Epilepsy

- Epilepsy implies a periodic recurrence of seizures with or without convulsions.

- A seizure results from an excessive discharge of cortical neurons and is characterized by changes in electrical activity as measured by the electroencephalogram (EEG).

- A convulsion implies violent, involuntary contraction(s) of the voluntary muscles.

- Seizures result from excessive excitation, or from disordered inhibition of a population of neurons. Initially, a small number of neurons fire abnormally.

- Then normal membrane conductances and inhibitory synaptic currents break down, excitability spreads locally (focal seizure) or more widely (generalized seizure).

- The incidence of epileptic seizures is around 50 cases per 100,000 of the population.

- About 70–80% of all those who develop epilepsy will become seizure free on treatment and about 50% will eventually withdraw their medication successfully.

Mechanisms that may contribute to synchronous hyperexcitability include:

✓ Alterations of ion channels in neuronal membranes

✓ Biochemical modifications of receptors

✓ Modulation of second messaging systems and gene expression

✓ Changes in extracellular ion concentrations

✓ Alterations in neurotransmitter uptake and metabolism in glial cells

✓ Modification in the ratio and function of inhibitory circuits

✓ Local neurotransmitter imbalances (e.g., glutamate, γ-aminobutyric acid [GABA]), acetylcholine, norepinephrine, and serotonin)

CLINICAL PRESENTATION:

- In most cases, the healthcare provider will not be in a position to witness a seizure.

- Many patients (particularly those with complex partial [CP] or GTC seizures) are amnestic to the actual seizure event.

- Obtaining an accurate history and description of the ictal event (including time course) from a third party is important.

- EEG is very useful in the diagnosis of various seizure disorders, but the EEG may be normal in some patients who still have the clinical diagnosis of epilepsy.

- A serum prolactin level obtained within 10 to 20 minutes of a tonic-clonic seizure can help differentiate seizure activity from pseudoseizure activity, but not from syncope.

- Although magnetic resonance imaging is very useful (especially imaging of the temporal lobes), computed tomography typically is not helpful except in the initial evaluation for a brain tumor or cerebral bleeding.

International Classification of Epileptic Seizures

I. Partial seizures (seizures begin locally)
- A. Simple (without impairment of consciousness)
  - 1. With motor symptoms
  - 2. With special sensory or somatosensory symptoms
  - 3. With psychic symptoms
- B. Complex (with impairment of consciousness)
  - 1. Simple partial onset followed by impairment of consciousness–with or without automatisms
  - 2. Impaired consciousness at onset–with or without automatisms
- C. Secondarily generalized (partial onset evolving to generalized tonic-clonic seizures)

II. Generalized seizures (bilaterally symmetrical and without local onset)
- A. Absence
- B. Myoclonic
- C. Clonic
- D. Tonic
- E. Tonic-clonic
- F. Atonic
- G. Infantile spasms

III. Unclassified seizures

IV. Status epilepticus

- Partial (focal) seizures begin in one hemisphere of the brain and, unless they become secondarily generalized, result in an asymmetric seizure.

- Partial seizures manifest as alterations in motor functions, sensory or somatosensory symptoms, or automatisms.

- Absence seizures generally occur in young children or adolescents and exhibit a sudden onset, interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes.

- In generalized seizures, motor symptoms are bilateral, and there is altered consciousness.

- Tonic-clonic seizures begin with a short tonic contraction of muscles followed by a period of rigidity.

- The patient may lose sphincter control, bite the tongue, or become cyanotic. The episode may be followed by unconsciousness, and frequently the patient goes into a deep sleep.

- Myoclonic jerks are brief shock-like muscular contractions of the face, trunk, and extremities. They may be isolated events or rapidly repetitive.

- In atonic seizures, there is a sudden loss of muscle tone that may be described as a head drop, dropping of a limb, or slumping to the ground.

Treatment:

- The goal of treatment is to control or reduce the frequency of seizures, minimize side effects, and ensure compliance, allowing the patient to live as normal a life as possible.

