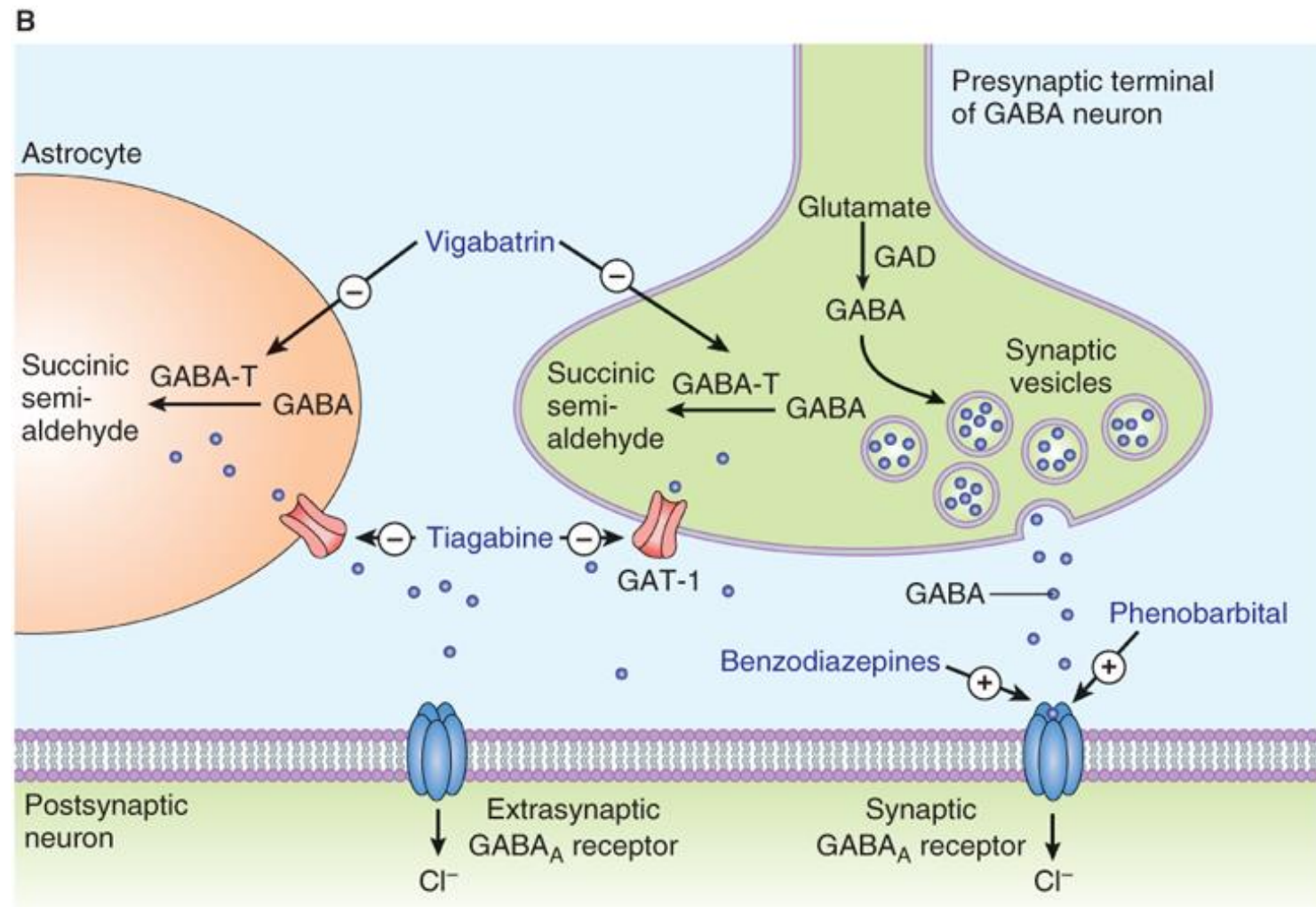
Mechanism of action of antiepileptics



Citation: Chapter 24 Antiseizure Drugs, Bertram G. Katzung, Todd W. Vanderah. *Basic & Clinical Pharmacology*, 15e; 2021. Available at: <https://accesspharmacy.mhmedical.com/ViewLarge.aspx?figid=250597716&gbosContainerID=0&gbosid=0&groupID=0§ionId=250597700&multimediaId=undefined> Accessed: March 22, 2025
Copyright © 2025 McGraw-Hill Education. All rights reserved



Mechanism of action of antiepileptics



Citation: Chapter 24 Antiseizure Drugs, Bertram G. Katzung, Todd W. Vanderah. *Basic & Clinical Pharmacology*, 15e; 2021. Available at: <https://accesspharmacy.mhmedical.com/ViewLarge.aspx?figid=250597716&gbosContainerID=0&gbosid=0&groupID=0§ionId=250597700&multimediaId=undefined> Accessed: March 22, 2025
Copyright © 2025 McGraw-Hill Education. All rights reserved



