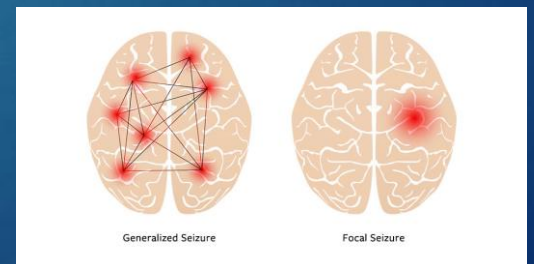


In the name of ALLAH

# Seizure Pharmacotherapy

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# Epilepsy

- ▶ Epilepsy is the **fourth most common neurologic** disorder globally and in the United States **following stroke, migraine, and Alzheimer's disease.**
- ▶ **According to the World Health Organization (WHO)**, more than **65 million** people worldwide suffer from epilepsy with 2.4 million people being diagnosed with epilepsy each year
- ▶ **US:** In the United States, approximately 2.2 million people suffer from epilepsy with 150,000 new cases being diagnosed each year.

**Iran:** 10-15 patient/ 1000

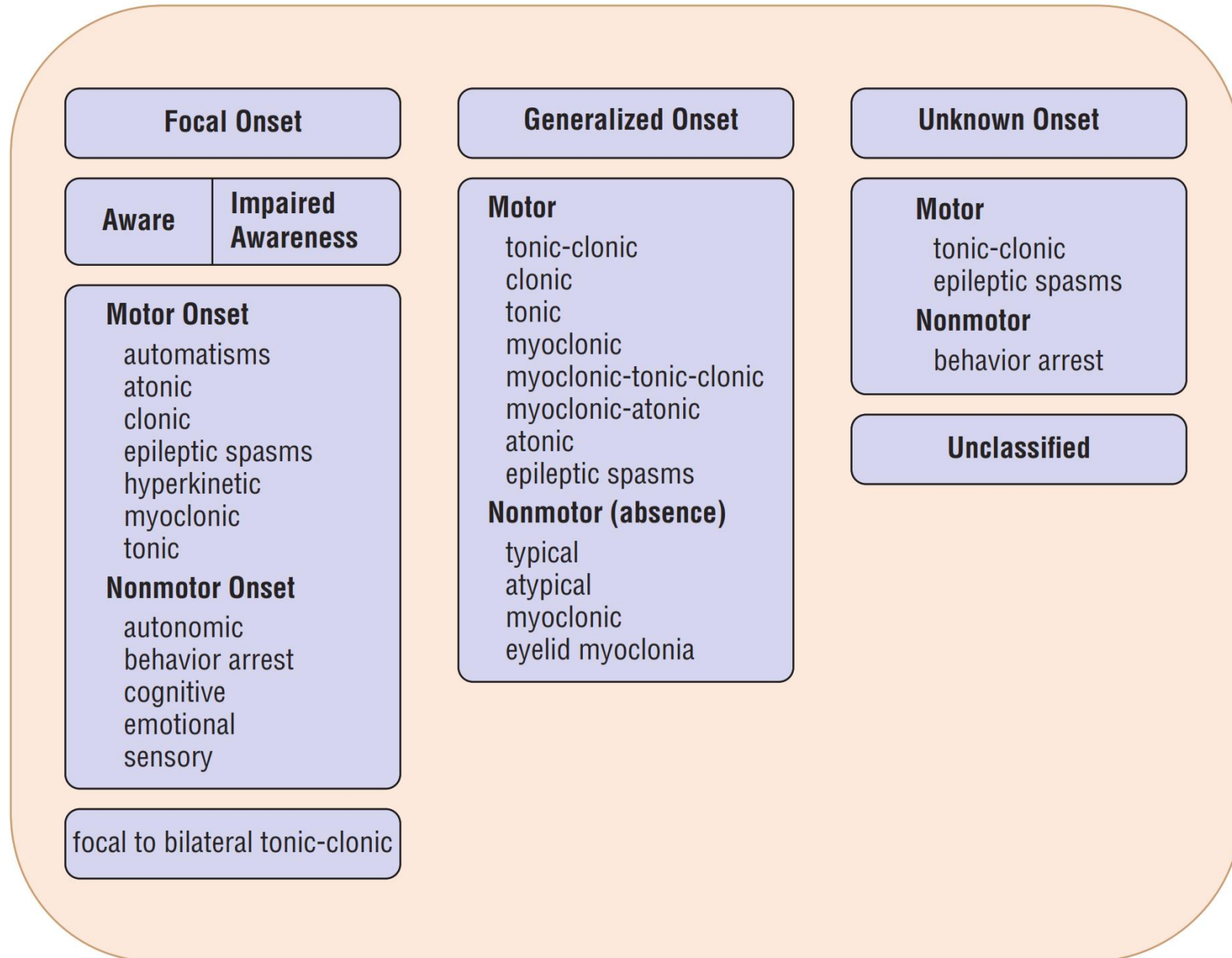
Prevalence: 1.5-2 % about **1.2 M**

**New case: 20-30 K/ yr**

# Etiology

- ▶ The underlying general pathophysiologic process at the heart of all
- ▶ epilepsies is neuronal **hyperexcitability** and **hyper synchronization**.
- ▶ (1) genetic:
- ▶ (2) structural stroke/ tumor
- ▶ (3) infectious: **most common** cause worldwide
- ▶ (4) metabolic: electrolyte imbalance/ hypoglycemia
- ▶ (5) immune
- ▶ (6) unknown

**Childhood seizure:** genetic/ infection  
**Elderly seizure:** tumor, stroke ,...



**FIGURE 73-1** ILAE 2017 Classification of seizure types—expanded version. (Adapted from Reference 26.)

# Principles of pharmacotherapy

- ▶ Antiseizure drug therapy is the **mainstay** of epilepsy treatment
- ▶ **The goal of pharmacotherapy** is **seizure freedom with minimal side effects**, and two-thirds to 80% of patients can achieve this.
- ▶ **Monotherapy/ monotherapy then.... Combination therapy**
- ▶ Pharmacotherapy of epilepsy is **highly individualized**
- ▶ **Drug selection:** seizure type/ age, gender, ethnicity, susceptibility to side effects, **comorbid** conditions, ability to adhere
- ▶ Accurate classification and diagnosis of seizure type/ epilepsy syndrome, including where seizures begin, is critical to selection of appropriate pharmacotherapy

# Epilepsy

- Initial treatment of focal epilepsy: Lamotrigine, levetiracetam, oxcarbazepine, carbamazepine, lacosamide
- Genetically mediated generalized epilepsies syndrome with mainly generalized tonic-clonic seizures: Lamotrigine, levetiracetam, valproate, topiramate, zonisamide
- Absence seizures: Ethosuximide, valproate, lamotrigine
- Genetically mediated generalized epilepsy syndrome with myoclonic seizures: Levetiracetam, valproate, zonisamide
- Female of childbearing age with either genetic generalized epilepsy or focal epilepsy: Lamotrigine, levetiracetam
- Older adult with focal epilepsy: Lamotrigine, levetiracetam, lacosamide
- Comorbid depression with focal epilepsy: Lamotrigine, lacosamide, oxcarbazepine
- Comorbid depression with genetically mediated generalized epilepsy: Lamotrigine, valproate
- Hepatic failure or after organ transplantation: Levetiracetam, gabapentin, lacosamide
- Renal failure on hemodialysis: Lamotrigine, oxcarbazepine, levetiracetam

# Anticonvulsant

- ▶ **First-generation ASDs** are very efficacious but have complex pharmacokinetics, multiple drug–drug interactions, and an increased incidence of adverse effects
- ▶ **Second-generation: first line in most of cases** ASDs have unique mechanisms of action / better tolerated/ less side effects and drug interactions
- ▶ **Third-generation ASDs** should be reserved for failure of other agents

**Titration to an adequate therapeutic** dose usually occurs over a few weeks and is necessary to allow the patient to slowly adjust to dose

