Pharmacology Lectures
by

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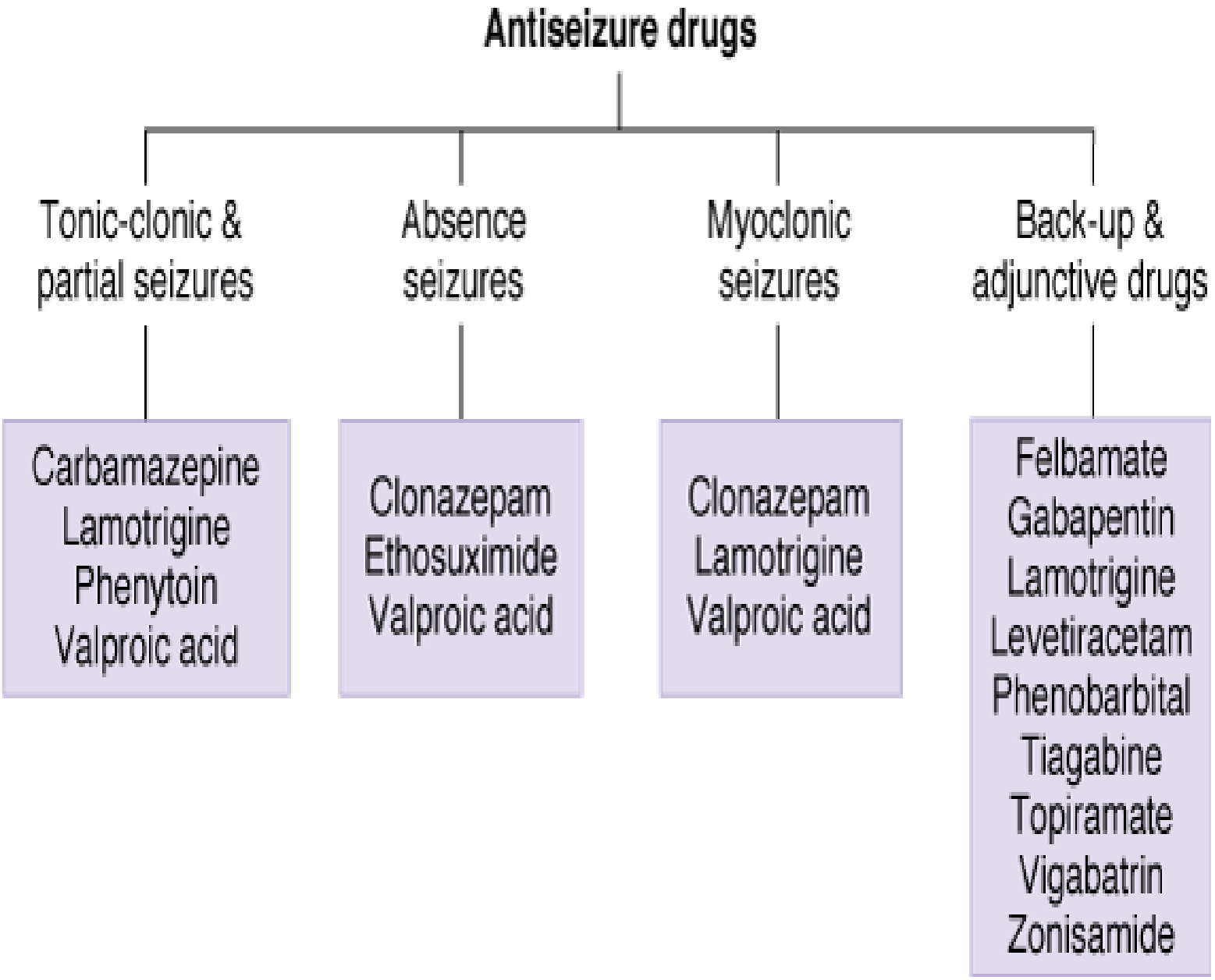
ANTIEPILEPTIC DRUGS

- Barbiturates
- Benzodiazepines
- *Carbamazepine*
- *Divalproex*
- *Ethosuximide*
- *Felbamate*
- *Gabapentin*
- *Lamotrigine*
- *Levetiracetam*
- *Oxcarbazepine*
- *Phenytoin*
- *Pregabalin*
- *Primidone*
- *Tiagabine*
- *Topiramate*
- *Zonisamide*


Antiseizure drugs
Tonic-clonic & partial seizures
Absence seizures
Myoclonic seizures
Back-up & adjunctive drugs
Carbamazepine
Lamotrigine
Phenytoin
Valproic acid
Clonazepam
Ethosuximide
Valproic acid
Clonazepam
Lamotrigine
Valproic acid
Felbamate
Gabapentin
Lamotrigine
Levetiracetam
Phenobarbital
Tiagabine
Topiramate
Vigabatrin
Zonisamide

- **Seizures** Finite episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons

- **Partial seizures, simple** Consciousness preserved; manifested variously as convulsive jerking, paresthesias, psychic symptoms (altered sensory perception, illusions, hallucinations, affect changes), and autonomic dysfunction

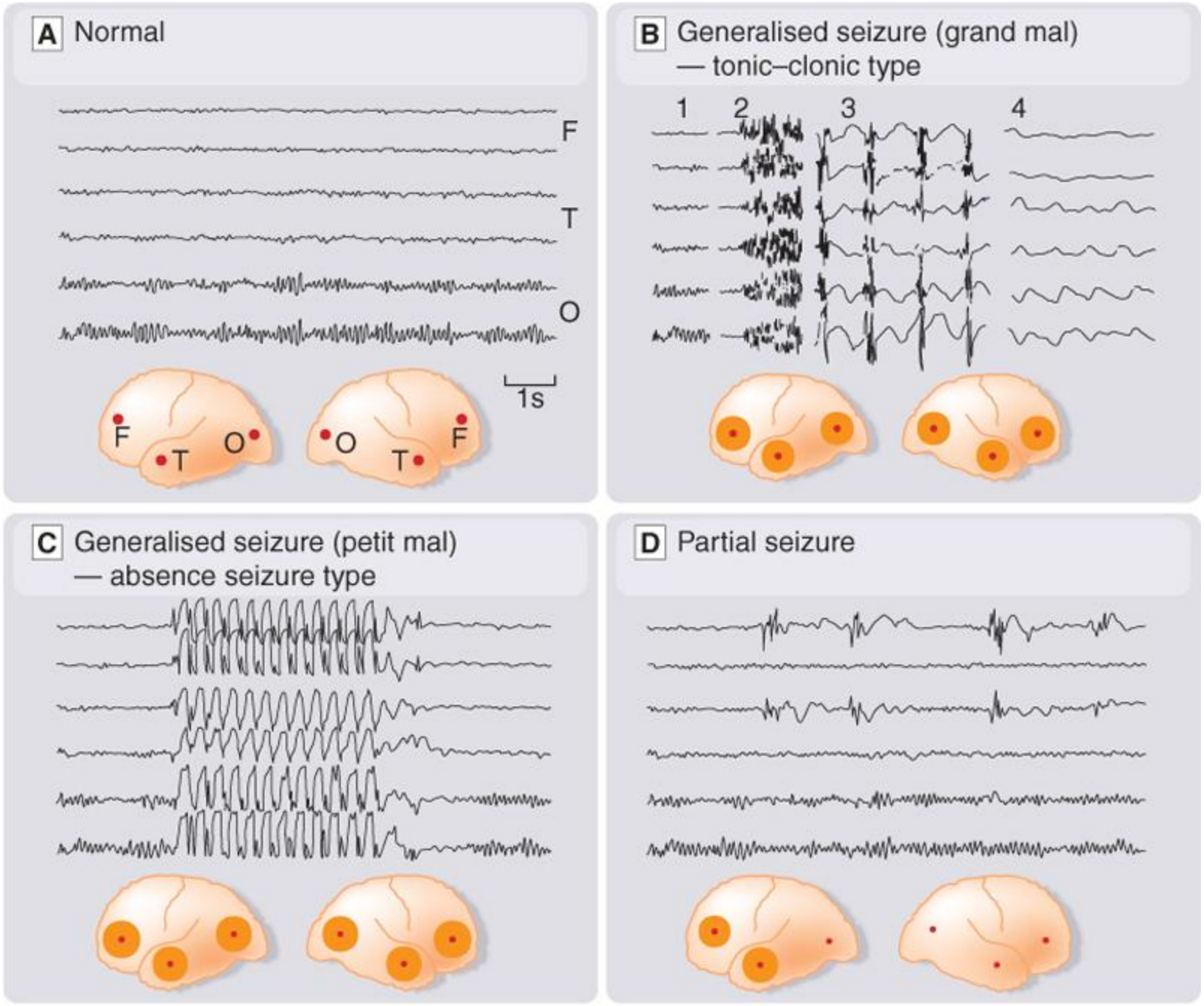
- **Partial seizures, complex** Impaired consciousness that is preceded, accompanied, or followed by psychological symptoms