Mechanism of action of antiepileptics

MECHANISM OF ACTION	ANTIEPILEPTIC DRUG
Sodium channel blockers:	
Fast-inactivated state	<i>Phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine</i>
Slow-inactivated state	<i>Lacosamide</i>
Calcium channel blockers:	
Low voltage-activated channel	<i>Ethosuximide</i>
High voltage-activated channel	<i>Gabapentin, pregabalin</i>
GABA-ergic drugs:	
Prolong chloride channel opening	<i>Barbiturates</i>
Increase frequency of chloride channel opening	<i>Benzodiazepines</i>
Inhibit GABA-transaminase	<i>Vigabatrin</i>
Block synaptic GABA reuptake	<i>Tiagabine</i>
Synaptic vesicle protein 2A modulation	<i>Levetiracetam</i>
Carbonic anhydrase inhibition	<i>Acetazolamide, topiramate, zonisamide</i>
Multiple pharmacological targets	<i>Sodium valproate, felbamate, topiramate, zonisamide, rufinamide</i>

Figure 12.4

Mechanism of action of antiepileptic drugs.



Mechanism of action of antiepileptics

Bertram G. Katzung, Todd W. Vanderah+

TABLE 24–2 Molecular targets of antiseizure drugs.

Molecular Target	Antiseizure Drugs That Act on Target
Voltage-gated ion channels	
Voltage-gated sodium channels (Na_V)	Phenytoin, fosphenytoin, ¹ carbamazepine, oxcarbazepine, ² eslicarbazepine acetate, ³ lamotrigine, lacosamide; possibly (or among other actions) topiramate, zonisamide, rufinamide, cenobamate
Voltage-gated calcium channels (T-type)	Ethosuximide
Voltage-gated potassium channels (K_V7)	Retigabine (ezogabine)
GABA Inhibition	
GABA _A receptors	Phenobarbital, primidone; benzodiazepines including diazepam, lorazepam, clonazepam, midazolam, clobazam; stiripentol; possibly topiramate, felbamate, cenobamate, ezogabine
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin



Mechanism of action of antiepileptics

Synaptic release machinery	
SV2A	Levetiracetam, brivaracetam
$\alpha 2\delta$	Gabapentin, gabapentin enacarbil, ⁴ pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
Disease specific	
mTORC1 signaling	Everolimus
Mixed/unknown ⁵	Valproate, felbamate, cenobamate, topiramate, zonisamide, rufinamide, adrenocorticotropin, cannabidiol

¹ Fosphenytoin is a prodrug for phenytoin.

² Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly *S*-licarbazepine.

³ Eslicarbazepine acetate is a prodrug for *S*-licarbazepine.

⁴ Gabapentin enacarbil is a prodrug for gabapentin.

⁵ There is no consensus as to the mechanism of valproate; felbamate, topiramate, zonisamide, and rufinamide may have actions on as yet unidentified targets in addition to those shown in the table.

Reproduced with permission from Wyllie E: *Wyllie's treatment of epilepsy: Principles and practice*, 6th ed. Philadelphia, PA: Wolters Kluwer; 2015.