**TABLE 73-2 Antiseizure Drug Pharmacokinetic Data**

ASD	$t_{1/2}$ (Hours)	Time to Steady State (Days)	Unchanged (%)	$V_D$ (L/kg)	Clinically Important Metabolite	Protein Binding (%)
<b>First Generation</b>						
Carbamazepine	12-17 34 (10,11-epoxide)	21-35 for completion of autoinduction	3	0.8-2	10,11-epoxide	76
Clonazepam	30-40	3-10	2	3.2	No	85
Ethosuximide	17-56	7-10	10-20	0.6-0.7	No	22
Phenobarbital	53-180	12-24	25-50	0.5-1	No	50
Phenytoin	22	7-10	unknown	0.5-1	No	90
Primidone	7-22 10-25 (PEMA) 75-126 (PB)	2-4	<1	0.4-1	Phenylethylmelanomide (PEMA); Phenobarbital (PB)	34
Valproic acid	9-16	2-4	<3	0.14-0.23	No	90
<b>Second Generation</b>						
Felbamate	16-22	3-4	40-50	0.73-0.85	No	25
Gabapentin	5-7	1-2	100	58 L	No	<3
Lamotrigine	12-60	3-15	10	0.9-1.3	No	55
Levetiracetam	6-8	2	66	0.7	No	<10
Oxcarbazepine	2 9 (MHD)	2-3	2	49 L	10-monohydroxy-carbazepine (MHD)	40
Tiagabine	7-9	2	2		No	96
Topiramate	21	4	70	0.6-0.8	No	15-41
Zonisamide	63	14	35	1.45	No	40
<b>Third Generation</b>						
Brivaracetam	9		<10	0.5	No	40
Cannabadiol	56-61	7	Minor	20963-42849 L	7-OH cannabadiol	>94
Clobazam	36-42	7-14	2	100 L	<i>N</i> -desmethyloclobazam	80-90
Eslicarbazepine	13-20	4-5	67	0.87	<i>S</i> -licarbazepine; oxcarbazepine	<40
Lacosamide	13	3	40	0.6	No	<15
Perampanel	105	14-21	74-80	77 L	No	96
Pregabalin	6	1-2	90	0.5	No	0
Rufinamide	6-10		<2	50 L	No	34
Vigabatrin	5-11		80	1.1	No	0

