Antiseizure Drugs

Pharmacology II

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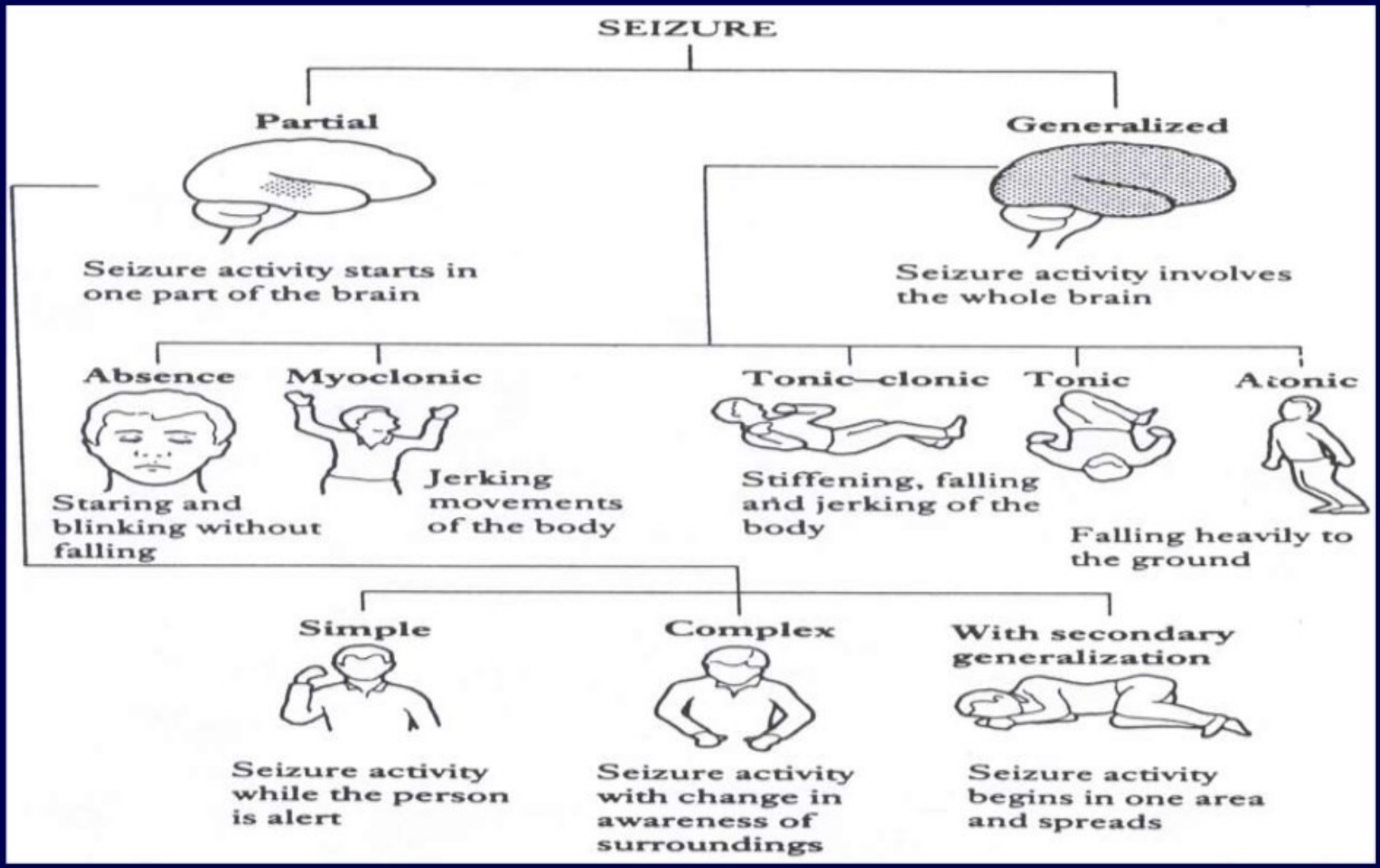
High-Yield Terms to Learn

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 mal
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

- **Epilepsy** is a chronic disorder characterized by recurrent seizures. (One isolated seizure is not epilepsy).
- After a first seizure, treatment is generally not needed unless specific problems are found on either electroencephalogram or imaging of the brain.

Antiseizure = Antiepileptic =Anticonvulsant

Classification of Epileptic Seizures



Epilepsy

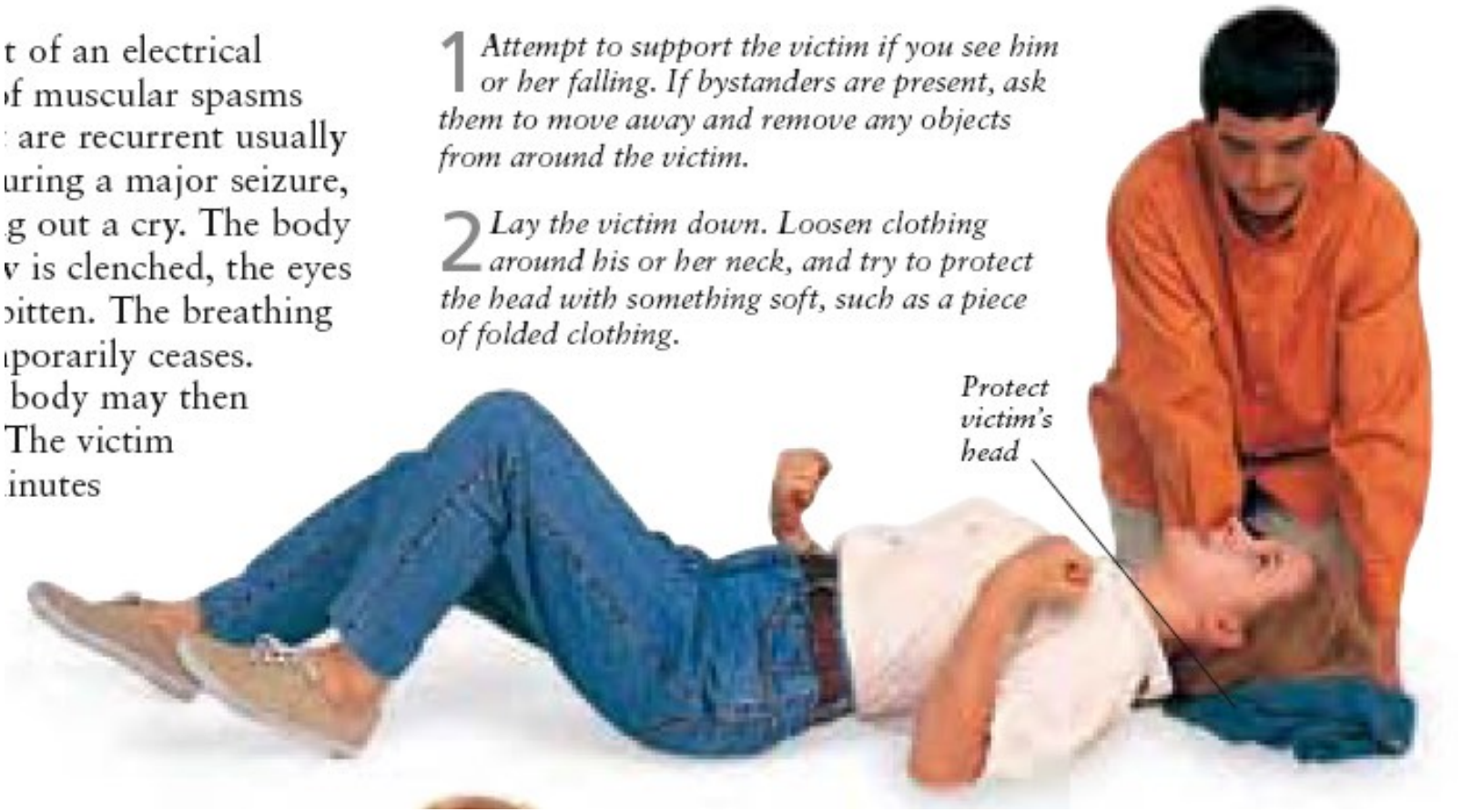
- Approximately 1% of the world's population has epilepsy.
- Although standard therapy permits control of seizures in 80% of these patients, millions (500,000 people in the USA alone) have uncontrolled epilepsy.
- The causes of seizures are many and include:
  - Tumor
  - Head injury
  - Hypoglycemia
  - Meningeal infection
  - High fever
  - Rapid withdrawal of alcohol from an alcoholic
  - Idiopathic

First Aid for Seizure

t of an electrical
of muscular spasms
are recurrent usually
uring a major seizure,
g out a cry. The body
v is clenched, the eyes
bitten. The breathing
porarily ceases.
body may then
The victim
inutes

1 *Attempt to support the victim if you see him or her falling. If bystanders are present, ask them to move away and remove any objects from around the victim.*

2 *Lay the victim down. Loosen clothing around his or her neck, and try to protect the head with something soft, such as a piece of folded clothing.*



First Aid for Seizure

3 When the seizures have finished, place the victim in the recovery position (p.292). Check the victim's breathing and pulse at regular intervals, and be prepared to resuscitate if necessary (see ABC of resuscitation, p.290).