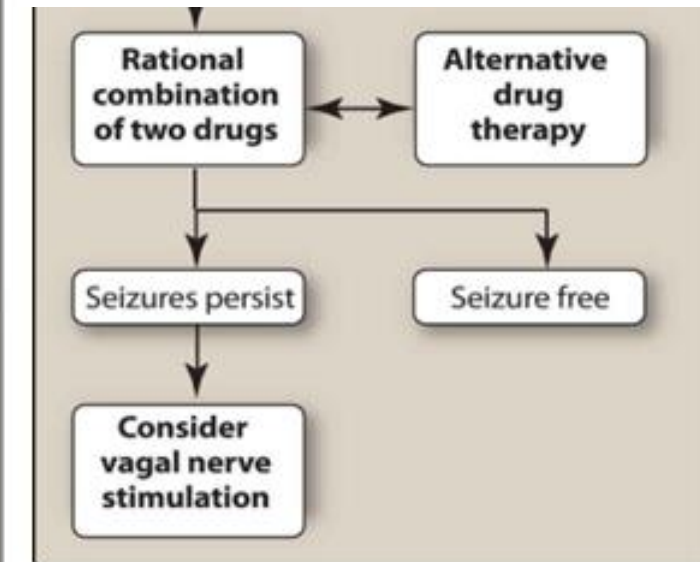
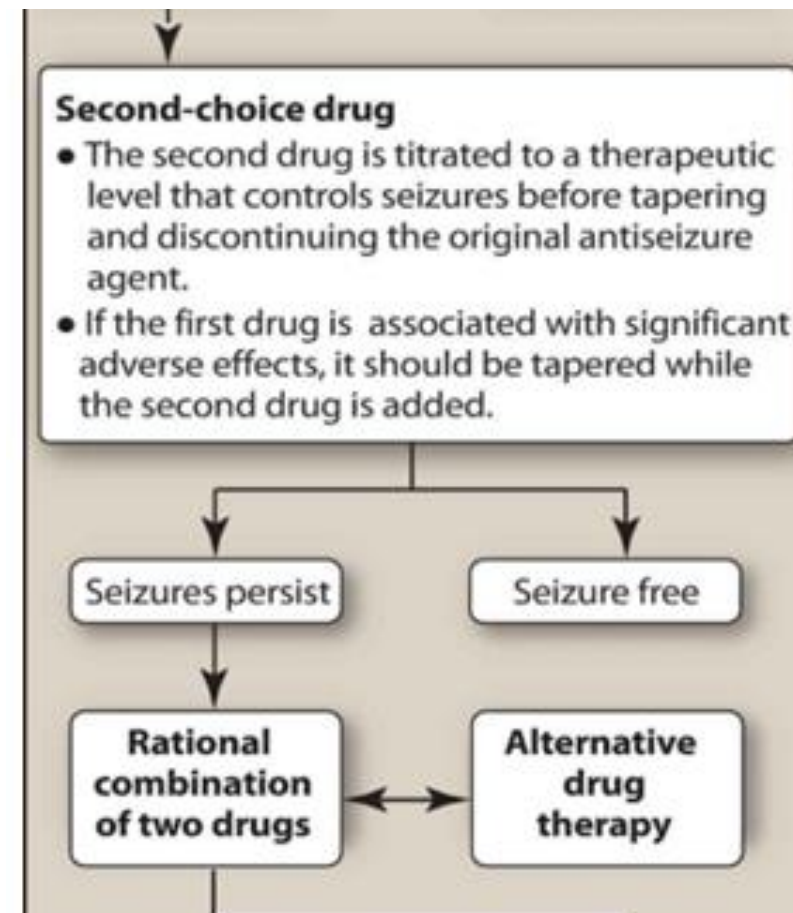
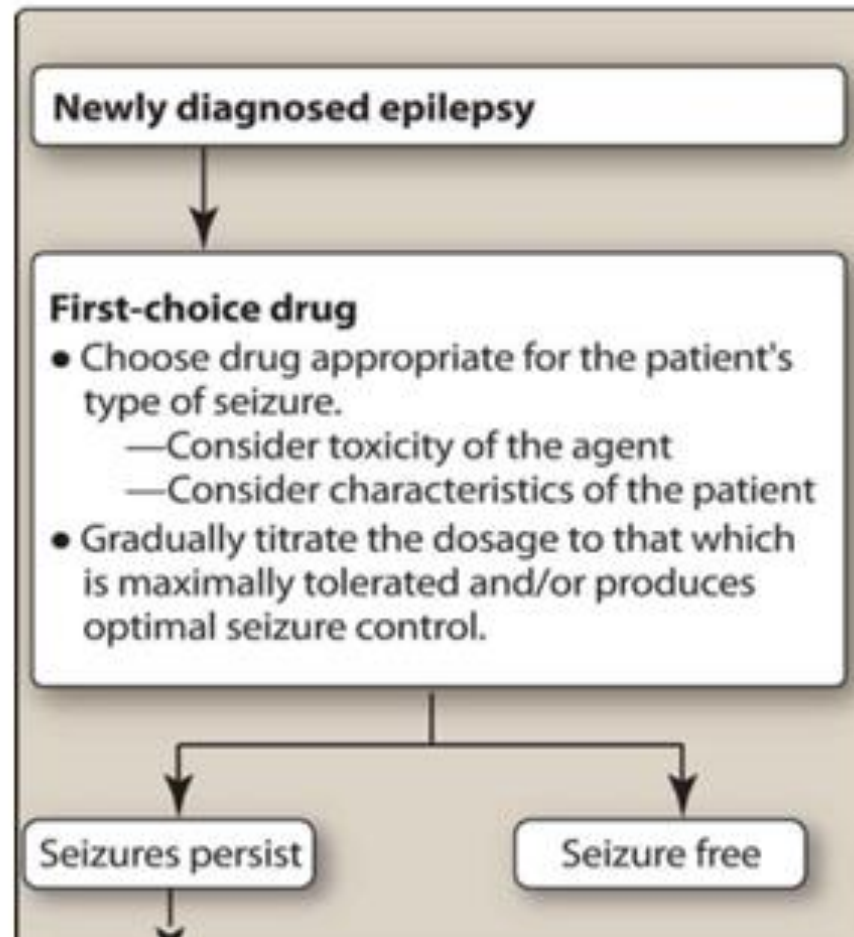
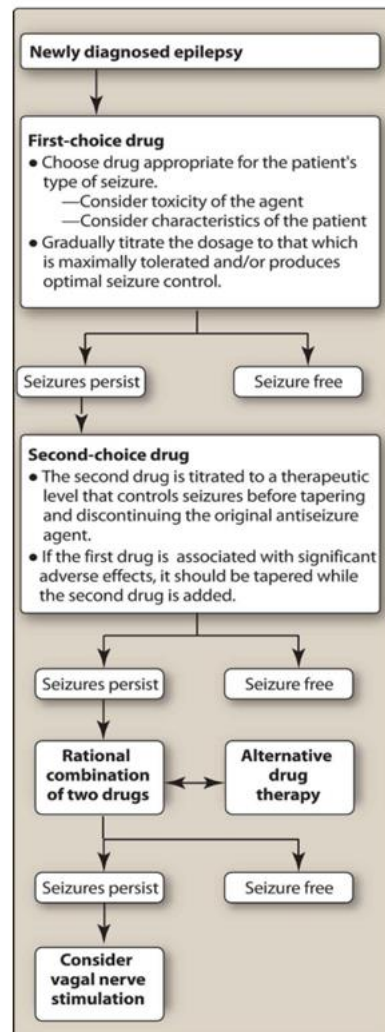