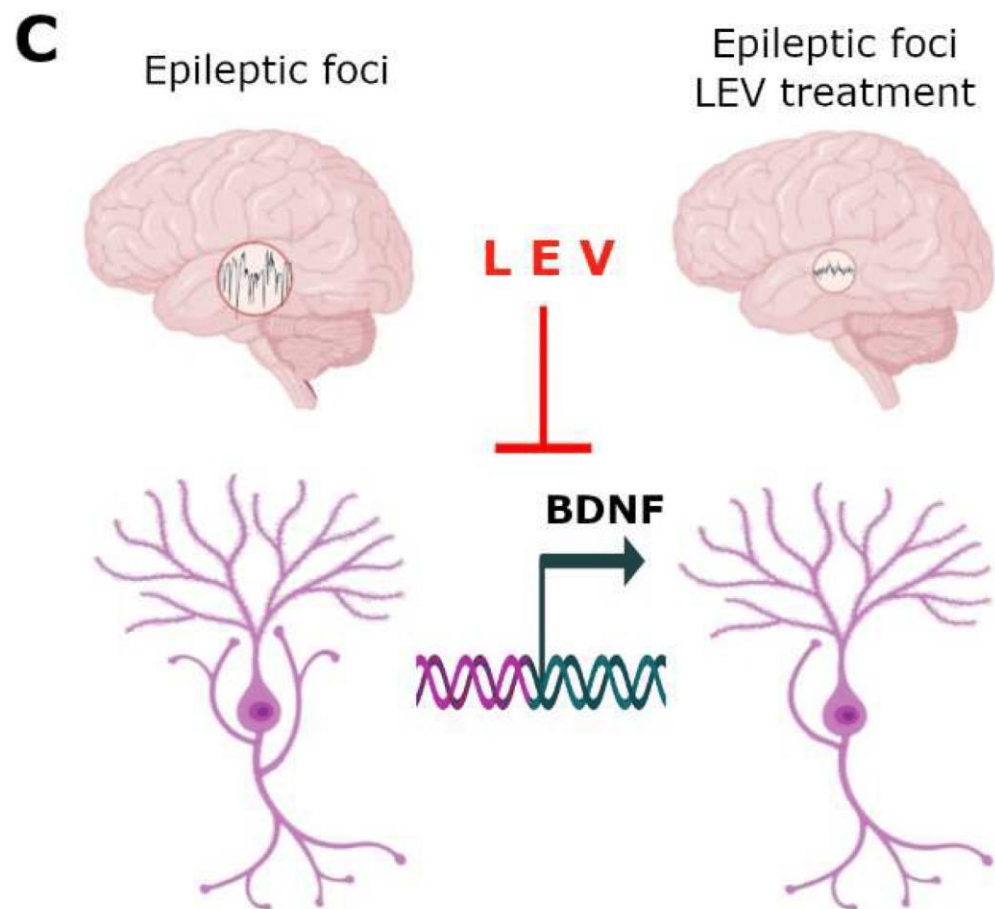
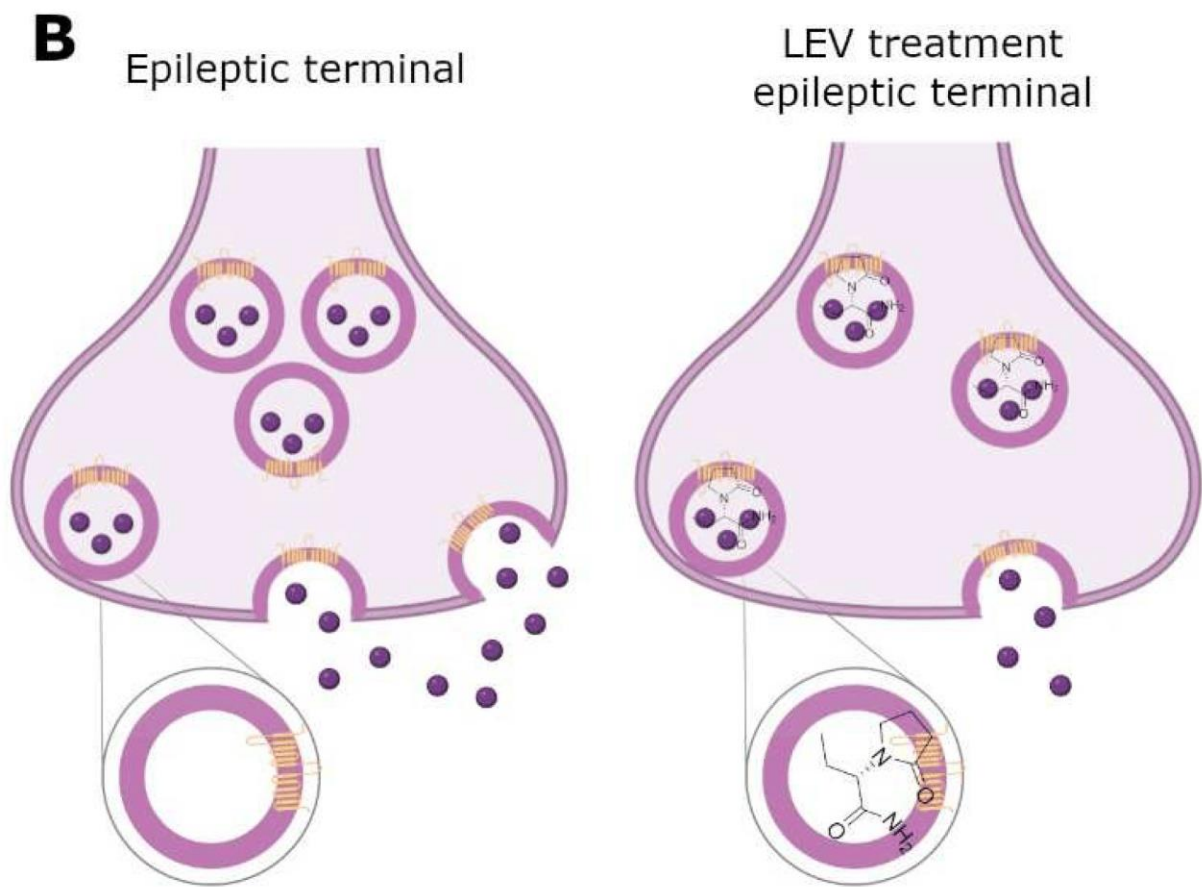
