Anti Epileptic Drugs (AEDs)

Presentation by:

Moosareza Memari
Clinical pharmacologist
2022 JULY

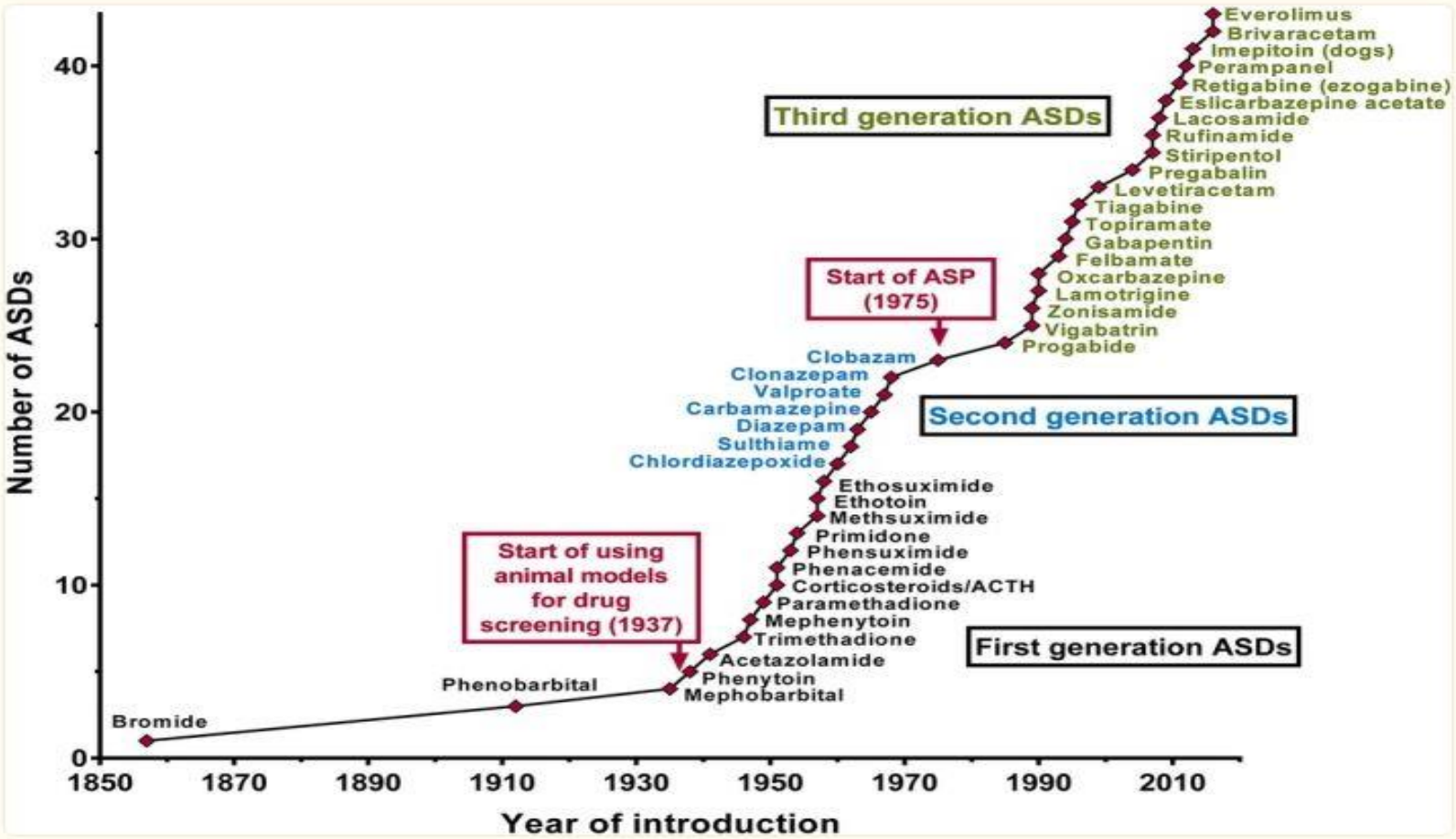
Topics

- History
- Epidemiology
- Etiology
- Classification of Epilepsy
- Basic Pharmacology of AEDs
- Pharmacotherapy of Epilepsy
- Teratogenicity of AEDs

History

- mid-1800s (potassium bromide)
- 1912 (phenobarbital)
- 1938 phenytoin
- 1960s and the mid-1970s valproate and carbamazepine
- 1960 chlordiazepoxide (Librium)
- 1963 diazepam (Valium)