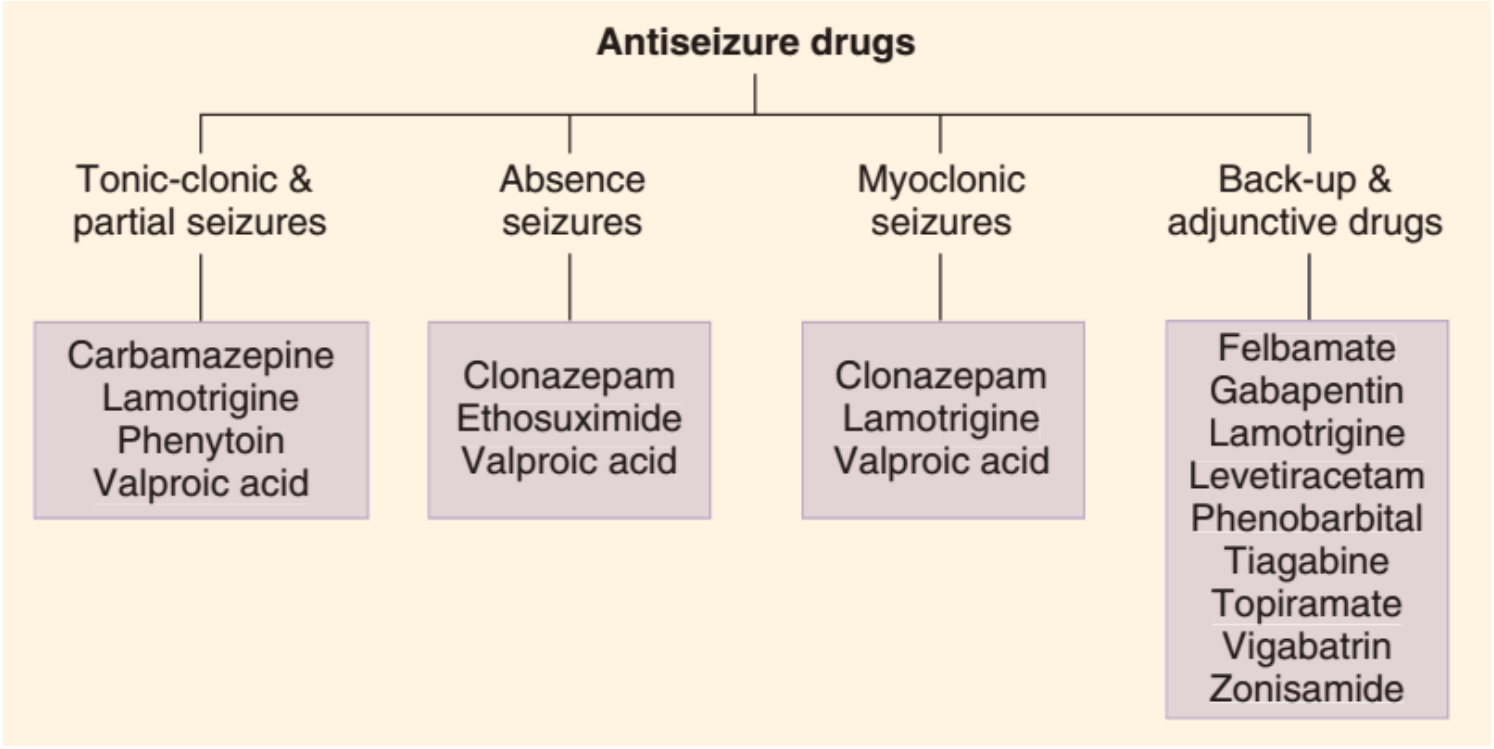
4 If the victim has a severe seizure, in which he or she remains unconscious for more than 10 minutes or convulses for more than 5 minutes, or if the person has repeated seizures, call an ambulance. Stay with the victim and monitor breathing and pulse until the ambulance arrives.

WARNING

- Do not use force in an attempt to restrain the victim.
- Do not put anything in the victim's mouth.

Antiseizure Drugs

- Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and interactions with other medications).



MOA of antiepileptic drugs

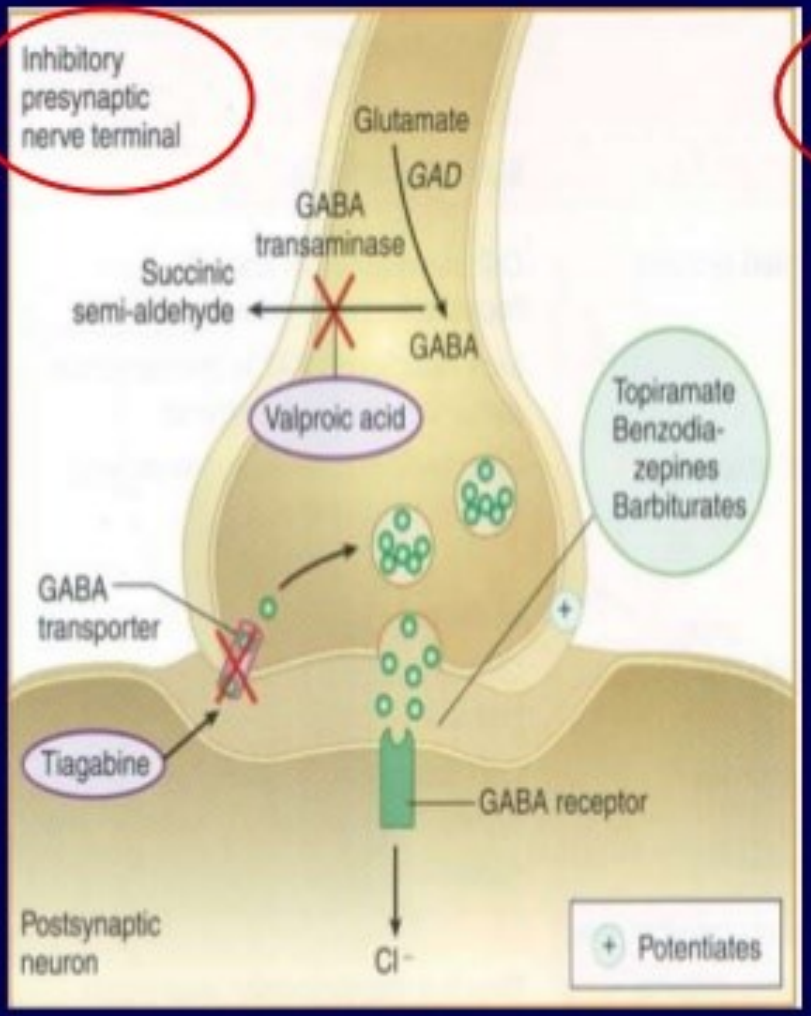
- Effective antiseizure drugs have, to varying degrees, selective depressant actions on the abnormal discharge of cerebral neurons