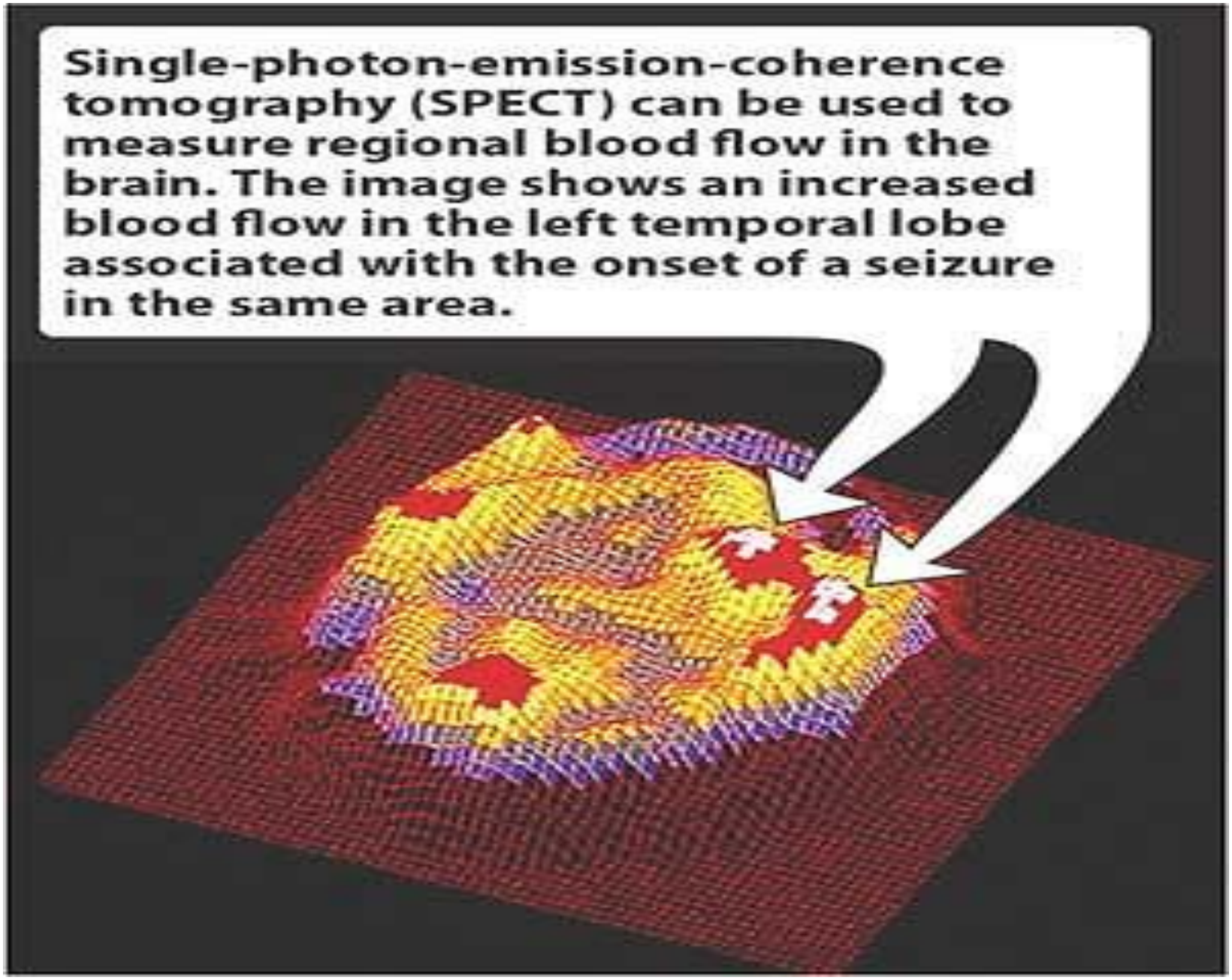
- **Tonic-clonic seizures, generalized** Tonic phase (less than 1 min) involves abrupt loss of consciousness, muscle rigidity, and respiration arrest; clonic phase (2–3 min) involves jerking of body muscles, with lip or tongue biting, and fecal and urinary incontinence; formerly called grand