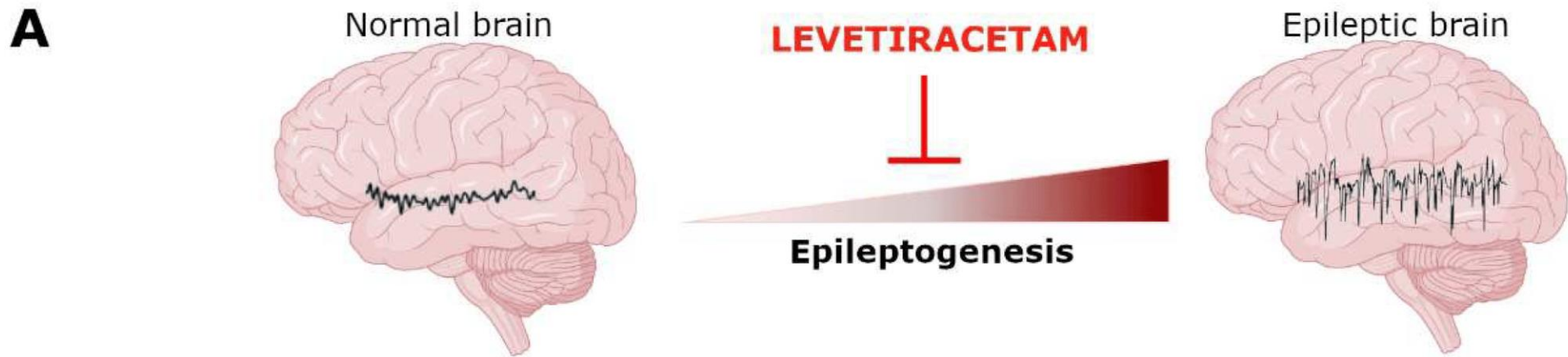