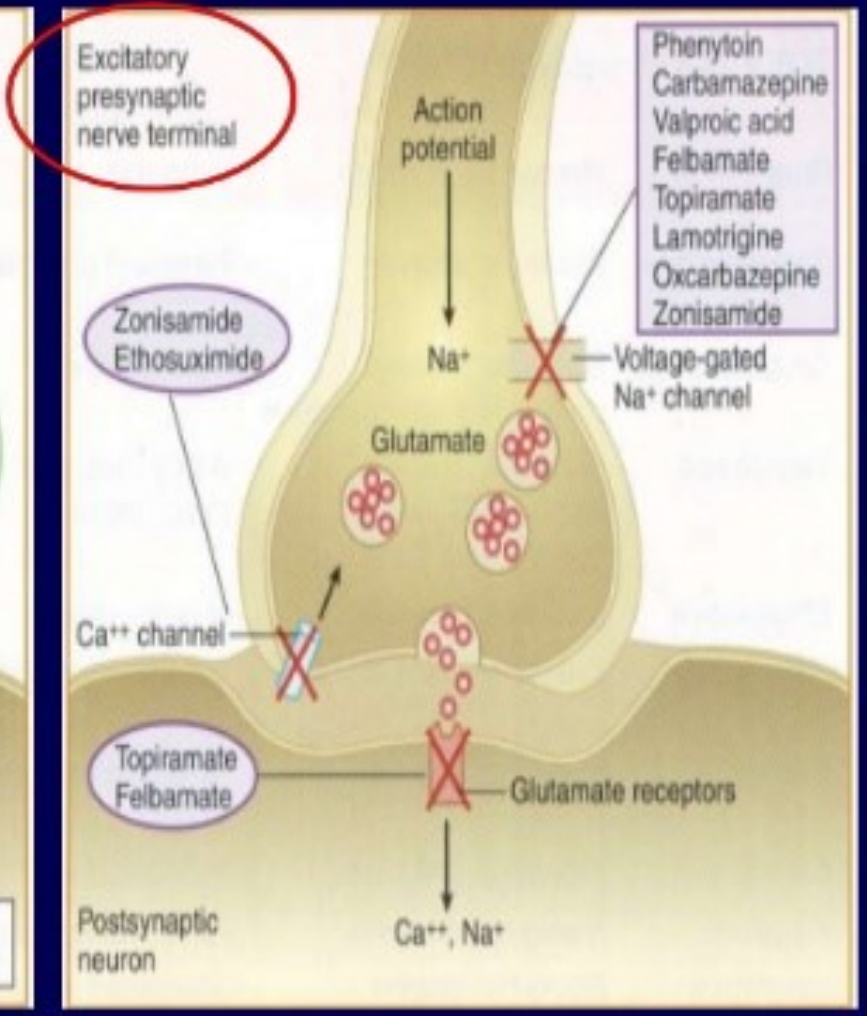
- Many different mechanisms are involved in achieving this effect:
  1. Blocking voltage gated Na+ channels
  2. Blocking voltage gated Ca2+ channels
  3. Interfering with excitatory glutamate transmission.
  4. Opening of K+ channels
  5. Enhancing γ-aminobutyric acid (GABA)-ergic transmission.

- Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined.

- Antiseizure drugs suppress seizures but do not “cure” or “prevent” epilepsy.

Mechanism of action of AEDs

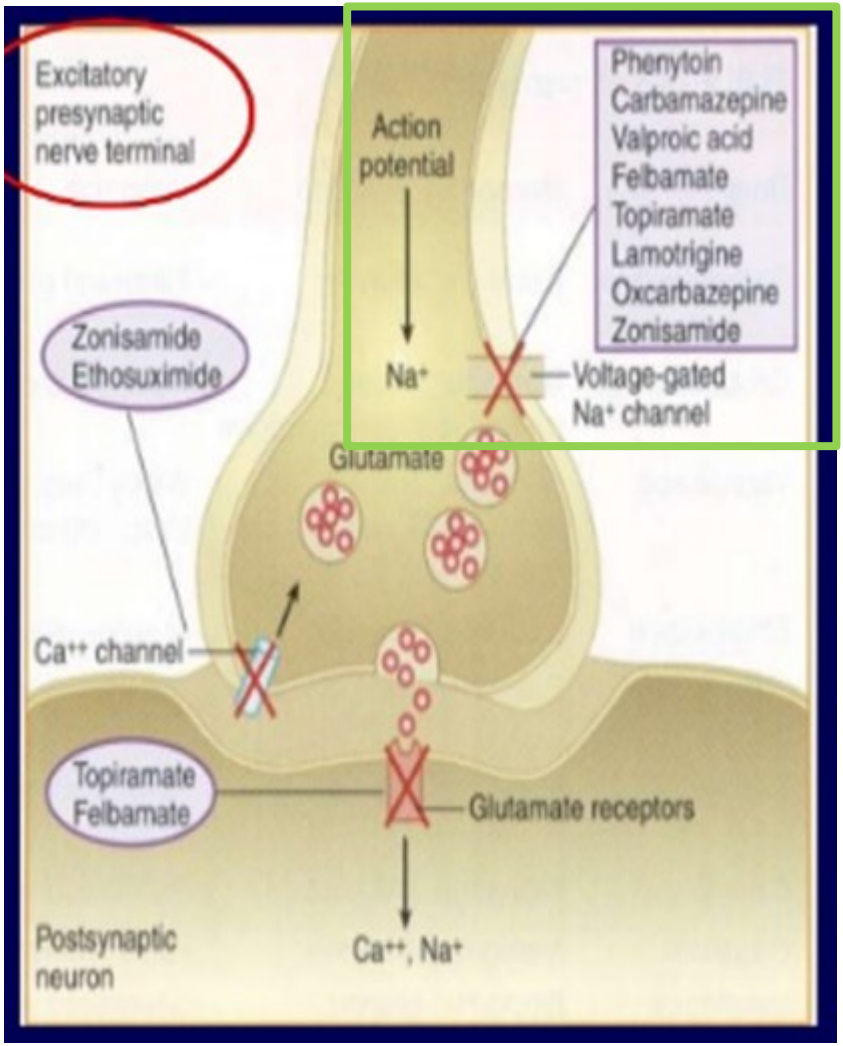




MOA of antiepileptic drugs

A. Sodium Channel Blockade

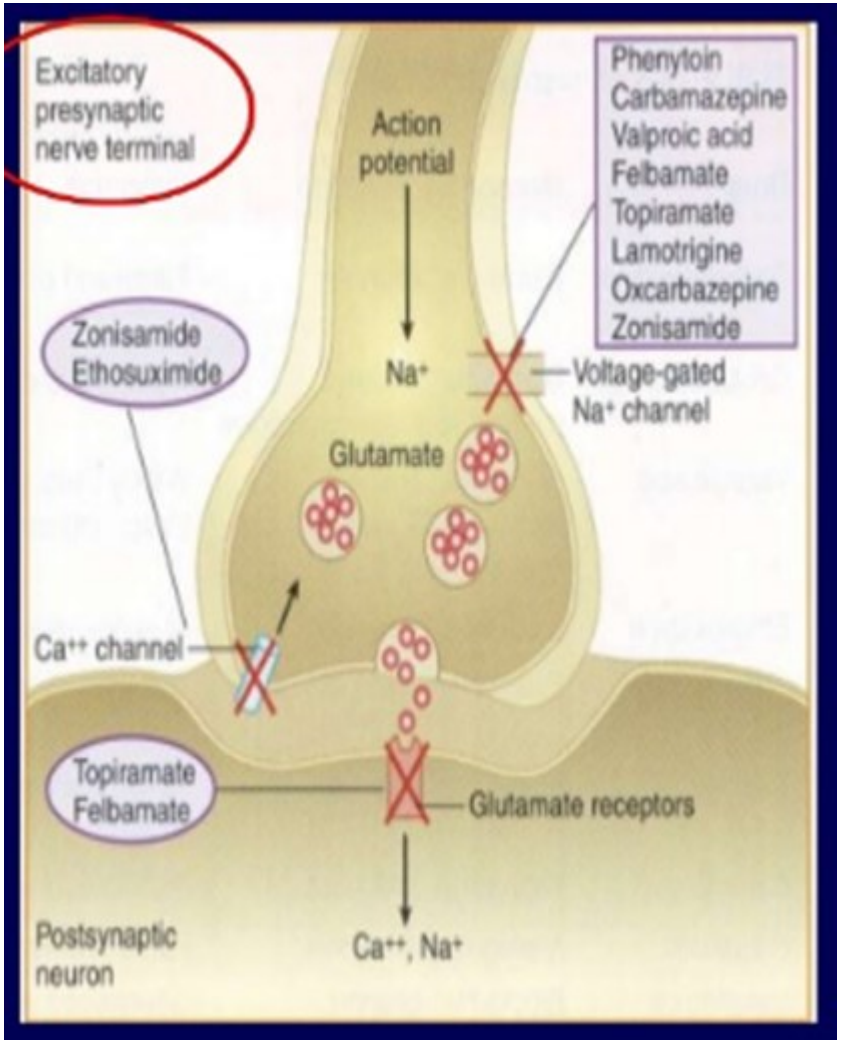
- At therapeutic concentrations, **phenytoin, carbamazepine, lamotrigine,** and **zonisamide** block voltage-gated sodium channels in neuronal membranes.
- **Phenobarbital** and **valproic acid** exert similar effects at high doses.