Drug choice

- Choice of drug treatment is based on:
 - Classification of the seizures
 - Patient-specific variables (age, comorbid medical conditions)
 - Characteristics of the drug (cost, toxicity and drug interactions)



Drug choice





Benzodiazepines

- Most are reserved for emergency or acute seizures
- Bind to GABA inhibitory receptors to reduce firing rate
- **Clonazepam, clobazam, diazepam** and **lorazepam** are used as adjunctive therapy for myoclonic, partial and generalized tonic-clonic seizures
- Diazepam is available for rectal administration
- **Diazepam** and **lorazepam** have well-defined roles in the management of status epilepticus.



Phenobarbital and Primidone

- **Phenobarbital**
- Enhances the inhibitory effects of GABA-mediated neurons
- Can be used for focal and tonic clonic seizures
- Phenobarbital in epilepsy should be used primarily in the treatment of status epilepticus (when other treatments fail!)
- It can produce fatigue, listlessness, and tiredness in adults and insomnia, hyper activity, and aggression in children.
- With chronic use: megaloblastic anemia and osteomalacia
- Nystagmus and ataxia occur at excessive dosage.
- Potent enzyme inducer: drug interactions especially with oral contraceptives



Phenobarbital and Primidone

- **Primidone**
- Metabolized to phenobarbital and phenylethylmalonamide
- Adverse effects: similar to phenobarbital
- Also used for essential tremor



Tiagabine

- Blocks GABA uptake (by blocking GABA transporter: GAT1) into presynaptic neurons, permitting more GABA to be available for receptor binding, and enhancing inhibitory activity
- Used as adjunctive treatment in focal seizures > usually for refractory seizures
- > 95% protein bound
- Adverse effects: fatigue, dizziness, GI upset



Vigabatrin

- Irreversible inhibitor of GABA transaminase
- Vigabatrin is effective in the treatment of focal seizures (but not generalized seizures) and in the treatment of infantile spasms.
- Usually only used for refractory seizures
- Adverse effects:
- Visual field loss (irreversible)



Stiripentol

- Modulate GABAA receptors.
- Its use is limited to patients with Dravet syndrome who are also taking clobazam.
- It is an inhibitor of CYP1A2, 2C19, 2D6 and 3A4.
- When administered with clobazam, it significantly increases the concentration of both clobazam and the active metabolite (norclobazam).
- Adverse effects: Somnolence, decreased appetite, agitation, ataxia, weight loss, hypotonia, nausea, tremor, dysarthria, insomnia



Carbamazepine

- Blocks sodium channels inhibiting generation of repetitive action potentials in the epileptic focus and preventing their spread
- Effective for partial seizures and generalized tonic-clonic seizures
- Also used for **trigeminal neuralgia and bipolar disorder**
- Absorbed slowly and erratically following oral administration and may vary from generic to generic
- Metabolized by CYP3A4
- Inducer of CYP1A2, CYP2C, CYP3A enzymes
- Not well tolerated by the elderly
- Adverse effects:
 - Hyponatremia may be noted in some patients, especially elderly
 - Rash
- Should not be prescribed for patients with absence seizures because it may increase seizures



Phenytoin and fosphenytoin

- Phenytoin blocks voltage-gated sodium channels (slows the rate of recovery from inactivation)
- Phenytoin is effective for treatment of partial seizures and generalized tonic-clonic seizures and status epilepticus
- Phenytoin is 90% bound to plasma albumin
- Phenytoin exhibits saturable enzyme metabolism at low concentration (zero-order pharmacokinetics)
- Small increases in a daily dose can produce large increases in the plasma concentration resulting in drug induced toxicity
- Induces CYP2C, CYP3A and UGT
- Subject to several interactions especially with warfarin (increased risk for bleeding) and OCPs (failure)