History


Number of ASDs
Year of introduction
0
10
20
30
40
1850
1870
1890
1910
1930
1950
1970
1990
2010
Bromide
Phenobarbital
Phenytoin
Mephobarbital
Acetazolamide
Trimethadione
Mephenytoin
Paramethadione
Corticosteroids/ACTH
Phenacemide
Phensuximide
Primidone
Methsuximide
Ethotoin
Ethosuximide
Chlordiazepoxide
Sulthiame
Diazepam
Carbamazepine
Valproate
Clonazepam
Clobazam
Progabide
Vigabatrin
Zonisamide
Lamotrigine
Oxcarbazepine
Felbamate
Gabapentin
Topiramate
Tiagabine
Levetiracetam
Pregabalin
Stiripentol
Rufinamide
Lacosamide
Eslicarbazepine acetate
Retigabine (ezogabine)
Perampanel
Imepitoin (dogs)
Brivaracetam
Everolimus
Start of using animal models for drug screening (1937)
Start of ASP (1975)
First generation ASDs
Second generation ASDs
Third generation ASDs

Epidemiology

- Around 50 million people worldwide
- Risk of premature death
- 70% of them could live seizure- free
- 80% in low- and middle-income countries
- Three quarters of them do not get the optimal treatment
- Discontinuing anti-seizure medicine can be considered after 2 years

Etiology

- Structural, genetic, infectious, metabolic, immune and unknown:
- Prenatal or perinatal brain damage (a loss of oxygen or trauma, low birth weight)
- Brain malformations (congenital or genetic conditions)
- Severe head injury
- Stroke that restricts the amount of oxygen to the brain

Etiology

- Meningitis, encephalitis or neurocysticercosis
- Certain genetic syndrome
- Brain tumour
- Vascular occlusion
- Drug withdrawal (CNS depressants)
- Fever in children (febrile convulsion)
- Hypoglycemia
- Hypocalcemia
- Photo epilepsy

Etiology

Psychotropics

- **Antidepressants**
- **Antipsychotics**

Sedative-hypnotic drug withdrawal

- **Alcohol**
- **Barbiturates**
- **Benzodiazepines**

Etiology

Drugs of abuse

- **Amphetamine**
- **Cocaine**
- **Methylphenidate**

Anesthetics and analgesics

- **Meperidine**
- **Tramadol**

Etiology

- One third of women with intractable focal epilepsy have seizures related to their menstrual cycle
- Estrogen lowers seizure threshold
- Progesterone raises threshold