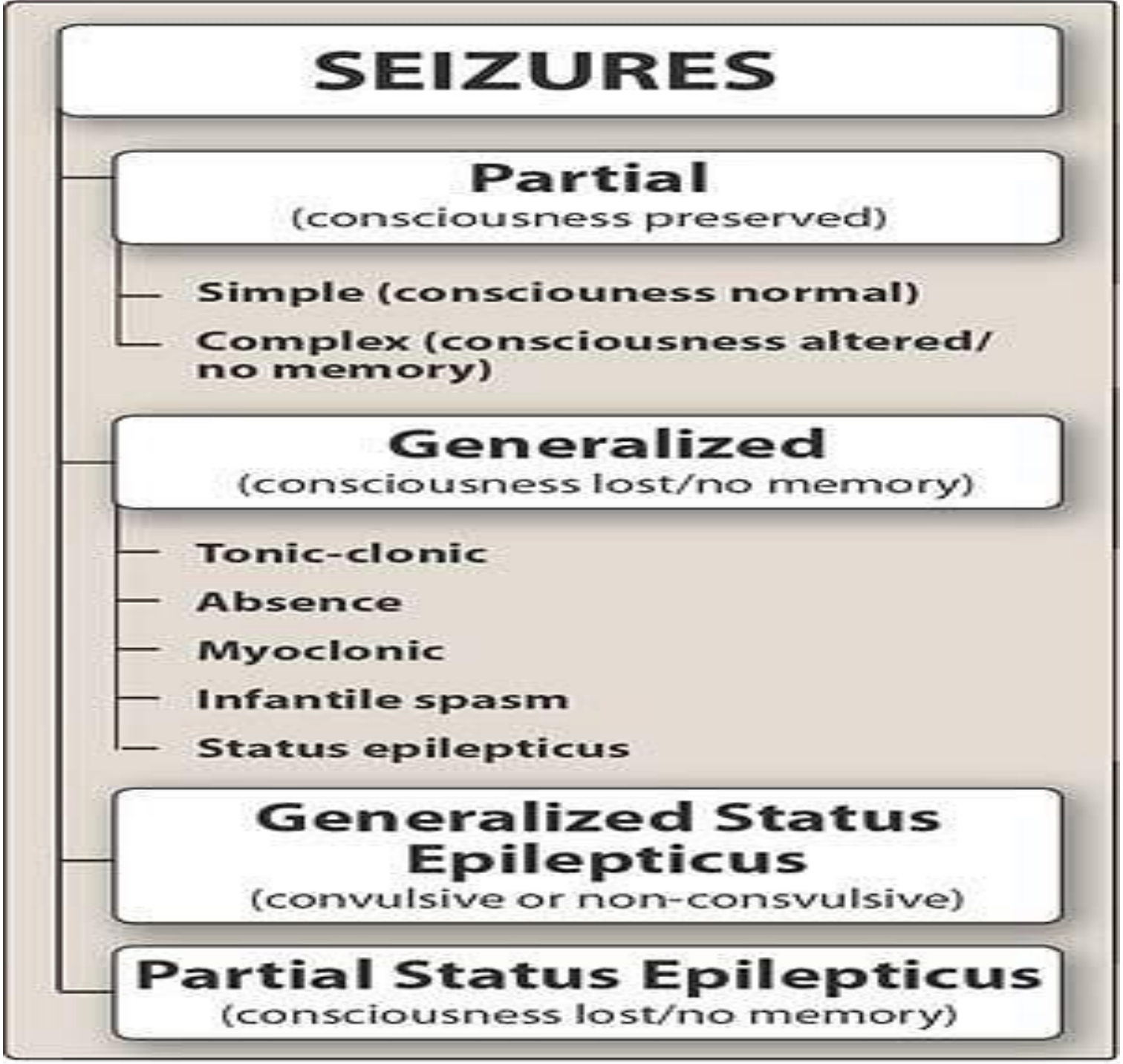
- **Absence seizures, generalized** Impaired consciousness (often abrupt onset and brief), sometimes with automatisms, loss of postural tone, or enuresis; begin in childhood (formerly, petit mal) and usually cease by age 20 yrs

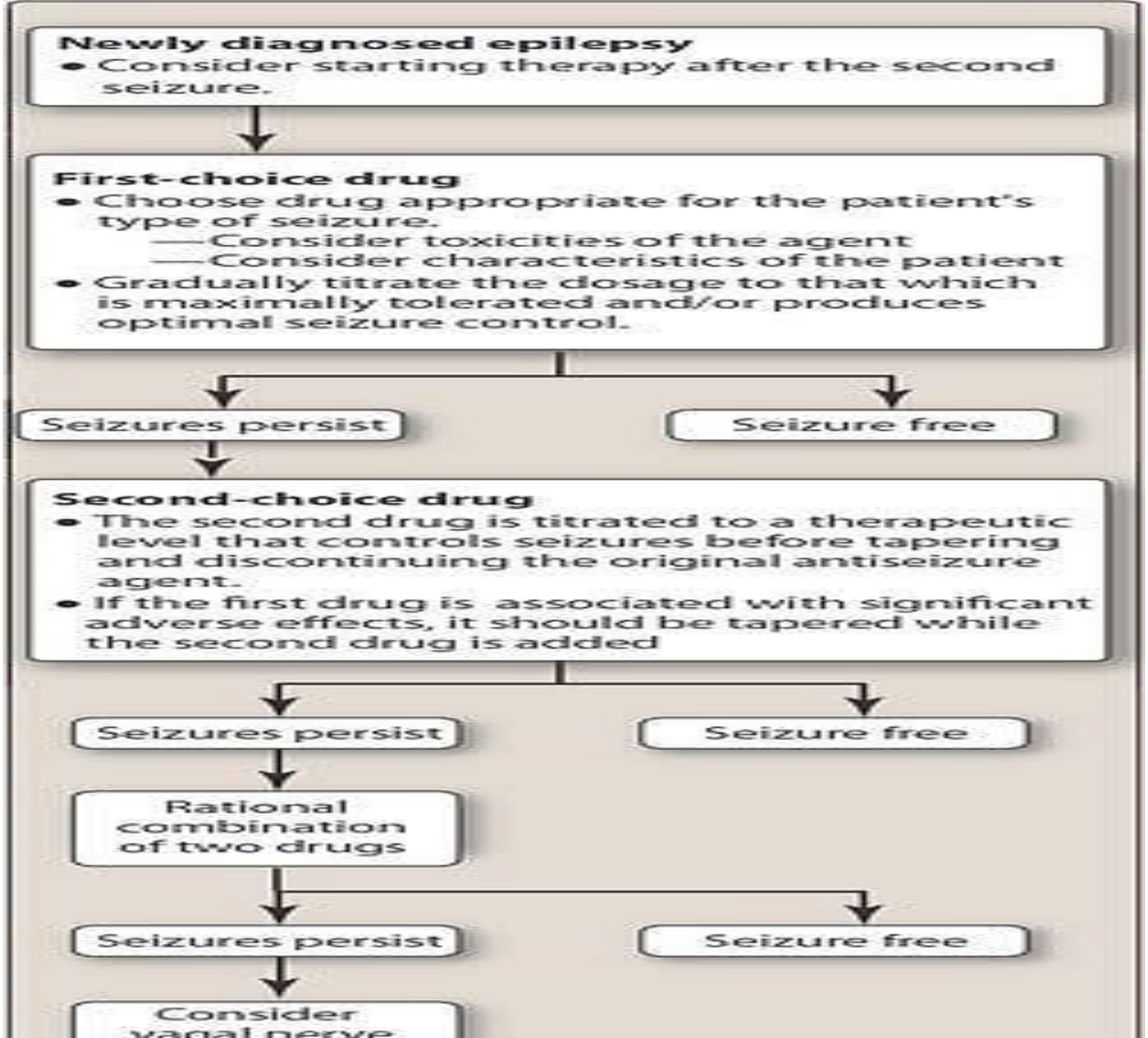
- **Myoclonic seizures** Single or multiple myoclonic muscle jerks