Phenytoin and fosphenytoin

- Side effects:
 - Gingival hyperplasia (the gums growing over the teeth), acne, hirsutism
 - Nystagmus, Ataxia (usually dose related)
 - Peripheral neuropathies
 - Osteoporosis with long term use
 - hepatotoxicity
 - Rash (Stevens-Johnson syndrome and toxic epidermal necrolysis)
 - Cardiotoxicity
- Fosphenytoin may also be administered intramuscularly (IM)
- Phenytoin sodium should never be given IM because it can cause tissue damage and necrosis. When given IV can also cause “purple glove syndrome”
- Fosphenytoin is the drug of choice for IV and IM administration

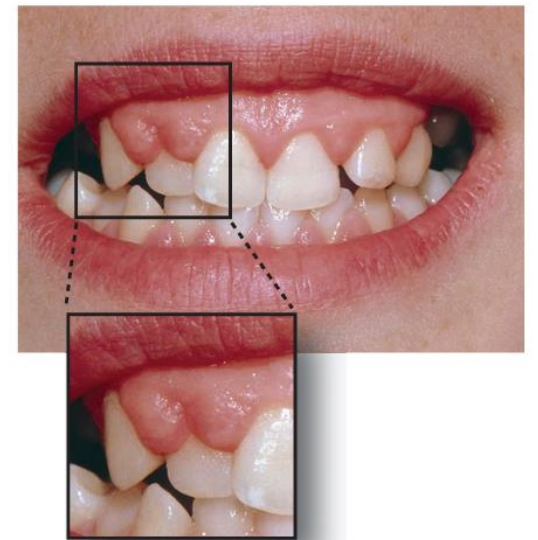


Figure 12.11

Gingival hyperplasia in patient treated with *phenytoin*. Science Source, New York, NY.



Rufinamide

- Acts at sodium channels
- Approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children one year of age and older and in adults.
- Weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes.
- Food increases absorption and peak serum concentrations
- Carbamazepine and phenytoin can reduce and valproate can increase the serum concentrations of rufinamide.



Lacosamide

- Affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.
- Approved for treatment of focal seizures and adjunctive treatment of primary generalized tonic–clonic seizures.
- Adverse events that limit treatment include dizziness, headache, and fatigue



Oxcarbazepine

- A prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity
- MHD blocks sodium channels, preventing the spread of the abnormal discharge
- Approved for use in adults and children with partial onset seizures
- Side effects similar to carbamazepine but higher risk for hyponatremia and lower risk for blood dyscrasias.
- Potential for cross sensitivity with CBZ



Eslicarbazepine

- UGT Eslicarbazepine acetate is a prodrug that is converted to the active metabolite eslicarbazepine (S-licarbazepine) by hydrolysis.
- S-licarbazepine is the active metabolite of oxcarbazepine.
- It is a voltage-gated sodium channel blocker and is approved for focal seizures in adults.
- The side effect profile includes dizziness, somnolence, diplopia, and headache. Serious
- adverse reactions such as rash, psychiatric side effects, and hyponatremia occur rarely.



Levetiracetam and Brivaracetam

- **Levetiracetam**
 - Approved for adjunct therapy of partial seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children
 - The exact mechanism of anticonvulsant action is unknown
 - Mechanism of action: May prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity through binding at synaptic vesicle protein (SV2A) receptor
 - Side effects: dizziness, sleep disturbances, headache, and weakness
- **Brivaracetam**
 - Approved for treatment of focal-onset seizures in adults.
 - It demonstrates high and selective affinity for a synaptic vesicle protein (SV2A); however, the exact mechanism of antiseizure action is unknown



Fenfluramine

- indicated for seizures associated with Dravet syndrome.
- Originally introduced as a drug for obesity but was withdrawn from the market due to concerns of valvular heart disease and pulmonary hypertension.
- Fenfluramine is an agonist at 5-HT₂ receptors, but the mechanism of its anticonvulsant activity in Dravet syndrome is unknown.
- Adverse effects: drowsiness, lethargy, reduced appetite, and weight loss.
- Monitor for the development of valvulopathy and pulmonary hypertension.



Ethosuximide and pregabalin

- **Ethosuximide**
 - Reduces propagation of abnormal electrical activity in the brain by inhibiting calcium channels
 - Effective in treating only primary generalized absence seizures (drug of choice)
 - Adverse effects are usually GI related e.g. gastric upset, nausea, vomiting, epigastric pain and anorexia
- **Pregabalin**
 - Binds to voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release
 - Effective for focal onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia
 - Side effects: Drowsiness, blurred vision, weight gain, and peripheral edema



Cannabidiol

- Approved for treatment of seizures due to Lennox- Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex.
- The drug is extracted from the Cannabis sativa plant, and it is both a substrate and inhibitor of several CYP450 enzymes, resulting in clinically relevant drug interactions.
- The drug does not have psychoactive effects
- Side effects: drowsiness, diarrhea, vomiting, and decreased appetite are the most frequent side effects.
- Cannabidiol is only available as a liquid formulated with sesame oil.