- Complete suppression of seizures must be balanced against tolerability of side effects, and the patient should be involved in defining the balance.

- The treatment of choice depends on the type of epilepsy and on drug-specific adverse effects and patient preferences.

- Begin with monotherapy; about 50% to 70% of patients can be maintained on one antiepileptic drug (AED), but all are not seizure free.

- Up to 60% of patients with epilepsy are noncompliant, and this is the most common reason for treatment failure.

- Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 4 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 years and before age 35 years, and a normal EEG.

- Poor prognostic factors include a history of a high frequency of seizures, repeated episodes of status epilepticus, a combination of seizure types, and development of abnormal mental functioning.

- The mechanism of action of most AEDs includes effects on ion channels (sodium and Ca), inhibitory neurotransmission (increasing CNS GABA), or excitatory neurotransmission (decreasing or antagonizing glutamate and aspartate).

- AEDs that are effective against GTC and partial seizures probably work by delaying recovery of sodium channels from activation.

- Drugs that reduce corticothalamic T-type Ca currents are effective against generalized absence seizures.

Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
Partial seizures (newly diagnosed)			
U.S. guidelines	*Adults & adolescents:* Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid		*FDA approved:* Carbamazepine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid
U.K. guidelines	Carbamazepine Lamotrigine Oxcarbazepine Topiramate Valproic acid		
ILAE guidelines	*Adults:* Carbamazepine Phenytoin Valproic acid *Children:* Oxcarbazepine *Elderly:* Gabapentin Lamotrigine	*Adults:* Gabapentin Lamotrigine Oxcarbazepine Phenobarbital Topiramate *Children:* Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid *Elderly:* Carbamazepine	
U.S. Expert Panel 2005	Carbamazepine Lamotrigine Oxcarbazepine	Levetiracetam	
Partial seizures (refractory monotherapy)			
U.S. guidelines	Lamotrigine Oxcarbazepine Topiramate		*FDA approved:* Carbamazepine Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Valproic acid
U.K. guidelines	Lamotrigine Oxcarbazepine Topiramate		
Partial seizures (refractory adjunct)			
U.S. guidelines	*Adults:* Gabapentin Lamotrigine Levetiracetam Oxcarbazepine		*FDA approved:* Carbamazepine Gabapentin Lamotrigine Levetiracetam

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Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
	Tiagabine Topiramate Zonisamide *Children:* Gabapentin Lamotrigine Oxcarbazepine Topiramate		Oxcarbazepine Phenobarbital Phenytoin Pregabalin Tiagabine Valproic acid Zonisamide
U.K. guidelines	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate		
Generalized seizures absence (newly diagnosed)			
U.S. guidelines	Lamotrigine		*FDA approved:* Ethosuximide Valproic acid
U.K. guidelines	Lamotrigine		
ILAE guidelines	None	Ethosuximide Lamotrigine Valproic acid	
U.S. Expert Panel 2005	Ethosuximide Valproic acid	Lamotrigine	
Primary generalized (tonic-clonic)			
U.S. guidelines	Topiramate		*FDA approved:* Lamotrigine Topiramate
U.K. guidelines	Lamotrigine Topiramate		
ILAE guidelines	None	*Adults:* Carbamazepine Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid *Children:* Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid	
U.S. Expert Panel 2005	Valproic acid	Lamotrigine Topiramate	
Juvenile myoclonic epilepsy			*FDA approved:* Levetiracetam (myoclonic seizures)