MOA of antiepileptic drugs

B. Calcium Channel Blockade

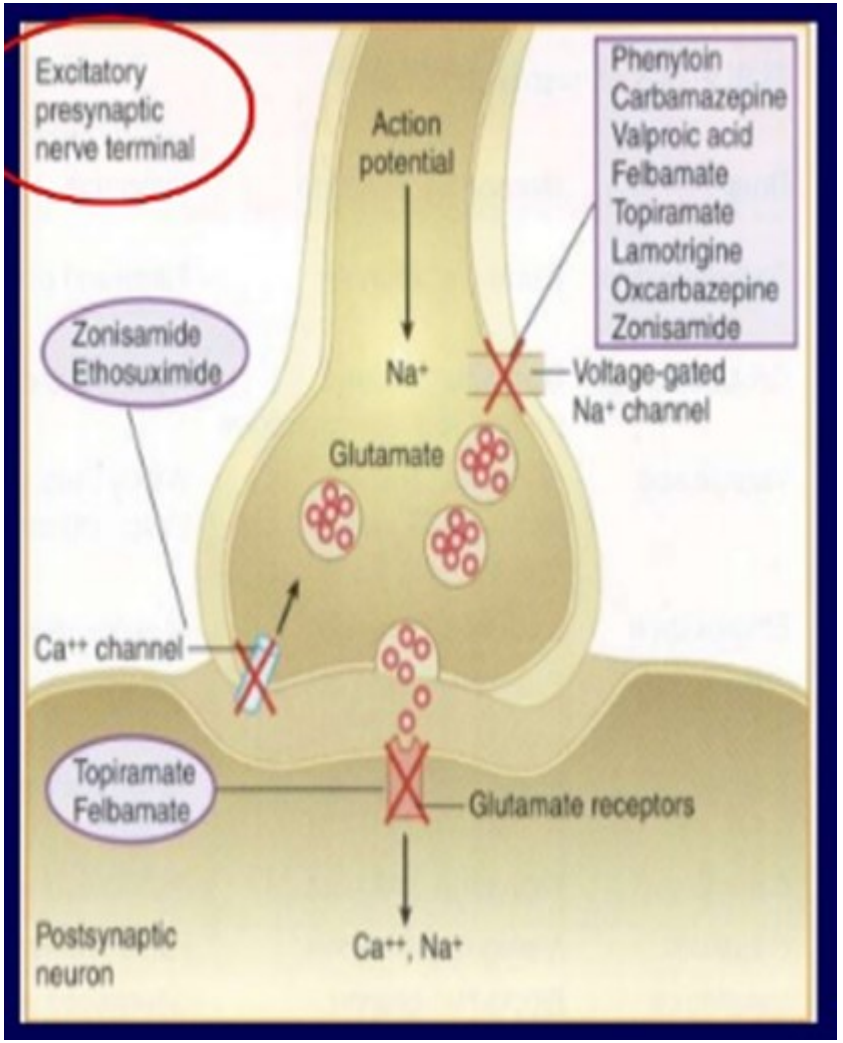
- **Ethosuximide** inhibits T type Ca2+ channels.
- A similar action is reported for **valproic acid**.
- In addition to its action on calcium channels, **valproic acid** causes neuronal membrane hyperpolarization, possibly by enhancing K+ channel permeability.



MOA of antiepileptic drugs

C. Inhibition of Glutamate transmission

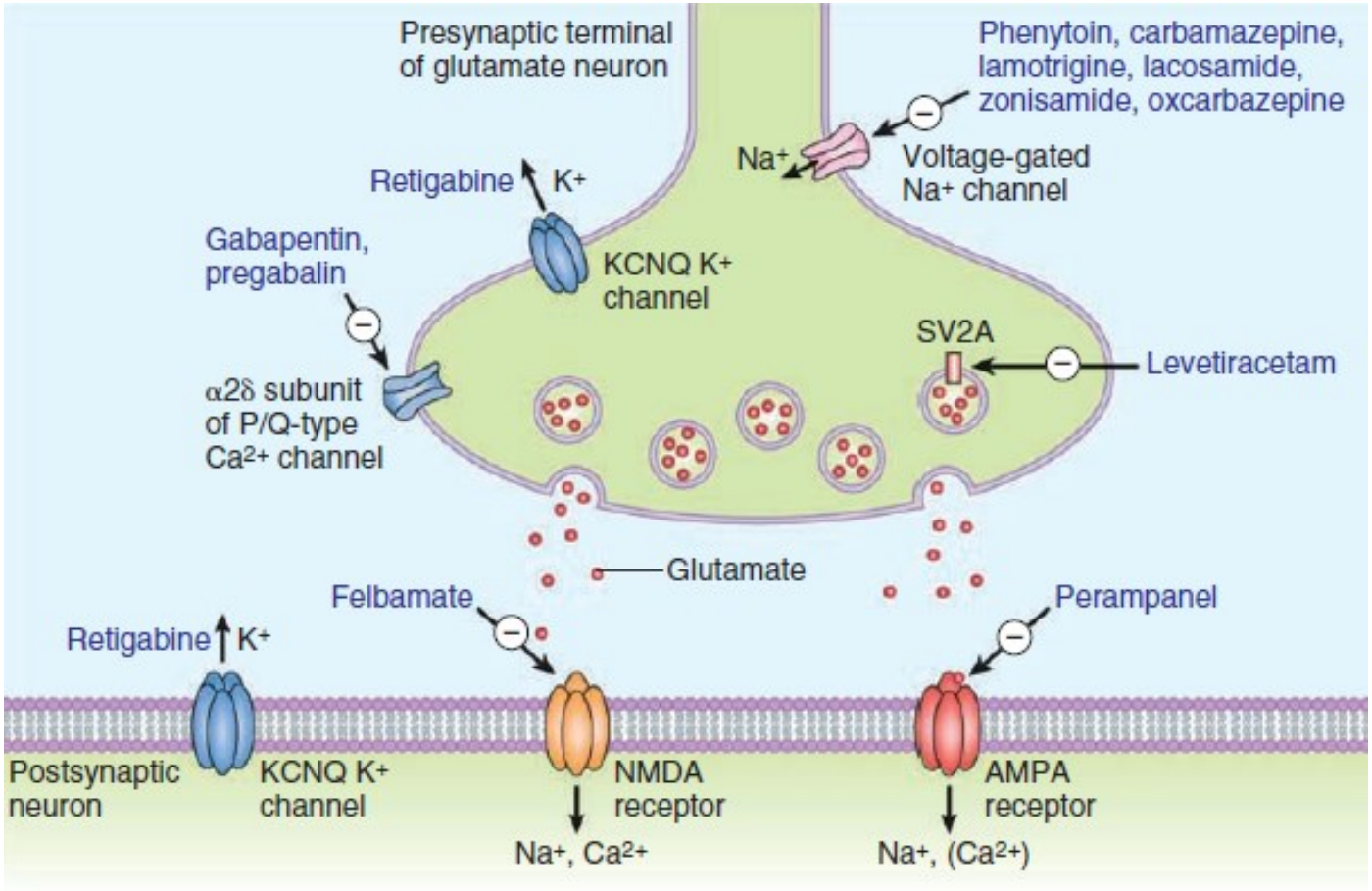
- Although **phenobarbital** acts on both sodium channels and GABA-chloride channels, it also acts as an antagonist at some glutamate receptors.
- **Felbamate** blocks glutamate receptors.
- **Topiramate** blocks sodium channels and potentiates the actions of GABA and also block glutamate receptors.