## Common mechanisms of antiseizure medication action

Drug	Na+ channels	Ca+ channels	K+ channels	Inhibitory transmission	Excitatory transmission	SV2A binding
Benzodiazepines				+++		
Brivaracetam						+++
Cannabidiol				++		
Carbamazepine	+++	+				
Cenobamate	++			+		
Clobazam				+++		
Eslicarbazepine	+++					
Ethosuximide		+++				
Felbamate	++	+		++	++	
Gabapentin		++		++		
Lacosamide	+++					
Lamotrigine	+++	+				
Levetiracetam		+	+	+	+	+++
Oxcarbazepine	+++	+	+			
Perampanel					+++	
Phenobarbital		+		+++	+	
Phenytoin	+++	+				
Pregabalin		++		++		
Primidone		+		+++	+	
Rufinamide	+++					
Stiripentol				+++		
Tiagabine				+++		
Topiramate	++	++		++	++	
Valproate	+	+		++	+	
Vigabatrin				+++		
Zonisamide	++	++				

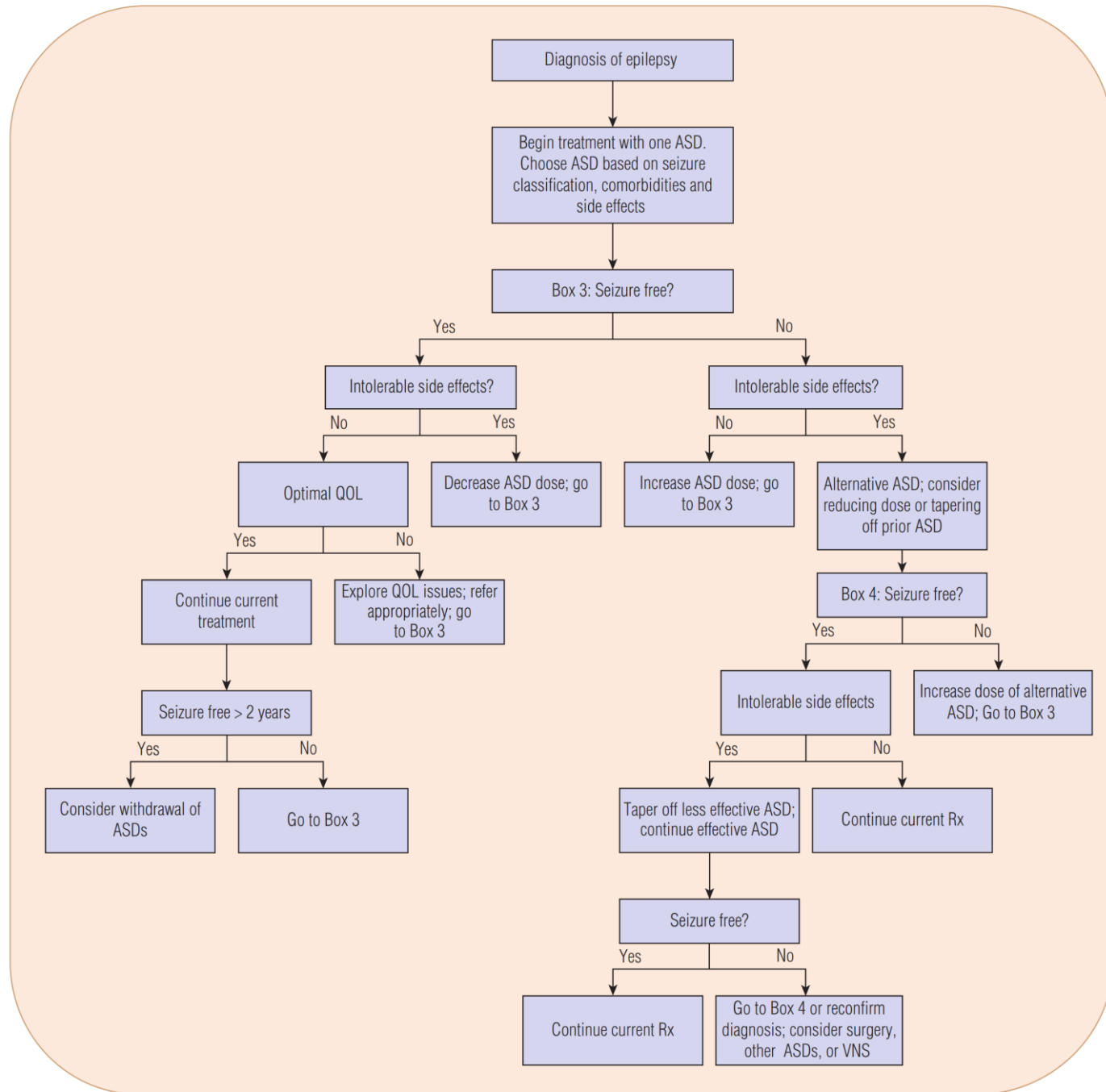
+++ : primary action; ++ : probable action; + : possible action.