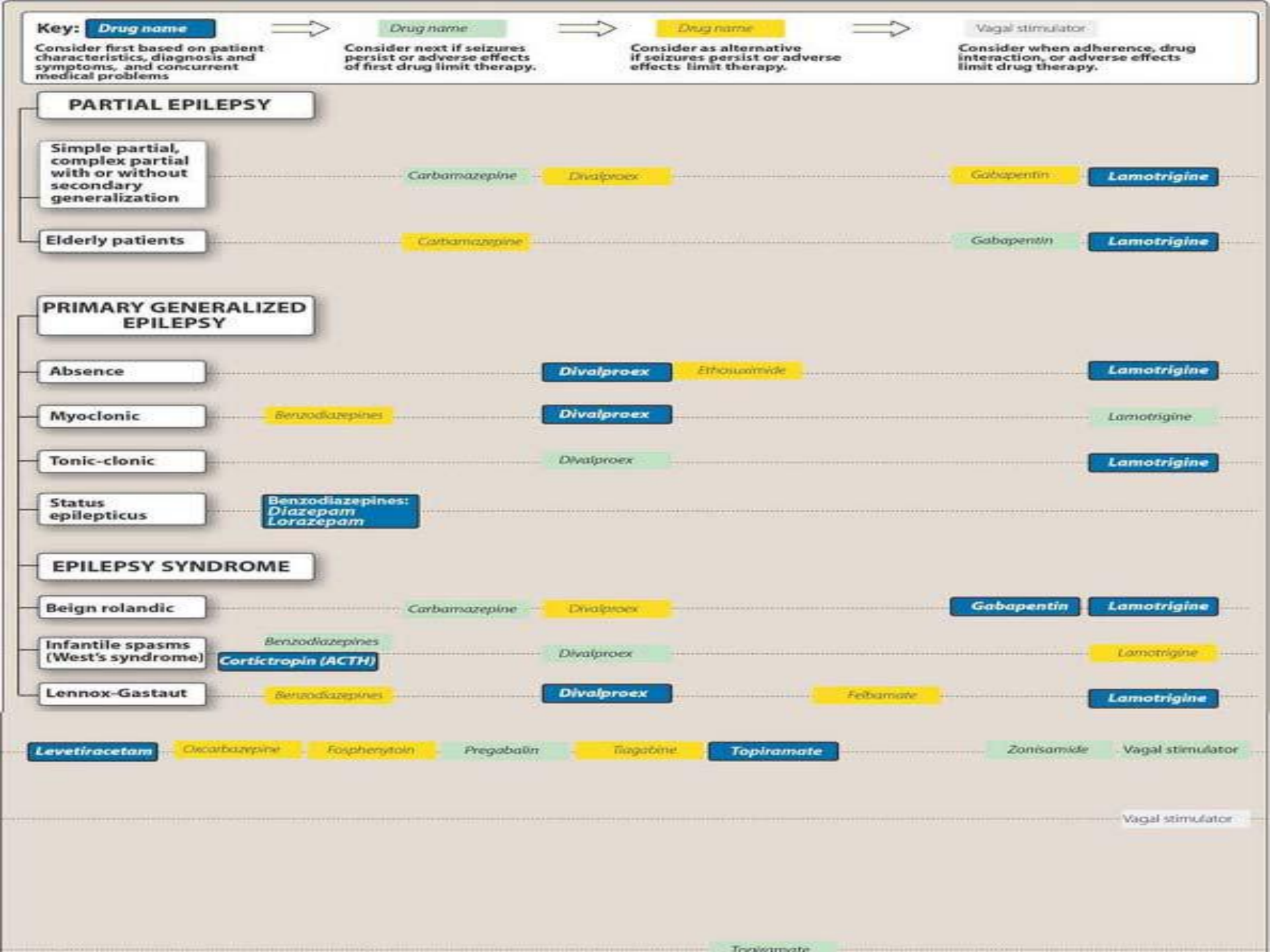
- **Status epilepticus** A series of seizures (usually tonic-clonic) without recovery of consciousness between attacks; it is a life-threatening emergency




Single-photon-emission-coherence tomography (SPECT) can be used to measure regional blood flow in the brain. The image shows an increased blood flow in the left temporal lobe associated with the onset of a seizure in the same area.


SEIZURES
Partial
(consciousness preserved)
Simple (consciouness normal)
Complex (consciousness altered/ no memory)
Generalized
(consciousness lost/no memory)
Tonic-clonic
Absence
Myoclonic
Infantile spasm
Status epilepticus
Generalized Status Epilepticus
(convulsive or non-consvulsive)
Partial Status Epilepticus
(consciousness lost/no memory)


Newly diagnosed epilepsy
• Consider starting therapy after the second seizure.
First-choice drug
• Choose drug appropriate for the patient's type of seizure.
—Consider toxicities of the agent
—Consider characteristics of the patient
• Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal seizure control.
Seizures persist
Seizure free
Second-choice drug
• The second drug is titrated to a therapeutic level that controls seizures before tapering and discontinuing the original antiseizure agent.
• If the first drug is associated with significant adverse effects, it should be tapered while the second drug is added
Seizures persist
Seizure free
Rational combination of two drugs
Seizures persist
Seizure free
Consider


Key: Drug name
Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems
Drug name
Consider next if seizures persist or adverse effects of first drug limit therapy.
Drug name
Consider as alternative if seizures persist or adverse effects limit therapy.
Vagal stimulator
Consider when adherence, drug interaction, or adverse effects limit drug therapy.
PARTIAL EPILEPSY
Simple partial, complex partial with or without secondary generalization
Carbamazepine
Divalproex
Gabapentin
Lamotrigine
Elderly patients
Carbamazepine
Gabapentin
Lamotrigine
PRIMARY GENERALIZED EPILEPSY
Absence
Divalproex
Ethosuximide
Lamotrigine
Myoclonic
Benzodiazepines
Divalproex
Lamotrigine
Tonic-clonic
Divalproex
Lamotrigine
Status epilepticus
Benzodiazepines:
Diazepam
Lorazepam
EPILEPSY SYNDROME
Beign rolandic
Carbamazepine
Divalproex
Gabapentin
Lamotrigine
Infantile spasms (West's syndrome)
Benzodiazepines
Corticotropin (ACTH)
Divalproex
Lamotrigine
Lennox-Gastaut
Benzodiazepines
Divalproex
Felbamate
Lamotrigine
Levetiracetam
Oxcarbazepine
Fosphenytoin
Pregabalin
Tiagabine
Topiramate
Zonisamide
Vagal stimulator
Vagal stimulator
Topiramate