MOA of antiepileptic drugs

D. Opening of K+ channels

- **Retigabine** (US Adopted Name: **ezogabine**), a potassium channel opener



MOA of antiepileptic drugs

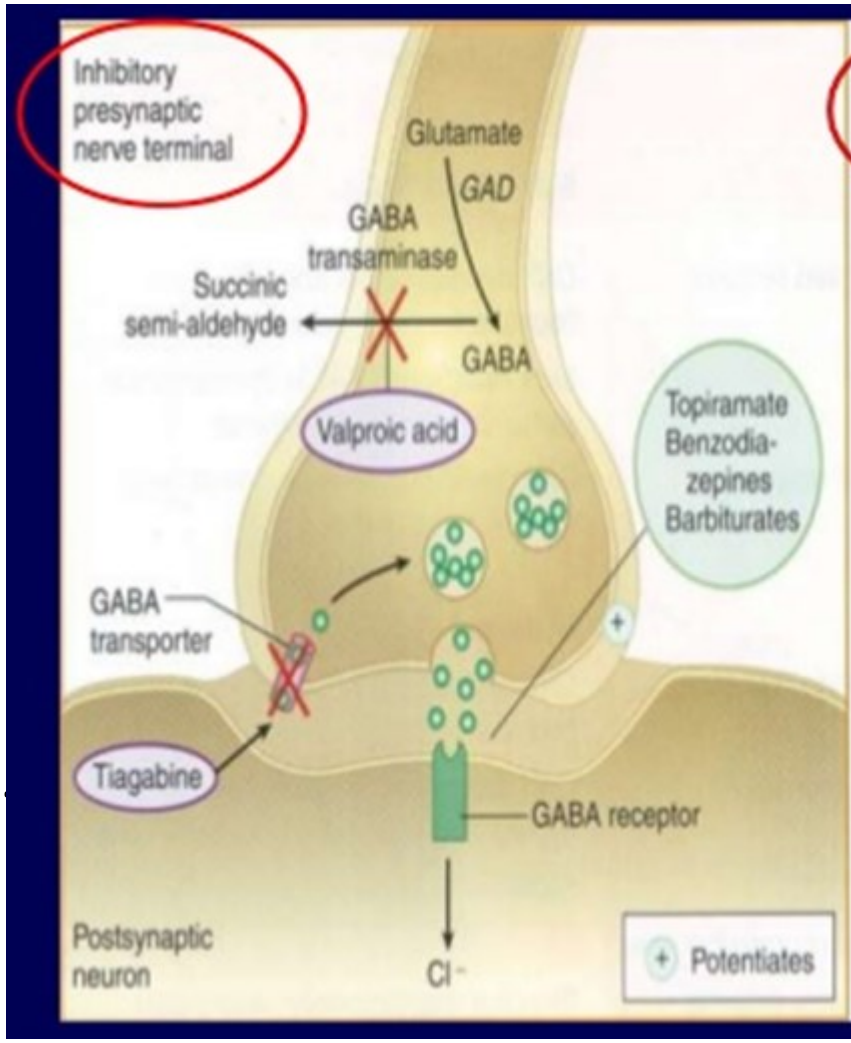
D. Opening of K+ channels

- **Retigabine** (US Adopted Name: **ezogabine**), a potassium channel opener,
- Retigabine is an allosteric opener of KCNQ2-5 (Kv7.2-Kv7.5) voltage-gated potassium channels, which are localized, in part, in axons and nerve terminals. Opening KCNQ potassium channels in presynaptic terminals inhibits the release of various neurotransmitters, including glutamate, which may be responsible for the seizure protection.
- Because **retigabine** causes pigment discoloration of the retina and skin and because of its ophthalmologic adverse reactions, its use is limited to those who have failed to respond to other agents (third-line treatment for focal seizures).

MOA of antiepileptic drugs

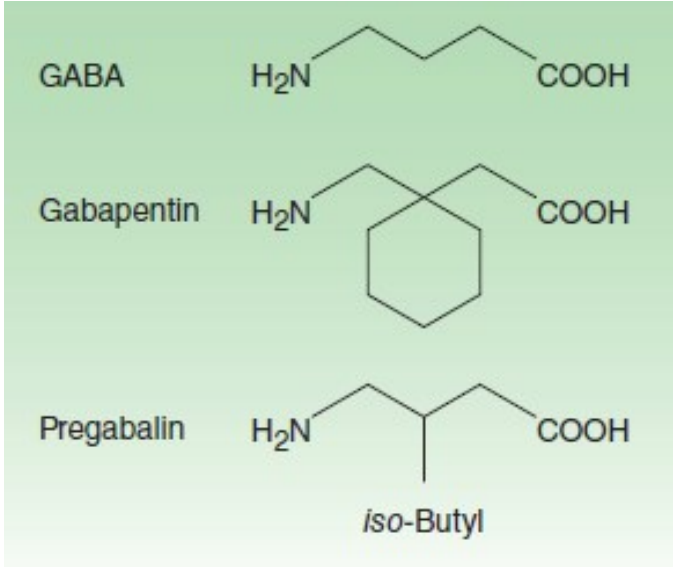
E. GABA-Related Targets

- **Benzodiazepines, phenobarbital** and other barbiturates enhance the inhibitory actions of GABA by increasing Cl- ion channel opening.
- **Vigabatrin** irreversibly inactivate GABA aminotransaminase (GABA-T), an important enzyme in the termination of action of GABA.
- **Tiagabine** inhibits a GABA transporter (GAT-1) in neurons and glia prolonging the action of the neurotransmitter GABA.



MOA of antiepileptic drugs

- **Gabapentin** and **pregabalin**, known as "gabapentinoids," are amino acid-like molecules that were originally synthesized as analogs of GABA but are now known not to act through GABA mechanisms.
- Rather, they bind avidly to **α2δ**, a protein that serves as an auxiliary subunit of **voltage-gated calcium channels** but may also have other functions.
- The precise way in which binding of gabapentinoids to α2δ protects against seizures is not known but may relate to a **decrease in glutamate release** at excitatory synapses.