SV2A: synaptic vesicle protein 2A.



**TABLE 73-4 Antiseizure Drug Dosing and Target Serum Concentration Ranges**

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maximum Dose	Comments Target Serum Concentration Range
<b>First Generation</b>				
Carbamazepine	Tegretol	400 mg/day	400-1,600 mg	4-12 mcg/mL <sup>a</sup> (17-51 μmol/L)
	Tegretol XR			
Clonazepam	Klonopin	1.5 mg/day	20 mg	20-70 ng/mL (67-233 pmol/L)
Ethosuximide	Zarontin	500 mg/day	500-1,500 mg	40-100 mcg/mL (282-708 μmol/L)
Phenobarbital	Various	1-3 mg/kg/day (10-20 mg/kg LD)	180-300 mg	10-40 mcg/mL <sup>a</sup> (43-172 μmol/L)
Phenytoin	Dilantin	3-5 mg/kg (200-400 mg)	300-600 mg	Total: 10-20 mcg/mL (40-79 μmol/L) Unbound: 0.5-3 mcg/mL ( 2-12 μmol/L)
		(15-20 mg/kg LD)		
Primidone	Mysoline	100-125 mg/day	750-2,000 mg	5-10 mcg/mL (23-46 μmol/L)
Valproic acid	Depakene	15 mg/kg (500-1,000 mg)	60 mg/kg (3,000-5,000 mg)	50-100 mcg/mL (347-693 μmol/L)
	Depakote DR/ER			
	Depacon			
<b>Second Generation</b>				
Felbamate	Felbatol	1,200 mg/day	3,600 mg	30-60 mcg/mL (126-252 μmol/L)
Gabapentin	Neurontin	300-900 mg/day	4,800 mg	2-20 mcg/mL (12-117 μmol/L)
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25-50 mg/day if not on VPA	100-200 mg if on VPA; 300-500 mg if not on VPA	4-20 mcg/mL (16-78 μmol/L)
	Lamictal XR			
Levetiracetam	Keppra	500-1,000 mg/day	3,000 mg	12-46 mcg/mL (70-270 μmol/L)
	Keppra XR			
Oxcarbazepine	Trileptal	300-600 mg/day	1,200-2,400 mg	3-35 mcg/mL (MHD) (12-139 μmol/L)
	Oxtellar XR			
Tiagabine	Gabitril	4 mg/day	56 mg	0.02-0.2 mcg/mL (0.05-0.5 μmol/L)
Topiramate	Topamax	25-50 mg/day	200-400 mg	5-20 mcg/mL (15-59 μmol/L)
	Trokendi XR			
Zonisamide	Zonegran	100 mg/day	600 mg	10-40 mcg/mL (47-188 μmol/L)
<b>Third Generation</b>				
Brivaracetam	Briviact	100 mg/day	200 mg/day	Not defined
Cannabadiol	Epidiolex	5 mg/kg/day	10-20 mg/kg/day	Not defined
Clobazam	Onfi	≤30 kg 5 mg/day; >30 kg 10 mg/day	≤30 kg up to 20 mg; >30 kg up to 40 mg	0.03-0.3 mcg/mL (0.1-1.0 μmol/L)
Eslicarbazepine	Aptiom	400 mg/day	800-1,600 mg	Not defined
Lacosamide	Vimpat	100 mg/day	400 mg	Not defined
Perampanel	Fycompa	2 mg/day	8-12 mg	Not defined
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Rufinamide	Banzel	400-800 mg/day	3,200 mg	Not defined
Vigabatrin	Sabril	1,000 mg/day	3,000 mg	0.8-36 mcg/mL (6-279 μmol/L)