Nausea and vomiting

Drowsiness-sedation

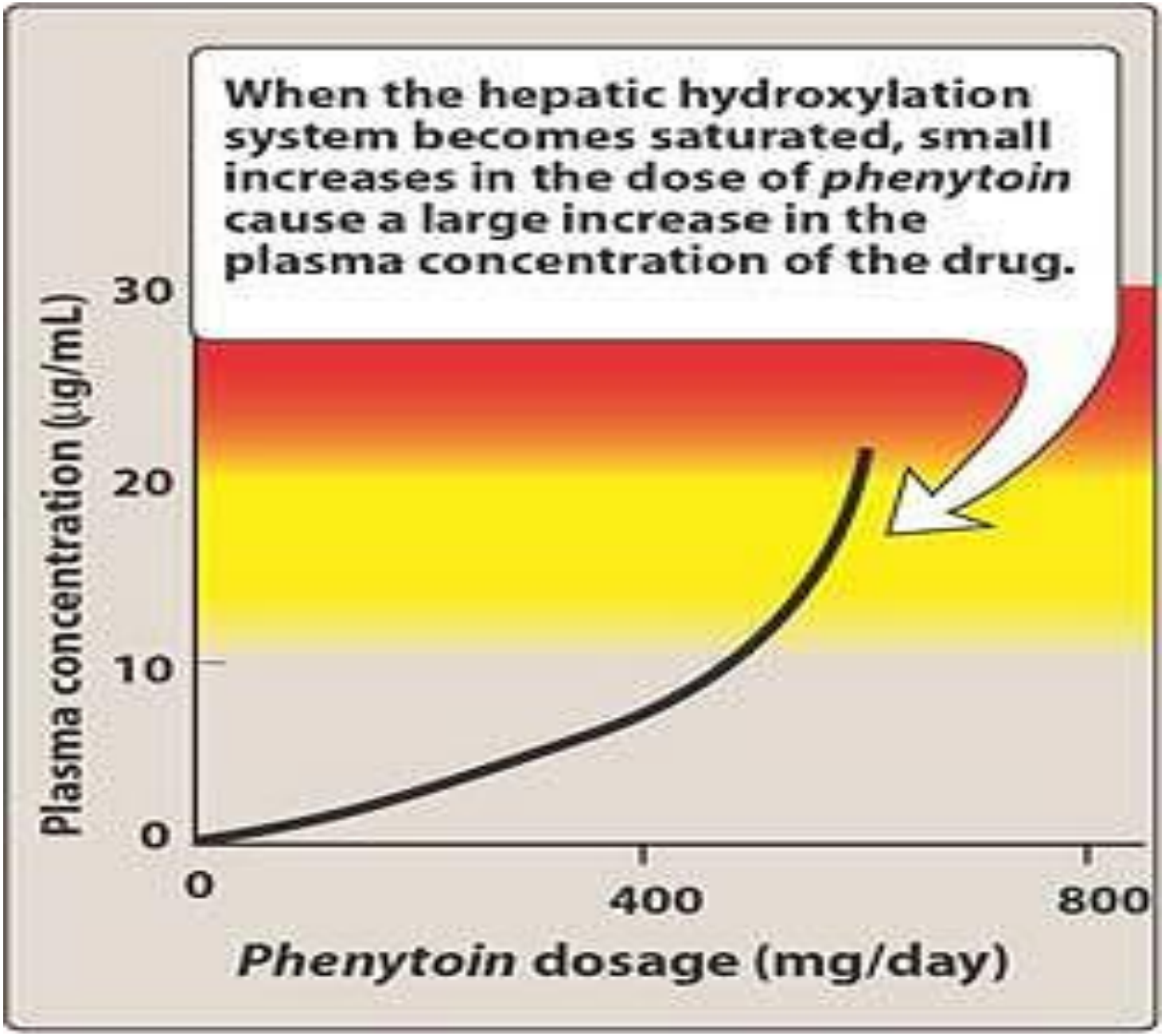
Ataxia

Rash

Hyponatremia

Weight gain
or
Weight loss

CYP1A2	
	Carbamazepine
CYP2C8	
	Carbamazepine
CYP2C9	
	Carbamazepine *Divalproex* *Phenobarbital* *Phenytoin*
CYP2C19	
	Divalproex *Felbamate* *Phenobarbital* *Phenytoin* *Zonisamide*
CYP3A4	
	Carbamazepine *Ethosuximide* *Tiagabine* *Zonisamide*
UDP-glucuronsyltransferases	