Felbamate

- Broad spectrum anticonvulsant
- Proposed mechanisms
 1. Blocking voltage-dependent sodium channels
 2. Competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor
 3. Blocking calcium channels
 4. Potentiating the action of GABA
- Reserved for use in refractory epilepsies because of the risk of **aplastic anemia and hepatic failure**



Gabapentin

- GABA analog
- Does not act at GABA receptors
- Mechanism of action is not known (possibly on voltage gated Ca and K channels)
- Approved as adjunct therapy for partial seizures
- Also used for Postherpetic neuralgia pain



Lamotrigine

- Blocks sodium channels and calcium channels
- Effective in a wide variety of seizures including partial seizures and generalized seizures (possibly due to additional actions that lower glutamate and aspartate)
- Approved for use in bipolar disorder
- Half life is decreased by enzyme inducing drugs like carbamazepine and phenytoin and increased by greater than 50% with the addition of valproate
- Rapid titration to high serum concentrations of lamotrigine can cause a rash, which may progress to a serious life-threatening reaction



Topiramate

- Broad spectrum anti-seizure activity
- MOA:
 1. Blocks voltage-dependent Na channels
 2. Increases the frequency of chloride channel opening by binding to the GABA receptor
 3. Reduces high-voltage Ca currents
 4. May act at glutamate (NMDA) sites
- Effective and approved for partial and primary generalized epilepsy
- Also approved for the prophylaxis of migraines and weight loss following antipsychotic use
- It inhibits CYP2C19 and is induced by phenytoin and carbamazepine
- Coadministration of topiramate reduces ethinyl estradiol
- Women taking the drug should be counseled to use additional methods of birth control
- Adverse effects: somnolence, weight loss, paresthesias, kidney stones, glaucoma, oligohidrosis, hyperthermia



Valproic acid and divalproex

- Valproic acid is available as a free acid
- Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the GIT
- Improved GI tolerance of valproic acid
- All forms are equivalent in efficacy
- Mechanisms of action:
 1. Sodium channel blockade
 2. Blockade of GABA transaminase
 3. Calcium channel blockade
- Broad spectrum of activity against seizures
- Effective for partial and primary generalized epilepsies
- Highly protein bound and enzyme inhibitor

- Adverse effects:
 - Rare hepatic toxicity, pancreatitis, alopecia
 - Teratogenic; cognitive and behavioral abnormalities and neural tube defects



Adverse effects of antiepileptics

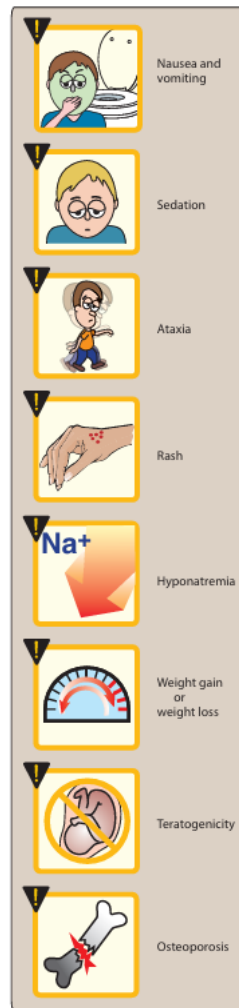
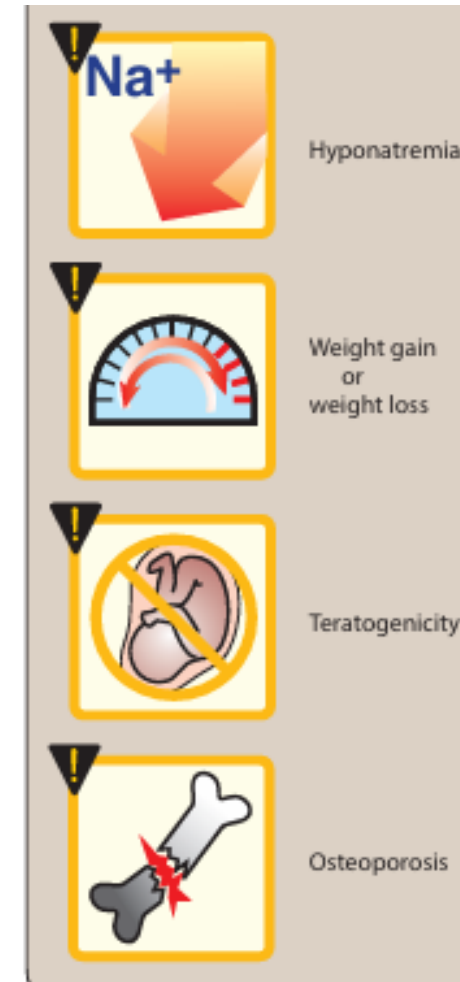


Figure 12.8
Notable adverse effects of antiepileptic medications.