Etiology

- **Hyssop, Rosemary & Sweet fennel**
- **St John's Wort**
- **Stress**

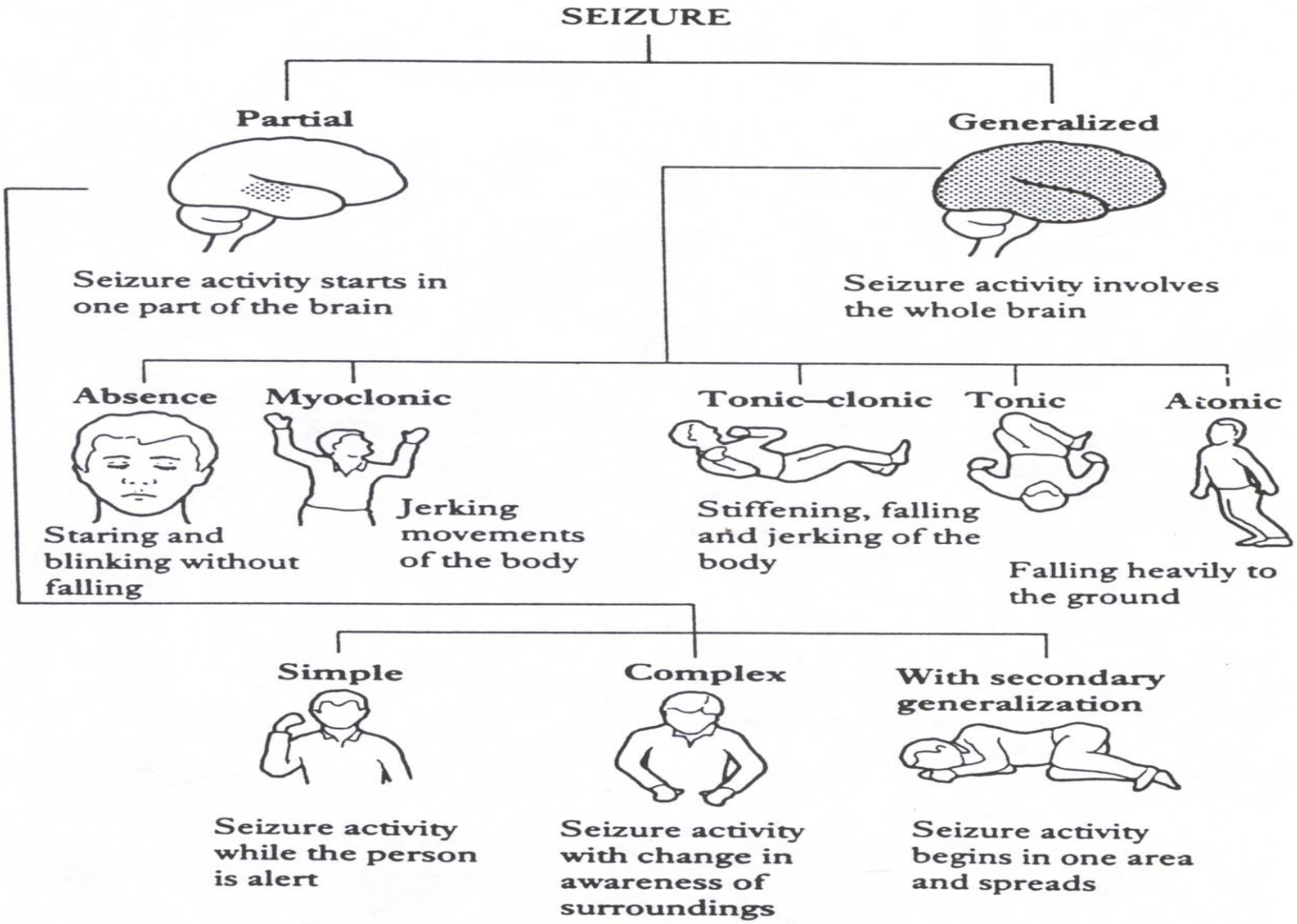