	Divalproex *Lamotrigine* *Lorazepam*


When the hepatic hydroxylation system becomes saturated, small increases in the dose of *phenytoin* cause a large increase in the plasma concentration of the drug.
Plasma concentration (μg/mL)
30
20
10
0
0
400
800
Phenytoin dosage (mg/day)

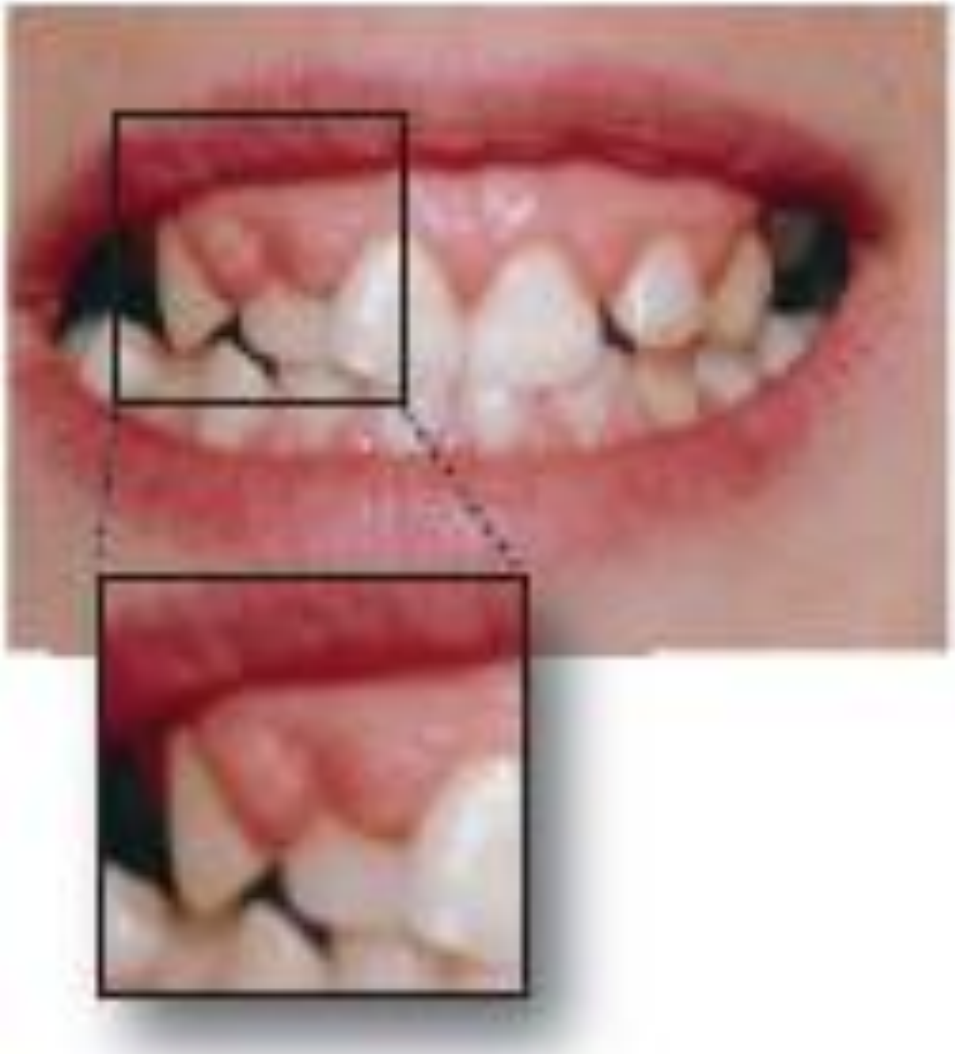
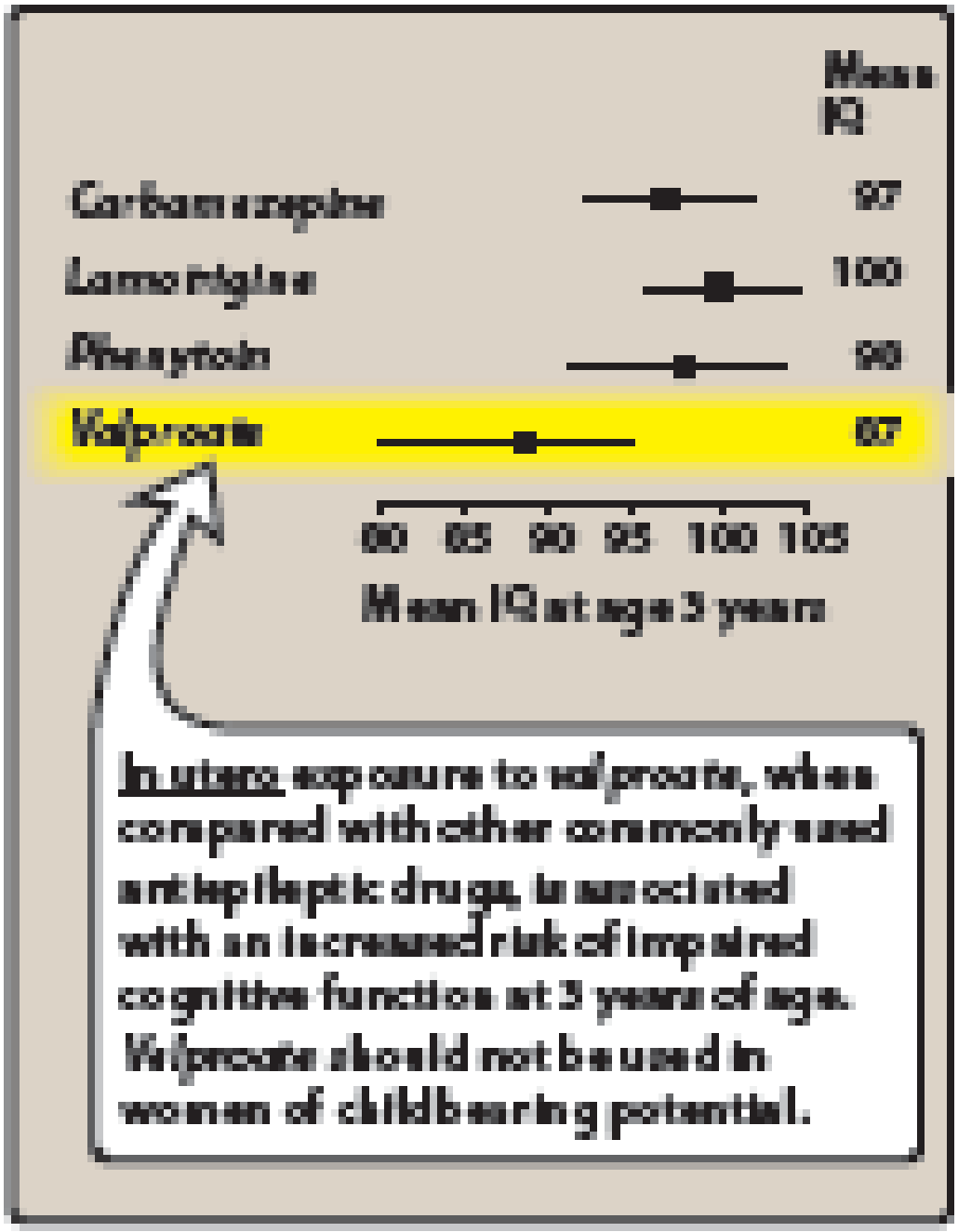
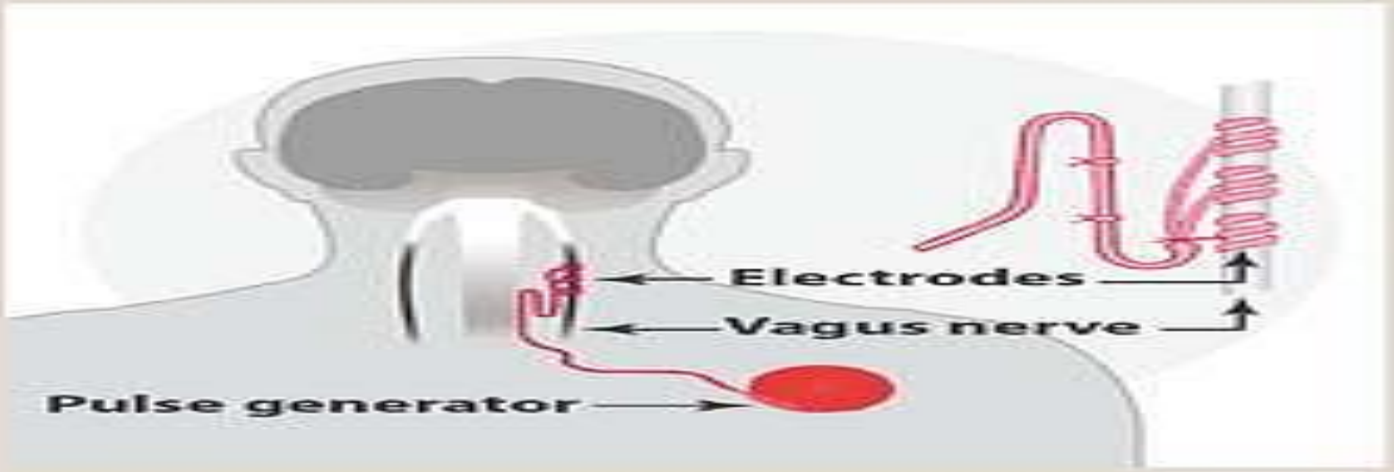