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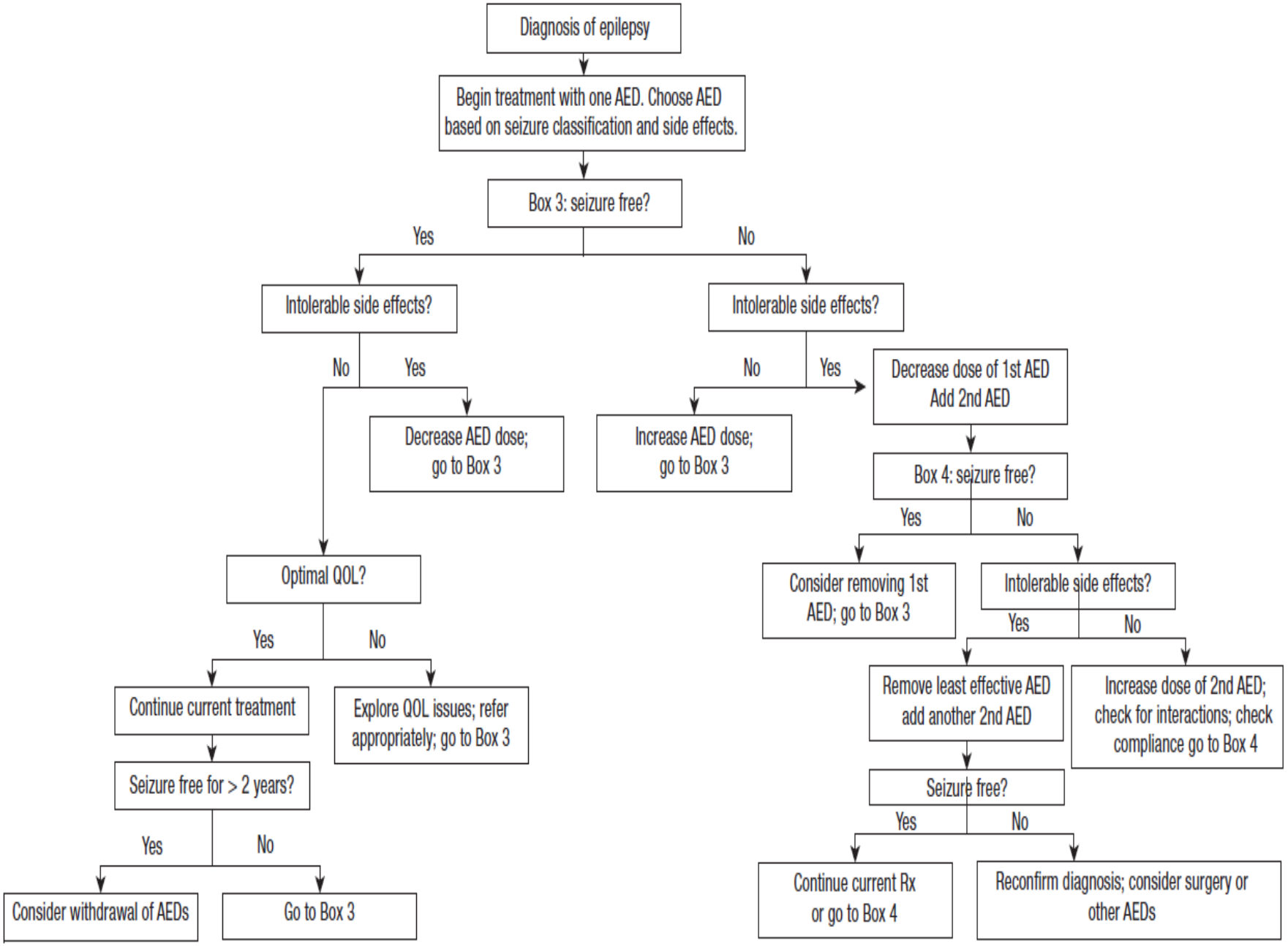
Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
ILAE	None	Clonazepam Lamotrigine Levetiracetam Topiramate Valproic acid Zonisamide	
U.S. Expert Panel 2005	Valproic acid	Levetiracetam Topiramate Zonisamide	