MOA of antiepileptic drugs

- **Gabapentin** and **pregabalin**

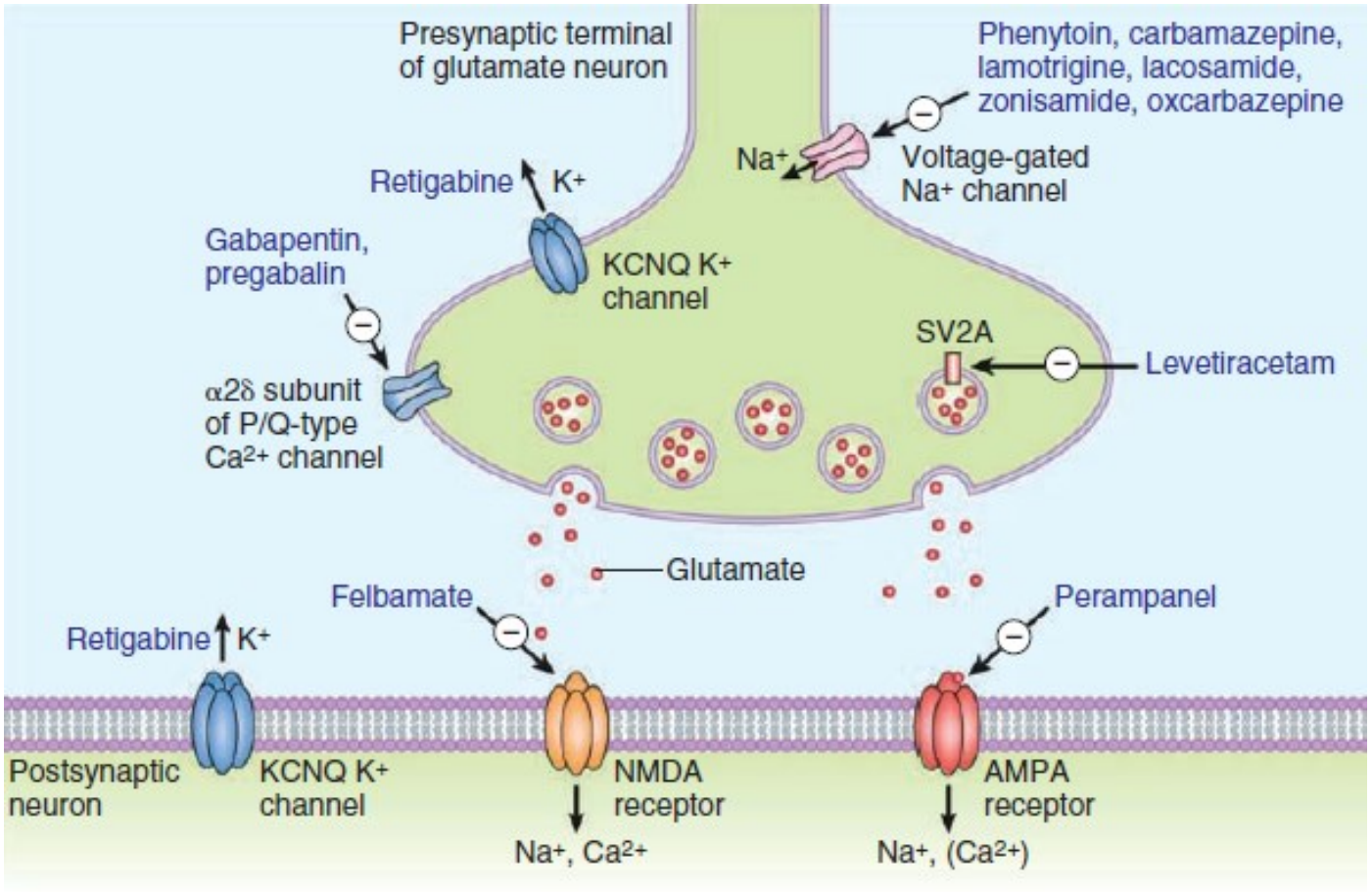


TABLE 24–2 Molecular targets of antiseizure drugs.

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 topiramate, zonisamide, rufinamide
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, and clonazepam; possibly topiramate, felbamate, ezogabine
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
Synaptic release machinery	
SV2A	Levetiracetam, brivaracetam
α2δ	Gabapentin, gabapentin enacarbil[4], pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
Mixed/unknown[5]	Valproate, felbamate, topiramate, zonisamide, rufinamide, adrenocorticotropin

[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.

Modified from Rogawski MA, Löscher W, Rho JM: Mechanisms of action of antiseizure drugs and the ketogenic diet. Cold Spring Harb Perspect Med 2016;6:a022780.

Pharmacokinetics of Antiseizure Drugs

- Antiseizure drugs are commonly used for long periods of time, and consideration of their pharmacokinetic properties is important for avoiding toxicity and drug interactions.
- For some of these drugs (eg, **phenytoin**), determination of plasma levels and clearance in individual patients may be necessary for optimum therapy.

- In general, antiseizure drugs are well absorbed orally and have good bioavailability.
- Most antiseizure drugs are metabolized by hepatic enzymes.
- **Gabapentin, pregabalin, levetiracetam**, and **vigabatrin** are unusual in that they are eliminated by the kidney, largely in unchanged form.
- Resistance to antiseizure drugs may involve increased expression of drug transporters at the level of the blood-brain barrier.

Pharmacokinetics of Antiseizure Drugs

- **Pharmacokinetic drug interactions** are common in this drug group.

- In the presence of drugs that inhibit antiseizure drug **metabolism** or that displace anticonvulsants from plasma **protein binding** sites, plasma concentrations of the antiseizure agents may reach toxic levels.

- On the other hand, drugs that induce hepatic drug-metabolizing enzymes (eg, rifampin) may result in plasma levels of the antiseizure agents that are inadequate for seizure control.

- Several antiseizure drugs are themselves capable of inducing hepatic drug metabolism, especially **carbamazepine** and **phenytoin**.

- Antiseizure drugs can also interact with other medications. Importantly, oral contraceptive levels may be reduced by strong inducers, resulting in failure of birth control.

Phenytoin and fosphenytoin

- At therapeutic concentrations, the major action of phenytoin is to block Na^+ channels and inhibit the generation of rapidly repetitive action potentials.
- Phenytoin is effective against partial seizures and generalized tonic-clonic seizures and for the acute treatment of status epilepticus.
- The therapeutic plasma level of phenytoin for most patients is between 10 and 20 mcg/mL.
- **Pharmacokinetics**
- Absorption of phenytoin is highly dependent on the formulation of the dosage form. Particle size and pharmaceutical additives affect both the **rate and the extent of absorption.**

Phenytoin and fosphenytoin

- **Pharmacokinetics**
- Absorption after IM injection of phenytoin is unpredictable, and some drug precipitation in the muscle occurs; this route of administration is not recommended for phenytoin.

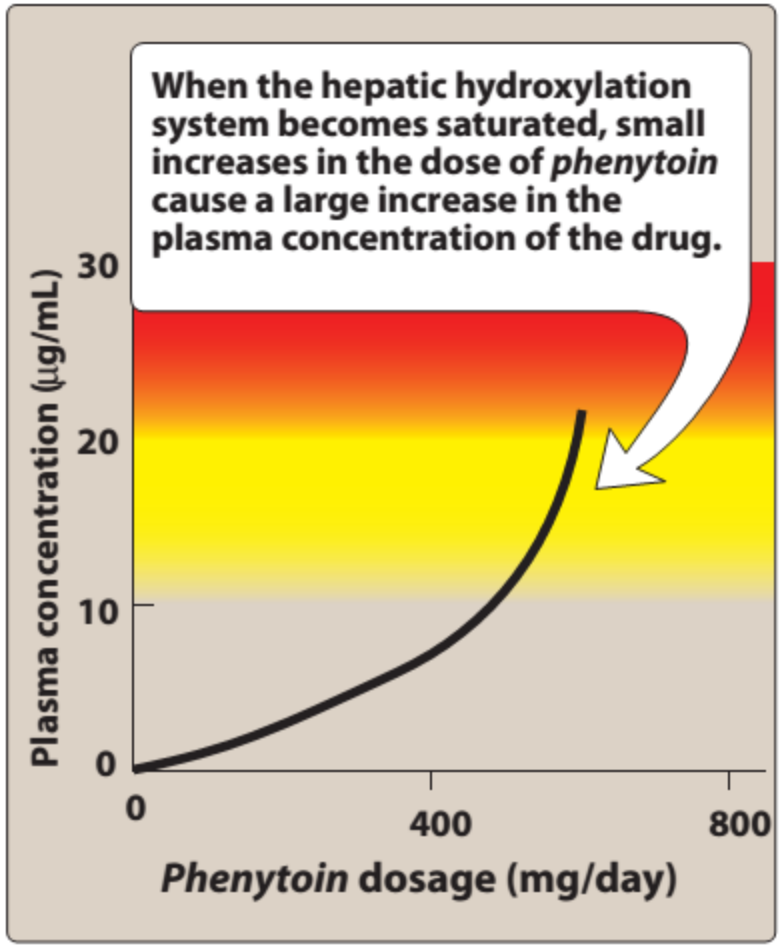
- In contrast, **fosphenytoin,** a more soluble phosphate prodrug of phenytoin, is well absorbed after IM administration (can be administered IV infusion)

- Because of sound-alike trade names, there is a risk for prescribing errors. The trade name of fosphenytoin is Cerebyx®, which is easily confused with Celebrex®, the cyclooxygenase-2 inhibitor, and Celexa®, the antidepressant.