Classification of Epilepsy

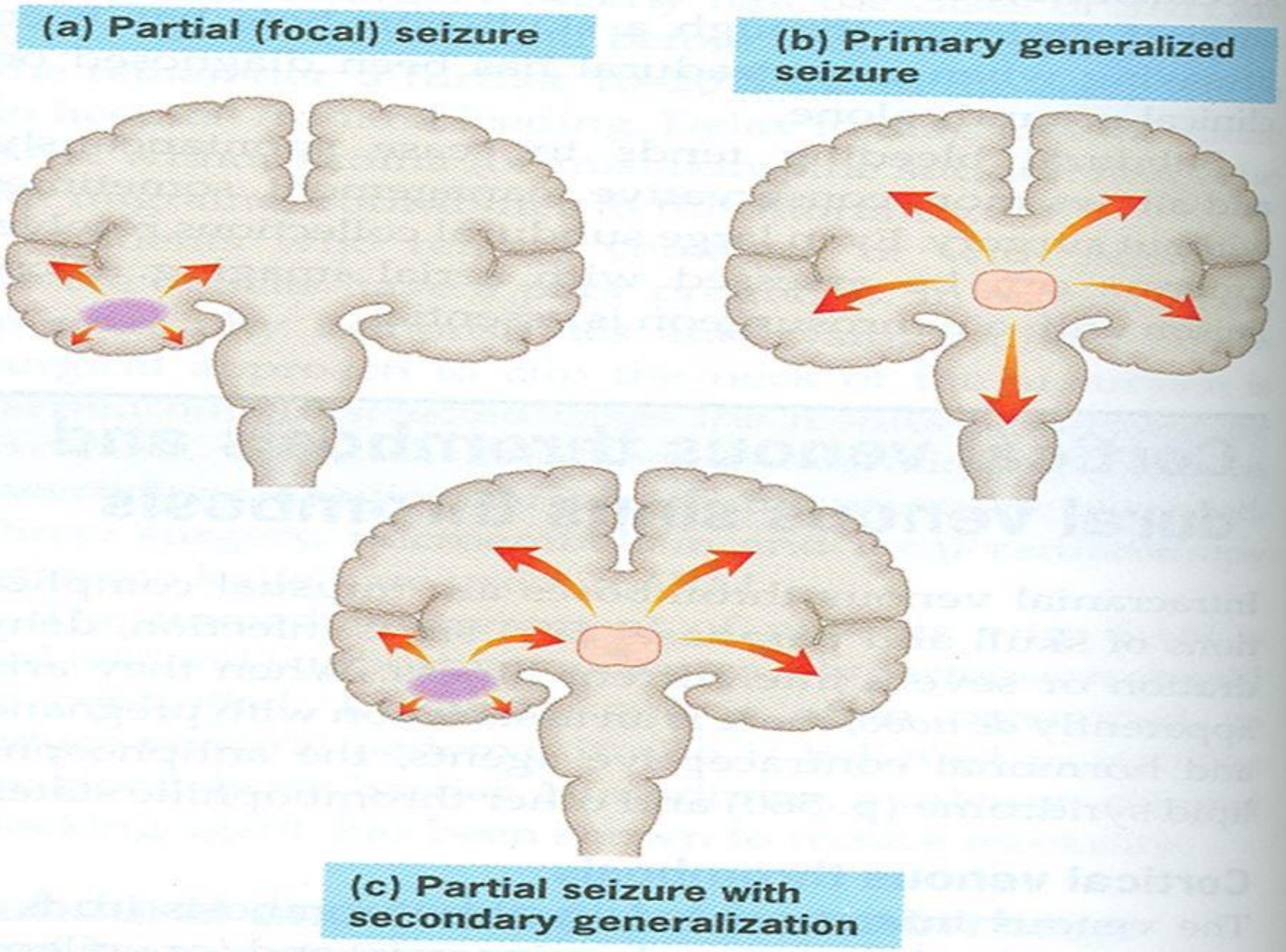
Focal onset (formerly *partial onset*) seizures