Diagnosis of epilepsy
Begin treatment with one AED. Choose AED based on seizure classification and side effects.
Box 3: seizure free?
Yes
No
Intolerable side effects?
Intolerable side effects?
No
Yes
No
Yes
Decrease AED dose; go to Box 3
Increase AED dose; go to Box 3
Decrease dose of 1st AED Add 2nd AED
Box 4: seizure free?
Yes
No
Optimal QOL?
Consider removing 1st AED; go to Box 3
Intolerable side effects?
Yes
No
Yes
No
Continue current treatment
Explore QOL issues; refer appropriately; go to Box 3
Remove least effective AED add another 2nd AED
Increase dose of 2nd AED; check for interactions; check compliance go to Box 4
Seizure free for > 2 years?
Seizure free?
Yes
No
Yes
No
Consider withdrawal of AEDs
Go to Box 3
Continue current Rx or go to Box 4
Reconfirm diagnosis; consider surgery or other AEDs

AED	$t_{1/2}$ (h)	Time to Steady State (days)	Unchanged (%)	V_D (L/kg)
Carbamazepine	12 M; 5–14 Co	21–28 for completion of auto-induction	<1	1–2
Ethosuximide	A 60; C 30	6–12	10–20	0.67
Felbamate	16–22	5–7	50	0.73–0.82
Gabapentin[a]	5–40[b]	1–2	100	0.65–1.04
Lamotrigine	25.4 M	3–15	0	1.28
Levetiracetam	7–10	2		0.7
Oxcarbazepine	3–13	2		0.7
Phenobarbital	A 46–136; C 37–73	14–21	20–40	0.6
Phenytoin	A 10–34; C 5–14	7–28	<5	0.6–8.0
Pregabalin	A 6–7[b]	1–2	90	0.5
Primidone	A 3.3–19; C 4.5–11	1–4	40	0.43–1.1
Tiagabine	5–13		Negligible	
Topiramate	18–21	4–5	50–70	0.55–0.8 (male); 0.23–0.4 (female)
Valproic acid	A 8–20; C 7–14	1–3	<5	0.1–0.5
Zonisamide	24–60	5–15		0.8–1.6

	Acute Side Effects		
AED	***Concentration Dependent***	***Idiosyncratic***	**Chronic Side Effects**
Carbamazepine	Diplopia Dizziness Drowsiness Nausea Unsteadiness Lethargy	Blood dyscrasias Rash	Hyponatremia
Ethosuximide	Ataxia Drowsiness GI distress Unsteadiness Hiccups	Blood dyscrasias Rash	Behavior changes Headache
Felbamate	Anorexia Nausea Vomiting Insomnia Headache	Aplastic anemia Acute hepatic failure	Not established
Gabapentin	Dizziness Fatigue Somnolence Ataxia	Pedal edema	Weight gain
Lamotrigine	Diplopia Dizziness Unsteadiness Headache	Rash	Not established

Levetiracetam	Sedation Behavioral disturbance	Not established	Not established
Oxcarbazepine	Sedation Dizziness Ataxia Nausea	Rash	Hyponatremia
Phenobarbital	Ataxia Hyperactivity Headache Unsteadiness Sedation Nausea	Blood dyscrasias Rash	Behavior changes Connective tissue disorders Intellectual blunting Metabolic bone disease Mood change Sedation
Phenytoin	Ataxia Nystagmus Behavior changes Dizziness Headache Incoordination Sedation Lethargy Cognitive impairment Fatigue Visual blurring	Blood dyscrasias Rash Immunologic reaction	Behavior changes Cerebellar syndrome Connective tissue changes Skin thickening Folate deficiency Gingival hyperplasia Hirsutism Coarsening of facial features Acne Cognitive impairment Metabolic bone disease Sedation