PK of antiepileptics

ANTISEIZURE MEDICATION	PROTEIN BINDING*	HALF-LIFE**	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Brivaracetam	Low	9		Liver	✓
Carbamazepine	Moderate	6-15	CBZ-10,11-epoxide	Liver	✓
Eslicarbazepine acetate [^]	Low	8-24	Eslicarbazepine (S-licarbazepine)	Kidney	✓
Ethosuximide	Low	25-26		Liver	✓
Felbamate	Low	20-23		Kidney/Liver	✓
Fosphenytoin [^]	High	12-60	phenytoin	Liver	✓
Gabapentin	Low	5-9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25-32		Liver	✓
Levetiracetam	Low	6-8		Hydrolysis	
Oxcarbazepine [^]	Low	5-13	Monohydroxy metabolite (MHD)	Liver	✓
Perampanel	High	105		Liver	✓
Phenobarbital	Low	72-124		Liver	✓
Phenytoin	High	12-60		Liver	✓
Pregabalin	Low	5-6.5		Kidney	
Primidone	High	72-124	Phenobarbital, PEMA	Liver	✓
Rufinamide	Low	6-10		Liver	✓
Tiagabine	High	7-9		Liver	✓
Topiramate	Low	21		Various	✓
Valproic acid (Divalproex)	Moderate/High	6-18	Various	Liver	✓
Vigabatrin	Low	7.5		Kidney	✓
Zonisamide	Low	63		Liver	✓

*Low = 60% or less, Moderate = 61%-85%, High = >85%. **Half-life in hours. [^]Prodrug. PEMA = phenylethylmalonamide.

Figure 12.5 Summary of the pharmacokinetics of antiseizure medications used as chronic therapy.



Metabolism of antiepileptics

CYP1A2	<i>Carbamazepine</i>
CYP2C8	<i>Carbamazepine</i>
CYP2C9	<i>Carbamazepine</i> <i>Divalproex</i> <i>Phenobarbital</i> <i>Phenytoin</i>
CYP2C19	<i>Clobazam</i> <i>Divalproex</i> <i>Felbamate</i> <i>Phenobarbital</i> <i>Phenytoin</i> <i>Zonisamide</i>
CYP3A4	<i>Carbamazepine</i> <i>Clobazam</i> <i>Ethosuximide</i> <i>Perampanel</i> <i>Tiagabine</i> <i>Zonisamide</i>
UDP-glucuronosyltransferase	<i>Divalproex</i> <i>Lamotrigine</i> <i>Lorazepam</i>

Figure 12.7 CYP metabolism of the antiseizure medications.



Summary of antiepileptics

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
<i>Brivaracetam</i>	Binds SV2A	Sedation, dizziness, fatigue, and irritability.
<i>Carbamazepine</i>	Blocks Na ⁺ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
<i>Divalproex</i>	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
<i>Eslicarbazepine acetate</i>	Blocks Na ⁺ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
<i>Ethosuximide</i>	Blocks Ca ²⁺ channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
<i>Felbamate</i>	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
<i>Gabapentin</i>	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
<i>Lacosamide</i>	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
<i>Lamotrigine</i>	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
<i>Levetiracetam</i>	Binds SV2A	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
<i>Oxcarbazepine</i>	Blocks Na ⁺ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
<i>Perampanel</i>	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
<i>Phenytoin</i>	Blocks Na ⁺ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (<i>fosphenytoin</i>).
<i>Pregabalin</i>	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination; Schedule V.
<i>Rufinamide</i>	Unknown	Shortened QT interval. Multiple drug interactions.
<i>Tiagabine</i>	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
<i>Topiramate</i>	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
<i>Vigabatrin</i>	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
<i>Zonisamide</i>	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

Figure 12.11 Summary of antiseizure drugs. AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBC = complete blood count; GABA = γ -aminobutyric acid; GABA-T = γ -aminobutyric acid transaminase; GI = gastrointestinal; SLE = systemic lupus erythematosus.