- Focal aware seizure (formerly *simple partial seizure*)
- Focal impaired awareness seizure (formerly *complex partial seizure*)
- Focal-to-bilateral tonic-clonic seizure (formerly *partial seizure secondarily generalized* or *grand mal seizure*)

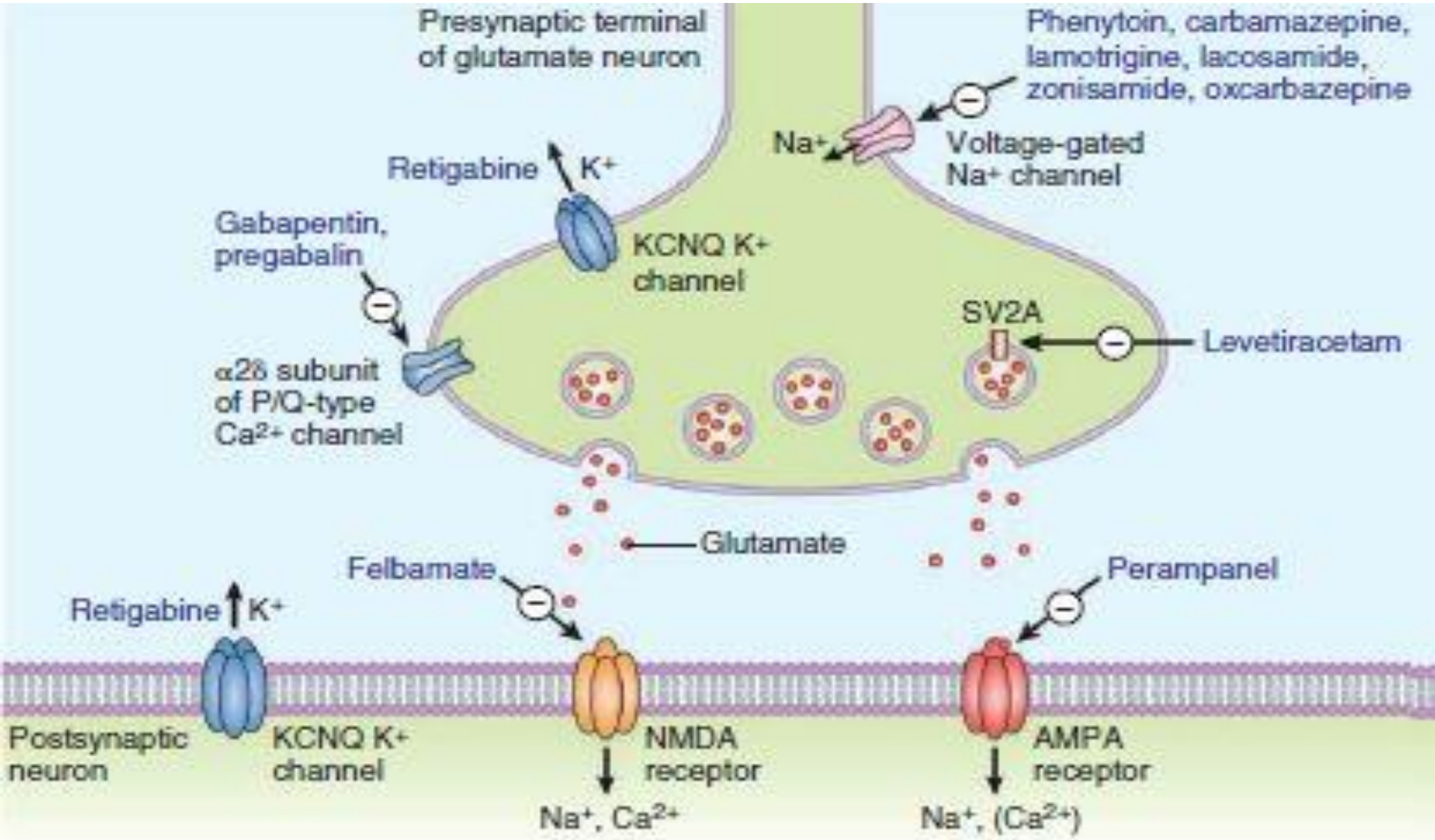
Generalized onset seizures

- Generalized tonic-clonic seizure (formerly *primary generalized tonic-clonic seizure* or *grand mal seizure*)
- Generalized absence seizure (formerly *petit mal seizure*; occurs, for example, in absence epilepsy)
- Myoclonic seizure (occurs, for example, in juvenile myoclonic epilepsy and Dravet's syndrome)
- Atonic seizure (*drop seizure* or *astatic seizure*; occurs, for example, in the Lennox-Gastaut syndrome)
- Epileptic spasms (as in infantile spasms also known as West's syndrome)