Phenytoin and fosphenytoin

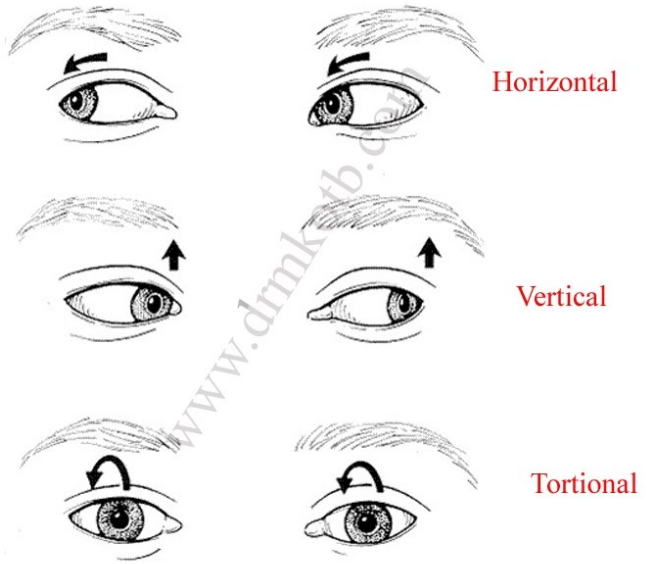
Self reading…
P. 418-419

- **Pharmacokinetics**
- **Phenytoin** binds extensively to plasma proteins (97–98%), and free (unbound) phenytoin levels in plasma are increased transiently by drugs that compete for binding (eg, carbamazepine, sulfonamides, valproic acid).
- Phenytoin induces drug-metabolizing enzymes.
- Phenytoin exhibits **saturable enzyme metabolism** at a low serum concentration. Therefore, small increases in a daily dose can produce large increases in the plasma concentration, resulting in drug-induced toxicity.

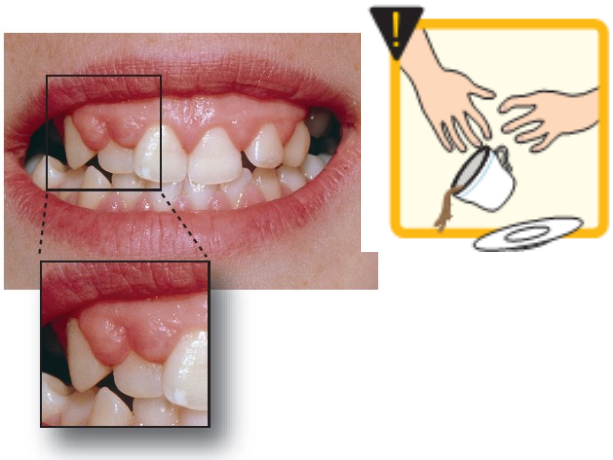


Phenytoin and fosphenytoin

- Adverse effects:
- Early signs of phenytoin administration include nystagmus and loss of smooth extraocular pursuit movements; neither is an indication for decreasing the dose.
  - Nystagmus is a vision condition in which the eyes make repetitive, uncontrolled movements, often resulting in reduced vision.
- Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment.
- Gingival hyperplasia may cause the gums to grow over the teeth.
- Long-term use may lead to development of peripheral neuropathies and abnormalities of vitamin D metabolism, leading to osteomalacia..

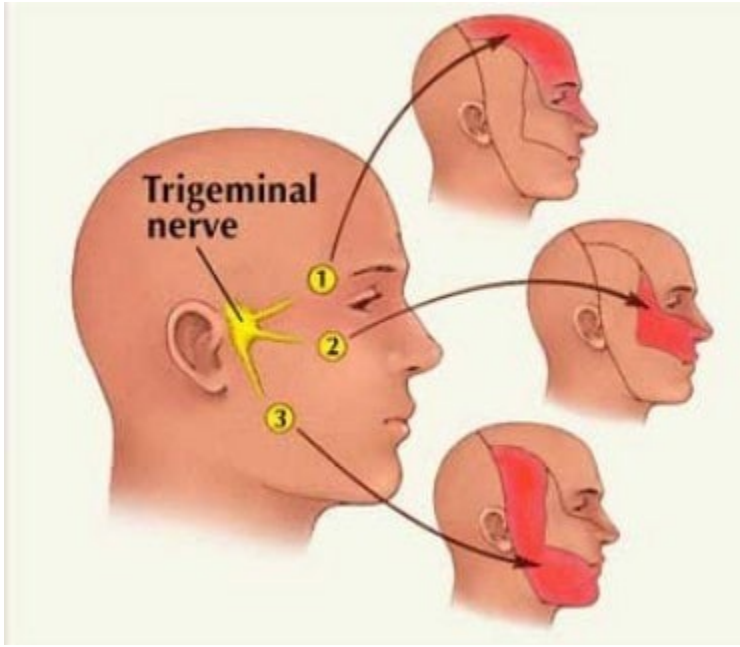


Types of Nystagmus

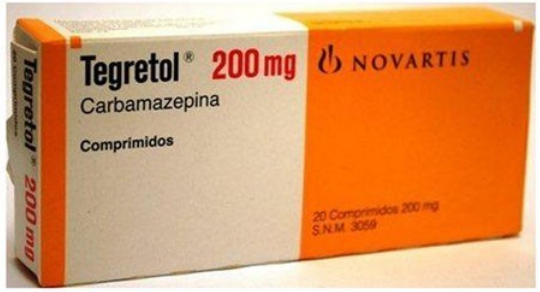


Carbamazepine

- **Carbamazepine** was initially marketed for the treatment of trigeminal neuralgia but has proved useful for epilepsy as well (for both partial seizures and generalized tonic-clonic seizures).
- In addition, carbamazepine is a mood stabilizer used to treat bipolar disorder.
- **Carbamazepine** is available only in oral form.



- Carbamazepine *exacerbate* certain seizure types in idiopathic generalized epilepsies, including *myoclonic and absence seizures*, and are generally avoided in patients with such a diagnosis.



Carbamazepine

- **Carbamazepine** induces formation of liver drug-metabolizing enzymes that increase metabolism of the drug itself and may increase the clearance of many other drugs.
  - The drug has a notable ability to induce its own metabolism, often causing serum concentrations to fall after a few weeks of treatment. Typically, the **half-life of 36 hours** observed in subjects after an initial single dose decreases to **as little as 8–12** hours in subjects receiving continuous therapy.
  - Considerable dosage adjustments are thus to be expected during the first weeks of therapy.
- Carbamazepine metabolism can be inhibited by other drugs (eg, valproic acid).
- A related drug, **oxcarbazepine**, is less likely to be involved in drug interactions.

Carbamazepine

- **Adverse effects:**
  - The most common dose-related adverse effects of carbamazepine are diplopia and ataxia.
    - The diplopia often occurs first and may last less than an hour during a particular time of day.
    - Rearrangement of the divided daily dose can often remedy this complaint.
  - Hyponatremia may be noted in some patients, especially the elderly, and could indicate a need for change of therapy.
  - A characteristic rash may develop early in therapy but may not require a change in treatment.

Gabapentin & pregabalin

- Gabapentin and pregabalin are effective in the treatment of **focal seizures.**
  - there is no evidence that they are efficacious in generalized epilepsies.
- Gabapentinoids are frequently used in the treatment of **neuropathic pain** conditions, including postherpetic neuralgia and painful diabetic neuropathy, and in the treatment of **anxiety disorders** and **restless leg syndrome**.
- Pregabalin is also approved for the treatment of **fibromyalgia**.

Postherpetic neuralgia is a complication of shingles, which is caused by the chickenpox (herpes zoster) virus. Postherpetic neuralgia affects nerve fibers and skin, causing burning pain that lasts long after the rash and blisters of shingles disappear.

Gabapentin & pregabalin

- **Adverse effects:**
- Gabapentin and pregabalin are generally well tolerated. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor.
  - These adverse effects are most troublesome at initiation of therapy and often resolve with continued dosing.
- Both gabapentinoids can cause weight gain and peripheral edema.