Figure 15.9
Gingival hyperplasia in patient treated with *phenytoin*.


Mean IQ
Carbamazepine
97
Lamotrigine
100
Phenytoin
98
Valproate
87
80 85 90 95 100 105
Mean IQ at age 3 years
In utero exposure to valproate, when compared with other commonly used antiepileptic drugs, is associated with an increased risk of impaired cognitive function at 3 years of age. Valproate should not be used in women of childbearing potential.

A

1. An implanted pulse generator connects to electrodes that coil around the vagus nerve.
2. The vagal nerve stimulator generates an electrical pulse that stimulates the vagus nerve.



3. This electrical stimulation prevents the abnormal electrical activity that can cause a seizure.
4. The patient activates the stimulator when they anticipate a seizure.

B

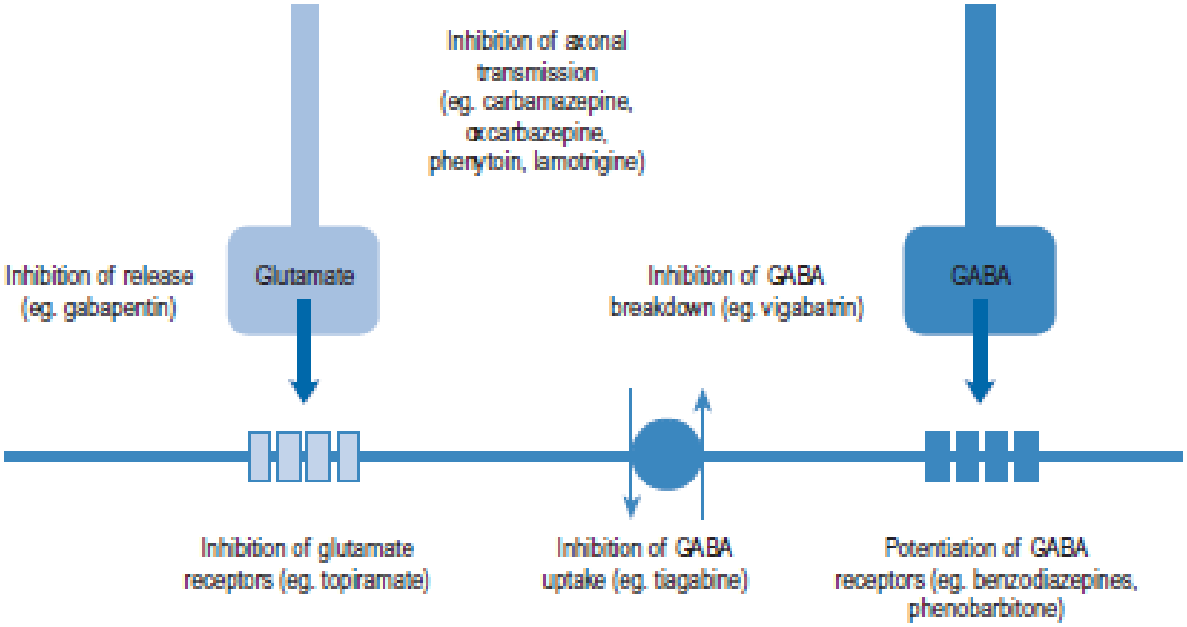
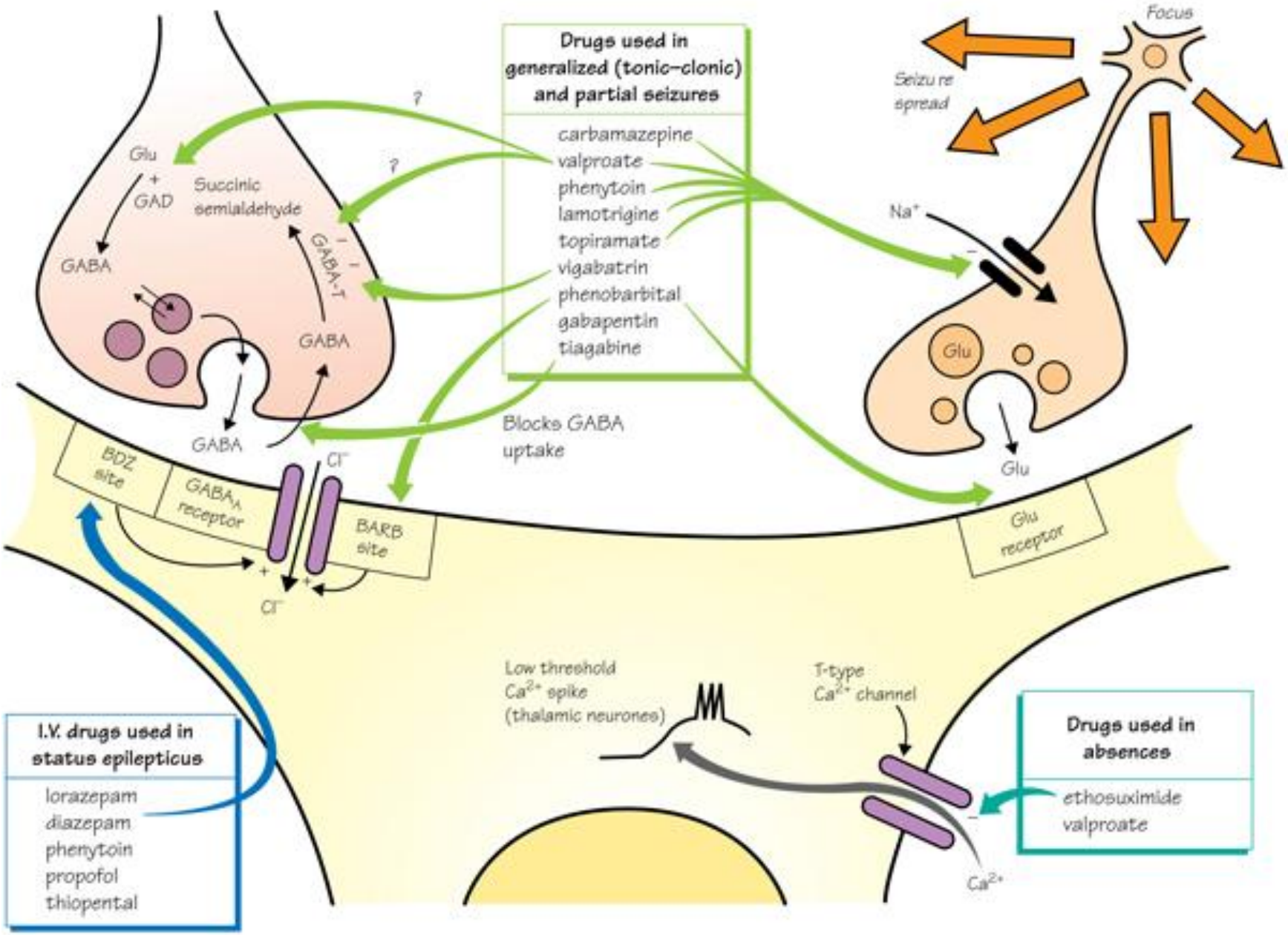
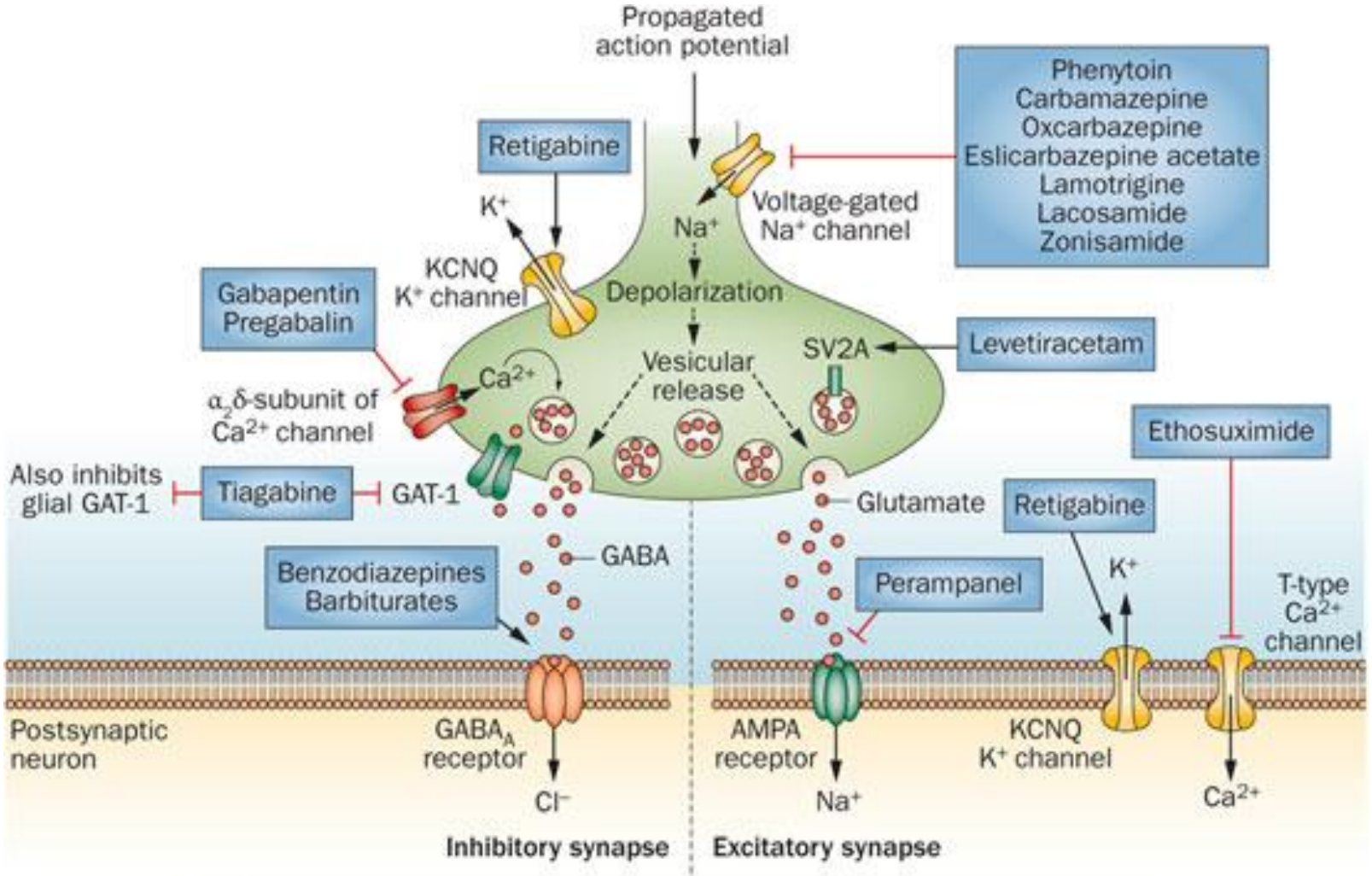


Fig. 31.1 Action of antiepileptic drugs (from Duncan et al., 2006).