**FIGURE 73-3** An algorithm for ASD therapy. (ASD, antiseizure drug; VNS, vagal nerve stimulation.)

# Side effects

- ▶ **1.Dose-related** (eg, concentration dependent)
- ▶ dose-related **CNS side effects** including sedation, dizziness, blurred or double vision, difficulty with concentration, ataxia, and impaired cognition ( most common with Barbiturates and sodium channel inhibitors)
- ▶ **2.idiosyncratic** adverse effects / uncommon / life threatening (SJS)
- ▶ **3. Chronic use** : **osteomalacia and osteoporosis.**
- ▶ phenytoin, phenobarbital, carbamazepine, oxcarbazepine, felbamate, and valproate, may interfere with **vitamin D metabolism / folic acid**
- ▶ **Supplementation: Ca-D / folic acid**

## Drug-Drug Interaction

**Least:** levetiracetam/ gabapentin

**Most:** carbamazepine phenytoin, phenobarbital, valproate sodium

# Pregnancy

- ▶ In general, higher ASD doses, higher ASD serum concentrations, polytherapy (especially polytherapy with **valproate**)
- ▶ **Use lower doses, monotherapy if possible**
- ▶ **Vit D/ folic acid** supplementation (higher doses)
- ▶ **Less risk (medications):** lamotrigine/ levetiracetam

## Common side effects of antiseizure medications

Antiseizure medication	Systemic side effects	Neurologic side effects
Brivaracetam*	Nausea, vomiting, constipation, fatigue	Headache, somnolence, dizziness, ataxia, abnormal coordination, nystagmus
Cannabidiol	Anemia, decreased appetite, diarrhea, infection, dose-related elevations of liver transaminases (ALT and/or AST), rash, fatigue	CNS depression (eg, drowsiness, lethargy, sedation), malaise, insomnia, sleep disturbance
Carbamazepine	Nausea, vomiting, diarrhea, hyponatremia, rash, pruritus	Drowsiness, dizziness, blurred or double vision, lethargy, headache
Cenobamate	Fatigue	Somnolence, dizziness, headache, diplopia
Clobazam	Increased salivation, nausea, vomiting, constipation	Somnolence, aggression, irritability, ataxia, insomnia
Eslicarbazepine	Nausea, vomiting, diarrhea, fatigue, hyponatremia, rash	Dizziness, drowsiness, headache, diplopia, vertigo, ataxia, attention disturbance, blurred vision, tremor (NOTE: Dizziness, diplopia, and ataxia reported more frequently in combination with carbamazepine)
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity
Felbamate	Nausea, vomiting, anorexia, weight loss	Insomnia, dizziness, headache, ataxia
Gabapentin	Infrequent	Somnolence, dizziness, ataxia
Lacosamide	Nausea, vomiting, fatigue	Ataxia, dizziness, headache, diplopia
Lamotrigine	Rash, nausea	Dizziness, tremor, diplopia
Levetiracetam	Fatigue, infection	Somnolence, dizziness, agitation, anxiety, irritability, depression
Oxcarbazepine	Nausea, rash, hyponatremia	Sedation, headache, dizziness, vertigo, ataxia, diplopia
Perampanel	Weight gain, fatigue, nausea	Dizziness, somnolence, irritability, gait disturbance, falls, aggression, mood alteration