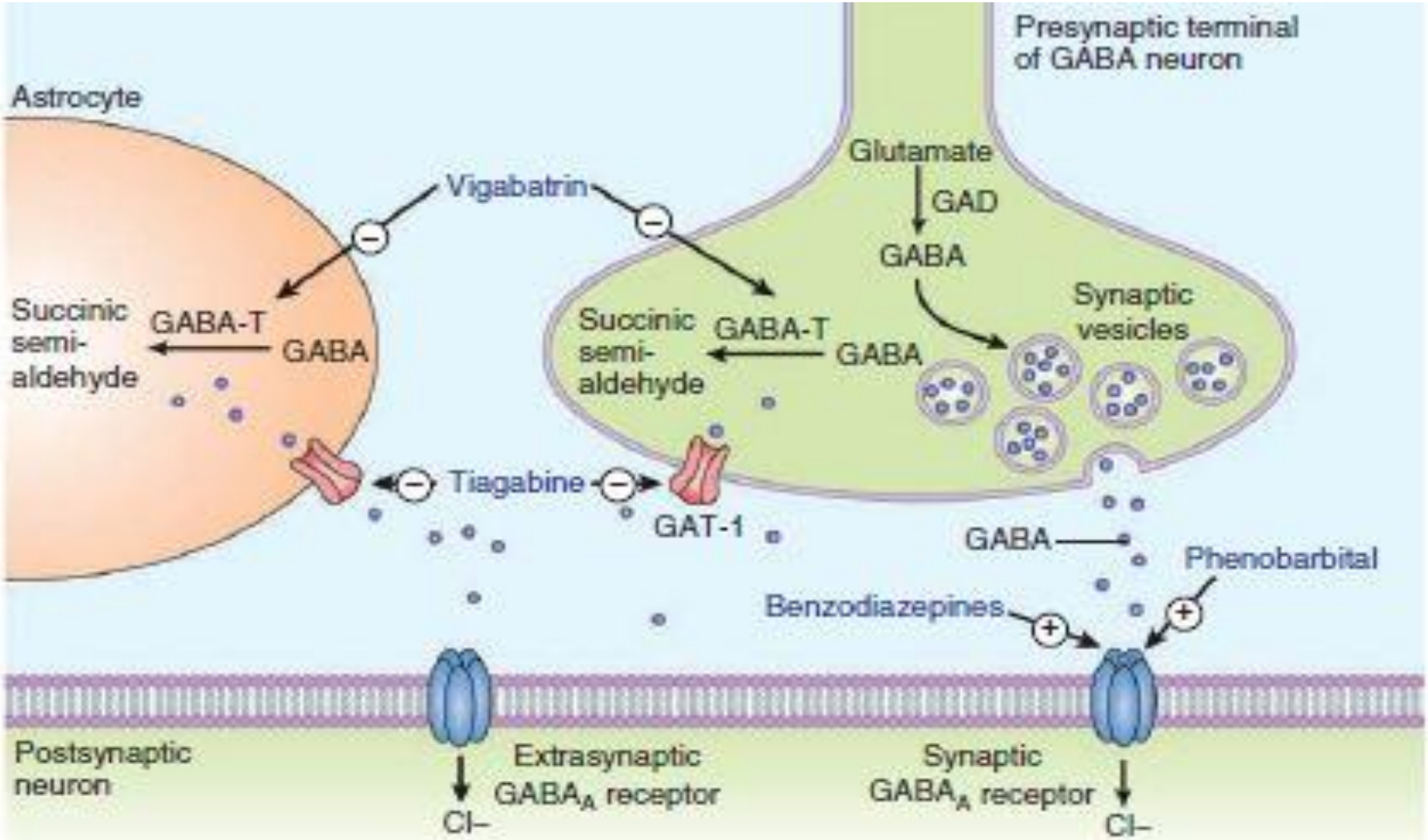

SEIZURE
Partial
Generalized
Seizure activity starts in one part of the brain
Seizure activity involves the whole brain
Absence
Myoclonic
Tonic–clonic
Tonic
Atonic
Staring and blinking without falling
Jerking movements of the body
Stiffening, falling and jerking of the body
Falling heavily to the ground
Simple
Complex
With secondary generalization
Seizure activity while the person is alert
Seizure activity with change in awareness of surroundings
Seizure activity begins in one area and spreads


(a) Partial (focal) seizure
(b) Primary generalized seizure
(c) Partial seizure with secondary generalization