Drugs used in generalized (tonic–clonic) and partial seizures
carbamazepine
valproate
phenytoin
lamotrigine
topiramate
vigabatrin
phenobarbital
gabapentin
tiagabine
Focus
Seizure spread
Glu
+
GAD
Succinic semialdehyde
GABA
GABA-T
GABA
GABA
?
?
Na+
Glu
Glu
Blocks GABA uptake
BDZ site
GABA$_A$ receptor
BARB site
Cl−
Cl−
Glu receptor
Low threshold Ca^{2+} spike (thalamic neurones)
T-type Ca^{2+} channel
Ca^{2+}
I.V. drugs used in status epilepticus
lorazepam
diazepam
phenytoin
propofol
thiopental
Drugs used in absences
ethosuximide
valproate



Not illustrated:

- Vigabatrin → ↓ GABA degradation

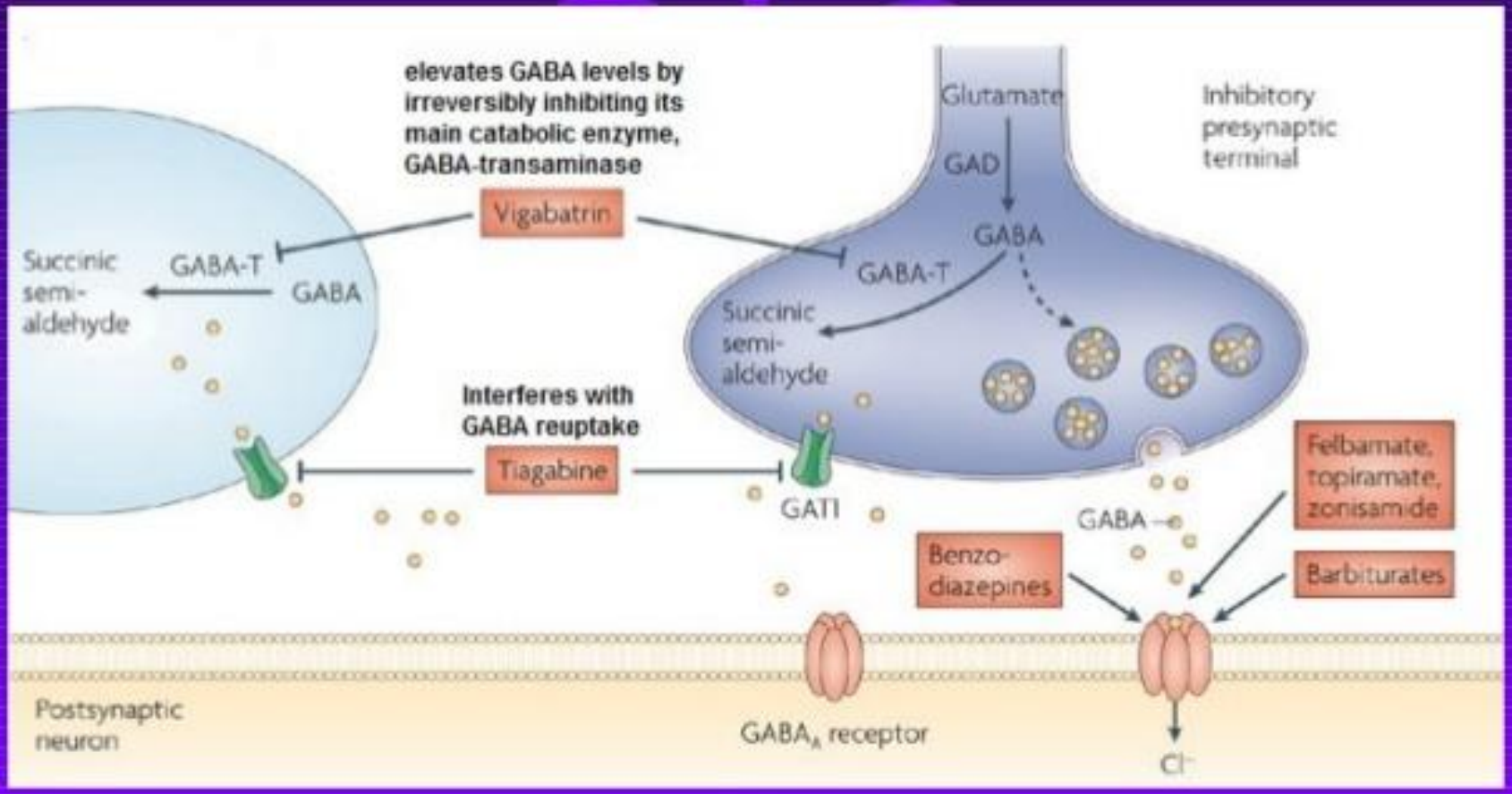
and drugs with multiple mechanisms:

- Valproate → ↑ GABA turnover, ↓ Na^+ channels, ↓ NMDA receptors
- Topiramate → ↓ Na^+ channels, ↓ AMPA/kainate receptors, ↑ $GABA_A$ receptors
- Felbamate → ↓ Na^+ channels, ↑ $GABA_A$ receptors, ↓ NMDA receptors

AEDs:

Mechanisms of Action

- GABA



DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has as been associated with Stevens-Johnson Syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, weight gain, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects such have been observed. Broad spectrum of antiseizure activity.
Ethosuximide	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 causes seizures.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia; hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One-hundred percent renal elimination.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life-threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Fosphenytoin	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.
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, weight gain, diplopia, and ataxia. One hundred percent renal elimination.
Primidone	GABA receptor	Sedation, lethargy, behavioral changes, ataxia, hyperactivity, and nausea. Not recommended for chronic use.
Tiagabine	GABA receptor	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	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.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia and oligohidrosis. Broad spectrum of antiseizure activity.

Checklist

When you complete this chapter, you should be able to:

List the drugs of choice for partial seizures, generalized tonic-clonic seizures, absence and myoclonic seizures, and status epilepticus.

Identify the mechanisms of antiseizure drug action at the levels of specific ion channels and/or neurotransmitter systems.

Describe the main pharmacokinetic features, and list the adverse effects of carbamazepine, phenytoin, and valproic acid.

Identify the distinctive toxicities of new antiseizure drugs.

Describe the important pharmacokinetic and pharmacodynamic considerations relevant to the long-term use of antiseizure drugs.

A nine-year-old boy is sent for neurologic evaluation because of episodes of confusion. Over the past year, the child has experienced episodes during which he develops a blank look on his face and fails to respond to questions. However, it appears to take several minutes before the boy recovers from the episodes. Which one the following best describes this patient's seizures?

A. Simple partial.

B. Complex partial.

C. Tonic-clonic.

D. Absence.

E. Myoclonic.