Perampanel	Weight gain, fatigue, nausea	Dizziness, somnolence, irritability, gait disturbance, falls, aggression, mood alteration
Phenobarbital	Nausea, rash	Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence
Phenytoin	Gingival hypertrophy, rash	Confusion, slurred speech, double vision, ataxia
Pregabalin	Weight gain, peripheral edema, dry mouth	Dizziness, somnolence, ataxia, tremor
Primidone	Nausea, rash	Alteration of sleep cycles, sedation, lethargy, behavioral changes, hyperactivity, ataxia, tolerance, dependence
Rufinamide	Nausea, vomiting, fatigue	Dizziness, somnolence, headache
Stiripentol	Nausea, decreased appetite, weight loss	Somnolence, agitation, ataxia, hypotonia, tremor, dysarthria, insomnia
Tiagabine	Abdominal pain, nausea, lack of energy	Dizziness, somnolence, nervousness, tremor, difficulty concentrating
Topiramate	Weight loss, paresthesia, fatigue	Nervousness, difficulty concentrating, confusion, depression, anorexia, language problems, anxiety, mood problems, tremor
Valproate	Weight gain, nausea, vomiting, hair loss, easy bruising	Tremor, dizziness
Vigabatrin	Vision loss, fatigue	Drowsiness, dizziness
Zonisamide	Nausea, anorexia	Somnolence, dizziness, ataxia, confusion, difficulty concentrating, depression

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CNS: central nervous system.

\* Based upon limited experience from preapproval clinical trials.



## Rare but serious side effects of antiseizure medications

Drug	Side effects*
Brivaracetam <sup>¶</sup>	Hypersensitivity reactions including bronchospasm and angioedema, leukopenia, neutropenia, psychosis
Cannabidiol	Hypersensitivity reactions (including angioedema, erythema, and pruritus), suicidal ideation
Carbamazepine	Agranulocytosis, aplastic anemia, SJS/TEN, hepatic failure, DRESS, dermatitis/rash, serum sickness, pancreatitis, lupus syndrome, hypogammaglobulinemia
Cenobamate	QT interval shortening, DRESS/multiorgan hypersensitivity
Clobazam	Respiratory depression, SJS/TEN, DRESS
Eslicarbazepine	Prolonged PR interval, atrioventricular block, hyponatremia (rarely severe), SJS/TEN
Ethosuximide	Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, drug-induced immune thrombocytopenia
Felbamate	Aplastic anemia, liver failure
Gabapentin	Multiorgan hypersensitivity, respiratory depression
Lacosamide	Prolonged PR interval, atrioventricular block, multiorgan hypersensitivity, neutropenia
Lamotrigine	SJS/TEN, DRESS/multiorgan hypersensitivity, aseptic meningitis, hypogammaglobulinemia, cardiac rhythm and conduction abnormalities
Levetiracetam	SJS/TEN, anaphylaxis and angioedema, pancytopenia, psychosis, hypogammaglobulinemia
Oxcarbazepine	SJS/TEN, DRESS/multiorgan hypersensitivity, agranulocytosis, pancytopenia, leukopenia



Perampanel	Severe neuropsychiatric effects (eg, hostility, aggression)
Phenobarbital	Agranulocytosis, SJS/TEN, hepatic failure, dermatitis/rash, serum sickness, connective tissue contractures (eg, Dupuytren), complex regional pain syndrome
Phenytoin	Agranulocytosis, SJS/TEN, DRESS, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, adenopathy, pseudolymphoma, neuropathy, ataxia, lupus syndrome, hirsutism
Pregabalin	Angioedema, hypersensitivity reactions, rhabdomyolysis
Primidone	Acute toxic reaction (sedation, dizziness, ataxia, nausea, and vomiting), agranulocytosis, SJS/TEN, hepatic failure, dermatitis/rash, serum sickness, connective tissue contractures (eg, Dupuytren)
Rufinamide	SJS/TEN, DRESS, dermatitis/rash, shortened QT interval
Stiripentol	Limited information: severe somnolence, marked weight loss, neutropenia and thrombocytopenia, suicidal ideation and behavior
Tiagabine	SJS/TEN, nonconvulsive status epilepticus
Topiramate	Acute myopia and glaucoma, kidney stones, oligohidrosis and hyperthermia (which primarily occur in children)
Valproate	Agranulocytosis, SJS/TEN, aplastic anemia, hepatic failure, dermatitis/rash, serum sickness, pancreatitis, polycystic ovary syndrome, hypogammaglobulinemia
Vigabatrin	MRI abnormalities, depression, weight gain
Zonisamide	Rash, SJS/TEN, aplastic anemia, agranulocytosis, nephrolithiasis; acute myopia and secondary angle closure glaucoma, hyperammonemia and encephalopathy; in children, fever and hyperhidrosis



*Thank you...*