Drug choice

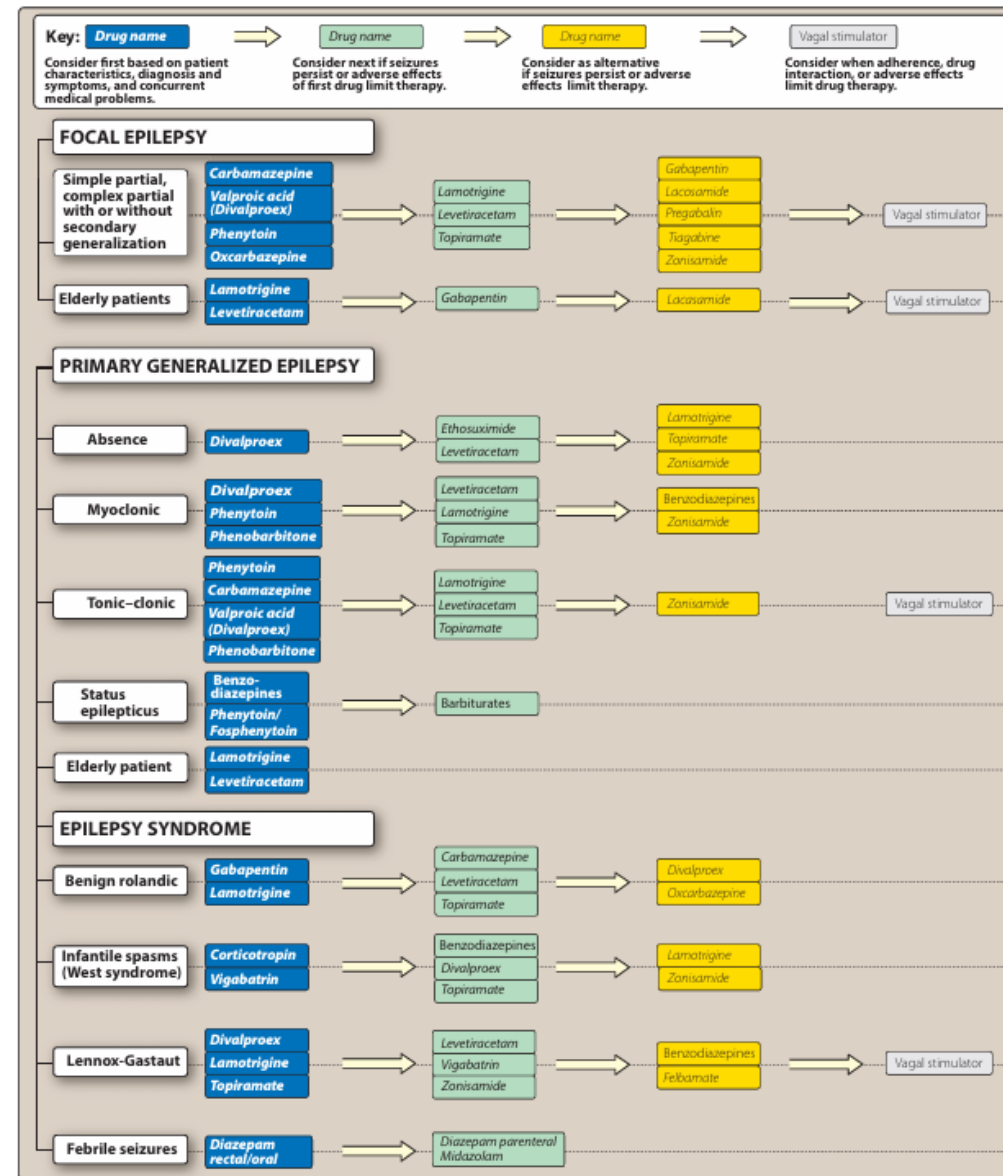


Figure 12.6

Therapeutic indications for the antiseizure agents. Benzodiazepines = diazepam and lorazepam.



Nonpharmacologic interventions

- Vagal nerve stimulation (VNS)
- Requires surgical implant of a small pulse generator with a battery and a lead wire for stimulus
- The device is implanted and its lead wires wrapped around the patient's vagal nerve
- The device is also approved for treatment of depression
- The mechanism of action is unknown
- Effective in treatment of partial onset seizures and has enabled reduction of drug therapy in some cases
- Used as an alternative when drug therapy is not successful
- VNS is a costly and invasive procedure.



Nonpharmacologic interventions

- Deep brain stimulation (DBS)
- Uses a pacemaker-like device to deliver targeted electrical stimulation to the anterior nucleus of the thalamus
- Approved with conditions for adjunctive treatment for partial-onset seizures in adults with medically refractory epilepsy
- DBS is also approved for advanced Parkinson disease



Status epilepticus

- Status epilepticus is caused either by the failure of the mechanisms responsible for seizure termination or by the initiation of mechanisms, which lead to abnormally prolonged seizures after 5 minutes. At this point, treatment for status epilepticus should be initiated. After 30 minutes, status epilepticus can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks (depending on the type and duration of seizures)
- Management principles:
 - ABCs (Airway, breathing, circulation)
 - Identify possible causes and correct
 - Emergency treatment:
 - Fast acting medications: Benzodiazepines (Drug of choice: lorazepam, alternatives: diazepam or midazolam)
 - Long acting: Phenytoin or fosphenytoin, levetiracetam or valproate



Epilepsy in pregnancy

- Planning is the most important component
- Some antiepilepsy medications increase the metabolism of hormonal contraceptives (phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, clobazam)
- All women considering pregnancy should be on high doses of folic acid prior to conception
- Divalproex and barbiturates should be avoided
- When seizures are controlled maintenance medication may be reduced if possible to the lowest dose that provides control
- If seizures are not controlled, medications and dosages will need to be adjusted prior to pregnancy if possible
- The frequency and severity of seizures may change during pregnancy
- Regular monitoring by both an obstetrician and a neurologist is important
- [Lamotrigine](#) is used extensively for people of childbearing potential planning for pregnancy due to its lower risk of teratogenicity.