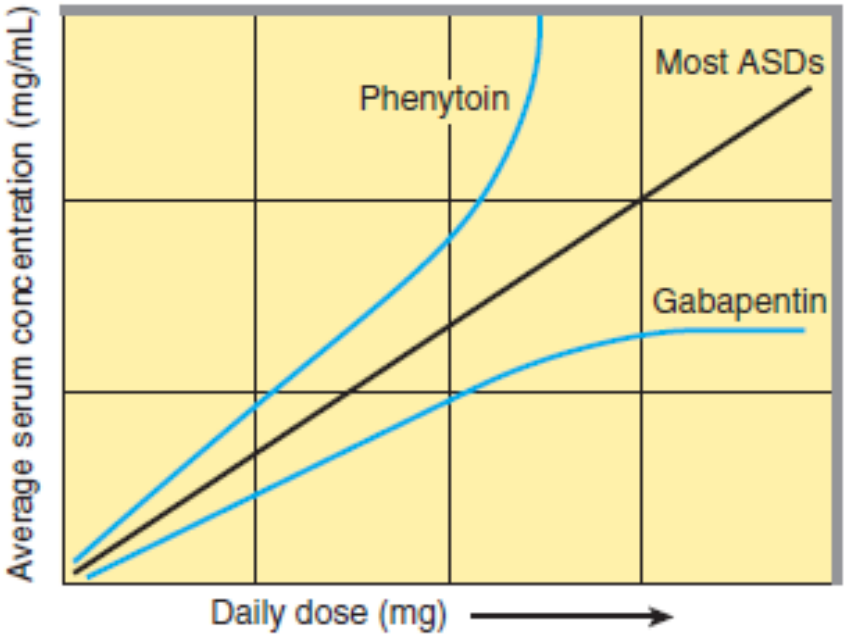


FIGURE 24–4 Relationship between dose and exposure for antiseizure drugs (ASDs). Most antiseizure drugs follow linear (first-order) kinetics, in which a constant fraction per unit time of the drug is eliminated (elimination is proportional to drug concentration). In the case of phenytoin, as the dose increases, there is saturation of metabolism and a shift from first-order to zero-order kinetics, in which a constant quantity per unit time is metabolized. A small increase in dose can result in a large increase in concentration. Orally administered gabapentin also exhibits zero-order kinetics, but in contrast to phenytoin where metabolism can be saturated, in the case of gabapentin, gut absorption, which is mediated by the large neutral amino acid system L transporter, is susceptible to saturation. The bioavailability of gabapentin falls at high doses as the transporter is saturated so that increases in blood levels do not keep pace with increases in dose.

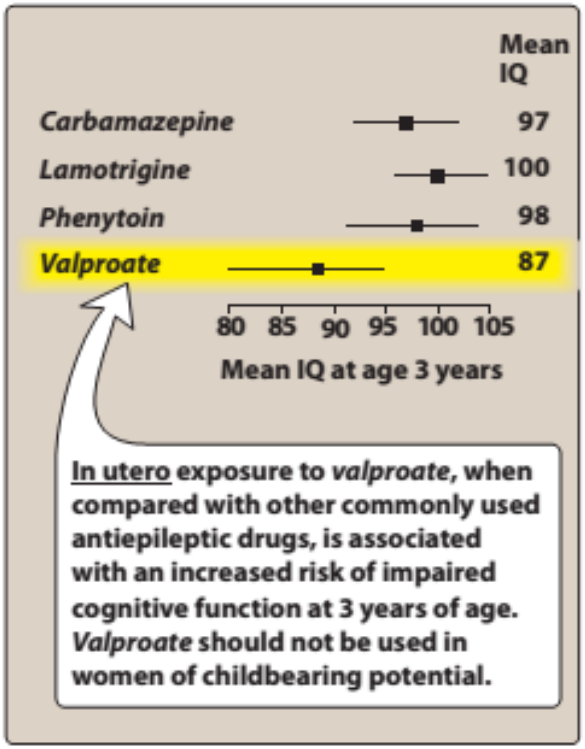
Valproic acid & sodium valproate

- 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 gastrointestinal tract. It was developed to improve GI tolerance of valproic acid.
- Valproate is a first-line **broad-spectrum antiseizure drug** that is thought to offer protection against many seizure types.
- Valproate is very effective against absence seizures and is often preferred to ethosuximide when the patient has concomitant generalized tonic-clonic attacks.
- In addition, it is used as a mood stabilizer in **bipolar disorder** and as prophylactic treatment for **migraine**.
- Intravenous formulations can be used to treat status epilepticus.

Valproic acid & sodium valproate

- Valproate inhibits drug-metabolising enzymes.
- Valproate is bound to albumin (greater than 90%), which can cause significant interactions with other highly protein-bound drugs.

- **Adverse effects:**
  - The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn (can be decreased if it is given after meals.
  - Rare hepatic toxicity (hepatic enzymes should be monitored frequently)
  - Teratogenicity



Strategies in selecting antiseizure drugs

- Diagnosis of a specific seizure type is important for prescribing the most appropriate antiseizure drug (or combination of drugs).

- Drug choice is usually made on the basis of:
  - Established efficacy in the specific seizure state that has been diagnosed.
  - The prior responsiveness of the patient.
  - The anticipated toxicity of the drug.

- Treatment may involve combinations of drugs, following the principle of adding known effective agents if the preceding drugs are not sufficient.

Clinical Uses of Antiseizure Drugs

A. Generalized Tonic-Clonic Seizures

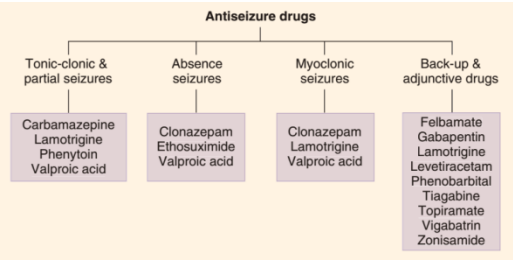
- **Valproic acid, carbamazepine,** and **phenytoin** are the drugs of choice for generalized tonic-clonic (grand mal) seizures.
- **Phenobarbital** (or primidone) is now considered to be an alternative agent in adults but continues to be a primary drug in infants.

B. Partial Seizures

- The drugs of first choice are **carbamazepine** (or **oxcarbazepine**) or **lamotrigine** or **phenytoin**.

C. Absence Seizures

- **Ethosuximide** or **valproic acid** are the preferred drugs because they cause minimal sedation.
- **Clonazepam** is effective as an alternative drug but has the disadvantages of causing sedation and tolerance.



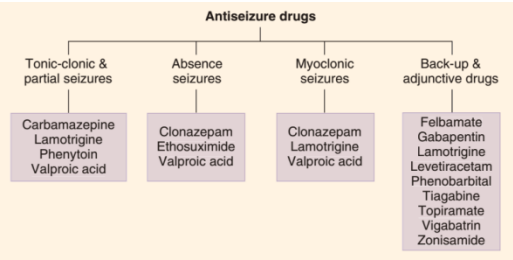
Clinical Uses of Antiseizure Drugs

D. Myoclonic Seizure

- Myoclonic seizure syndromes are usually treated with **valproic acid**.
- **Lamotrigine** is approved for adjunctive use, but is commonly used as monotherapy.
- **Clonazepam** can be effective, but the high doses required cause drowsiness.

E. Status Epilepticus

- Intravenous **diazepam** or **lorazepam** is usually effective in terminating attacks and providing short-term control.
- For prolonged therapy, intravenous **phenytoin** has often been used because it is highly effective and less sedating than benzodiazepines or barbiturates. However, phenytoin may cause cardiotoxicity (perhaps because of its solvent propylene glycol), and **fosphenytoin** (water soluble) is a safer parenteral agent.
- **Phenobarbita**l has also been used in status epilepticus, especially in children.



Withdrawal

- Antiseizure drugs may not need to be taken indefinitely. Children who are seizure free for periods longer than 2–4 years while on antiseizure medications will remain so when medications are withdrawn in 70% of cases.
- Drugs are generally withdrawn slowly over a 1- to 3-month period or longer. Abrupt cessation may be associated with return of seizures and even a risk of status epilepticus.
- In general, withdrawal from anti-absence drugs is more easily accomplished than withdrawal from drugs used in partial or generalized tonic-clonic seizure states.

Questions??