AED	Acute Side Effects: *Concentration Dependent*	Acute Side Effects: *Idiosyncratic*	Chronic Side Effects
Pregabalin	Dizziness Somnolence Blurred vision	Pedal edema Creatine kinase elevation Decrease platelets	Weight gain
Primidone	Behavior changes Headache Nausea Sedation Unsteadiness	Blood dyscrasias Rash	Behavior change Connective tissue disorders Cognitive impairment Sedation
Tiagabine	Dizziness Fatigue Difficulties concentrating Nervousness Tremor Blurred vision Depression Weakness	Spike-wave stupor	Not established
Topiramate	Difficulties concentrating Psychomotor slowing Speech or language problems Somnolence, fatigue Dizziness Headache	Metabolic acidosis Acute angle glaucoma Oligohidrosis	Kidney stones Weight loss

Valproic acid	GI upset	Acute hepatic failure	Polycystic ovary–like syndrome
	Sedation	Acute pancreatitis	Weight gain
	Unsteadiness	Alopecia	Hyperammonemia
	Tremor		Menstual cycle irregularities
	Thrombocytopenia		
Zonisamide	Sedation	Rash	Kidney stones
	Dizziness		Weight loss
	Cognitive impairment	Oligohidrosis	
	Nausea		

	Trade Name	Usual Initial Dose	Usual Maximum Daily Dose	Target Serum Concentration Range
Barbiturates				
Mephobarbital	Mebaral	50–100 mg/day	400–600 mg	Not defined
Phenobarbital	Various	1–3 mg/kg/day (10–20 mg/kg LD)	180–300 mg	10–40 mcg/mL
Primidone	Mysoline	100–125 mg/day	750–2,000 mg	5–10 mcg/mL
Benzodiazepines				
Clonazepam	Klonopin	1.5 mg/day	20 mg	20–80 ng/mL
Clorazepate	Tranxene	7.5–22.5 mg/day	90 mg	Not defined
Diazepam	Valium	po: 4–40 mg IV: 5–10 mg	po: 4–40 mg IV: 5–30 mg	100–1,000 ng/mL
Lorazepam	Ativan	po: 2–6 mg IV: 0.05 mg/kg IM: 0.05 mg/kg	po: 10 mg IV: 0.044 mg/kg	10–30 ng/mL
Hydantoins				
Ethotoin	Peganone	<1,000 mg/day	2,000–4,000 mg with food	15–50 mcg/mL
Mephenytoin	Mesantoin	50–100 mg/day	200–800 mg	25–40 mcg/mL
Phenytoin	Dilantin	po: 3–5 mg/kg (200–400 mg) (15–20 mg/kg LD)	po: 500–600 mg	Total: 10–20 mcg/mL Unbound: 0.5–3 mcg/mL
Succinimides				
Ethosuximide	Zarontin	500 mg/day	500–2,000 mg	40–80 mcg/mL
Methsuximide	Celontin	300 mg/day	300–1,200 mg	*N*-desmethyl metabolite 10–40 mcg/mL

Other				
Carbamazepine	Tegretol	400 mg/day	400–2,400 mg	4–14 mcg/mL
Felbamate	Felbatol	1,200 mg/day	3,600 mg	40–100 mcg/mL[a]
Gabapentin	Neurontin	900 mg/day	4,800 mg	4–16 mcg/mL[a]
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25–50 mg/day if not on VPA	100–150 mg if on VPA; 300–500 mg if not on VPA	4–20 mcg/mL[a]
Levetiracetam	Keppra	500–1,000 mg/day	3,000–4,000 mg	5–40 mcg/mL[a]
Oxcarbazepine	Trileptal	300–600 mg/day	2,400–3,000 mg	12–30 mcg/mL[a] (MHD)
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Tiagabine	Gabitril	4–8 mg/day	80 mg	100–300 mcg/mL[a]
Topiramate	Topamax	25–50 mg/day	200–1,000 mg	2–25 mcg/mL
Valproic acid	Depakene Depakote Depacon	15 mg/kg (500–1,000 mg)	60 mg/kg (3,000–5,000 mg)	50–150 mcg/mL[a]
Zonisamide	Zonegran	100–200 mg/day	600 mg	10–40 mcg/mL[a]