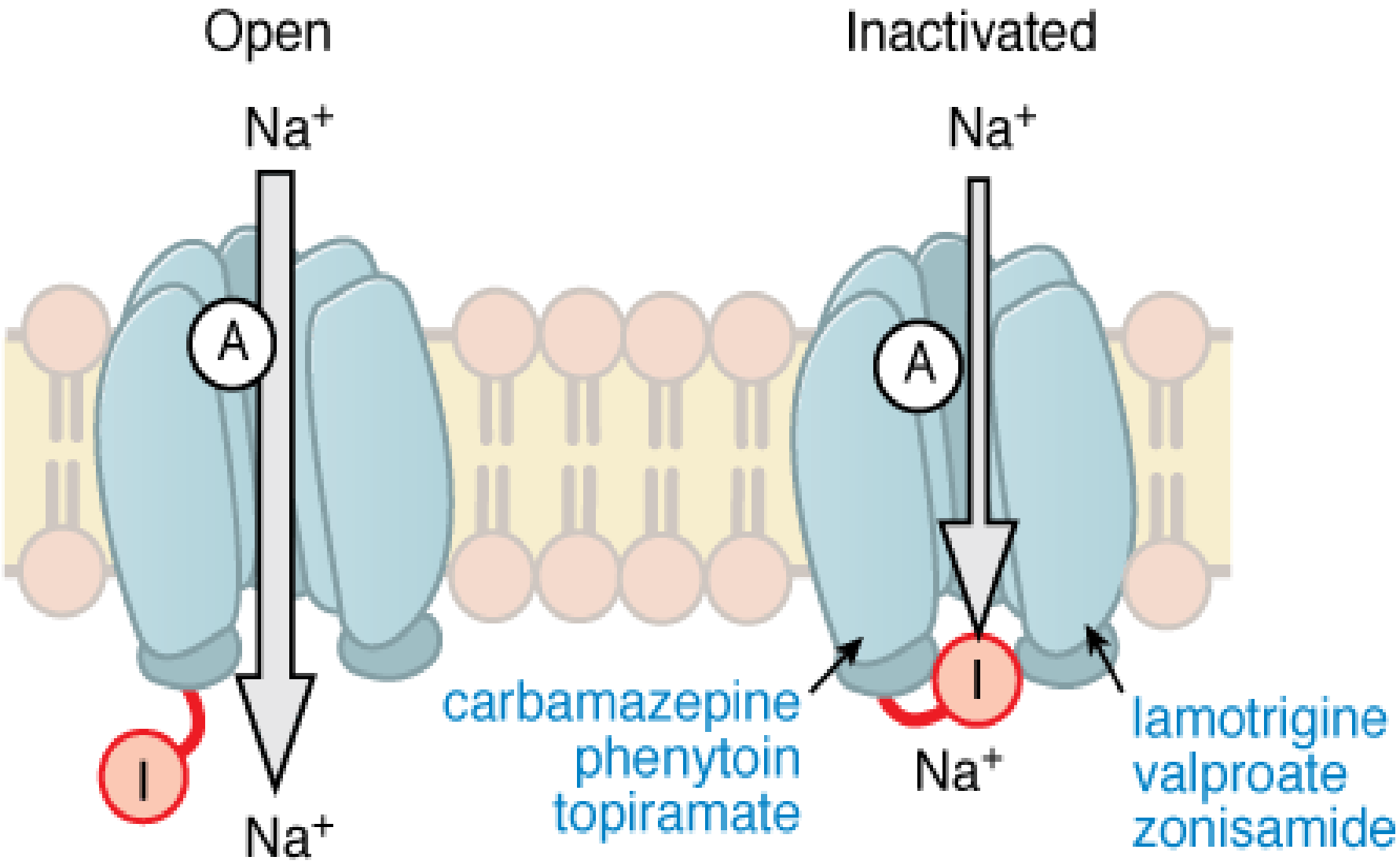
Basic Pharmacology of AEDs



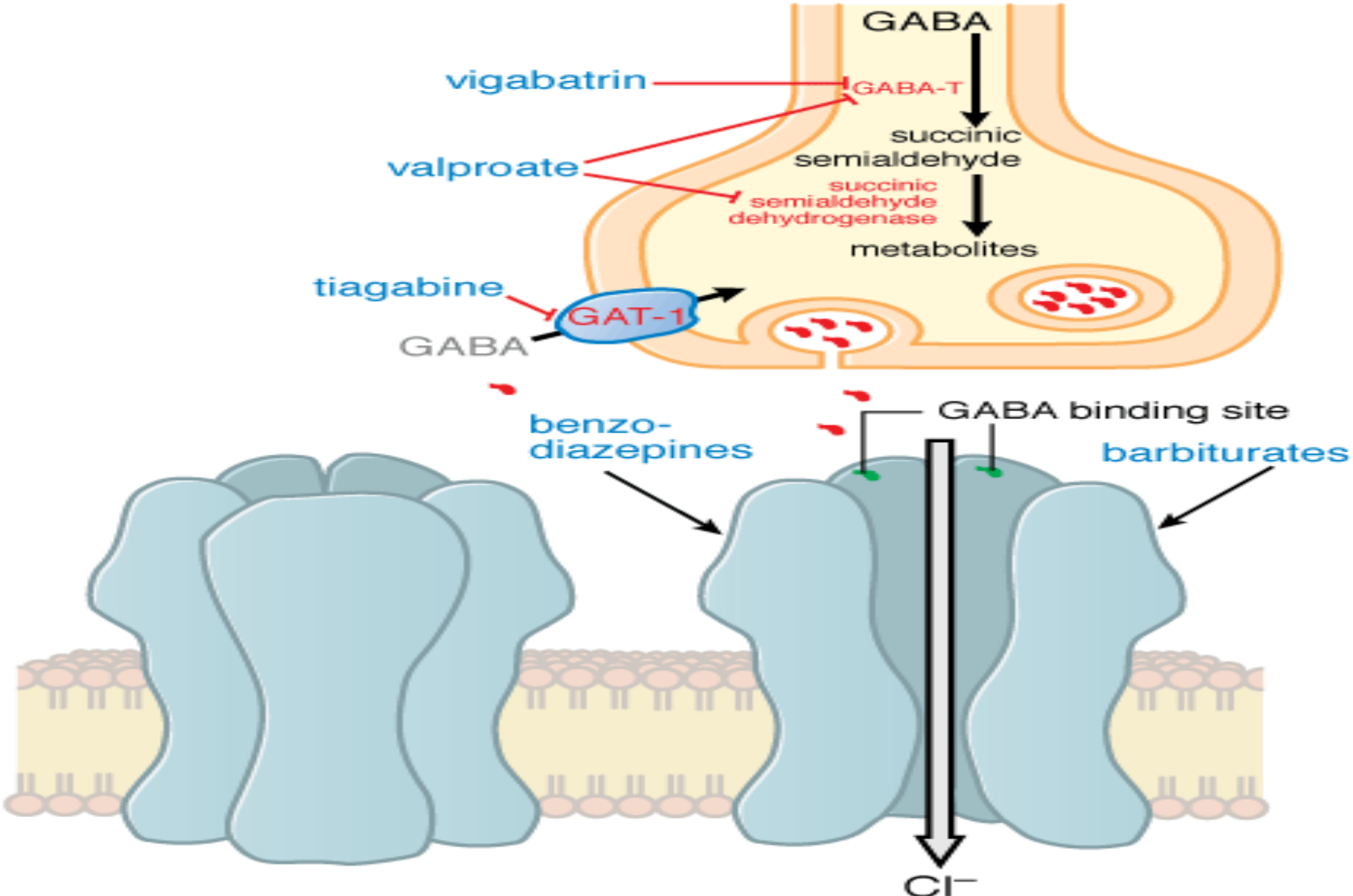
Basic Pharmacology of AEDs



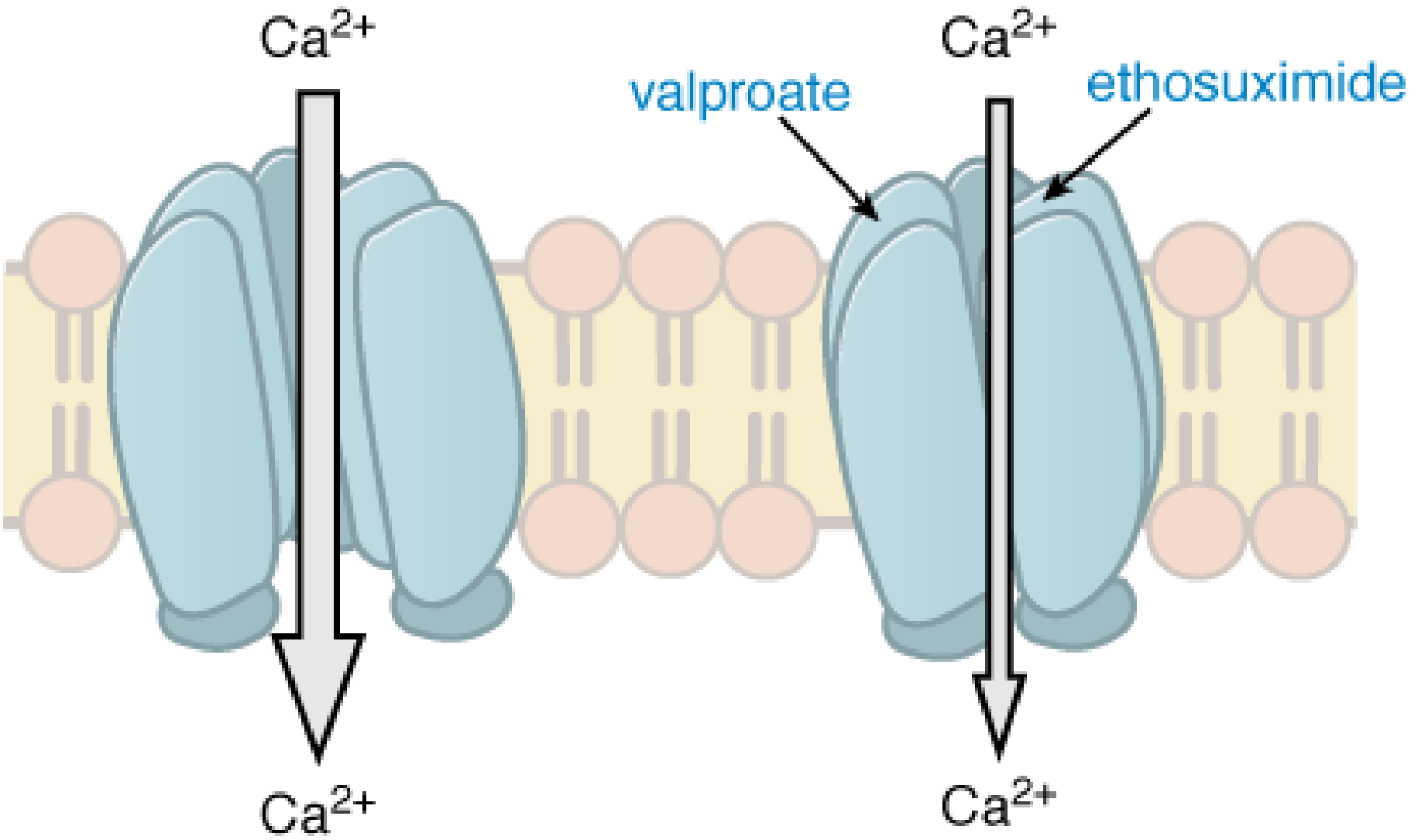
Basic Pharmacology of AEDs



Basic Pharmacology of AEDs



Basic Pharmacology of AEDs



Basic Pharmacology of AEDs

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

MOLECULAR TARGET AND ACTIVITY	DRUG	CONSEQUENCES OF ACTION
Na^+ channel modulators that:		
enhance fast inactivation	PHT, CBZ, LTG,	• block action potential propagation
	FBM, OxCBZ,	• stabilize neuronal membranes
	TPM, VPA	• ↓ neurotransmitter release, focal firing, and seizure spread
enhance slow inactivation	LCM	• ↑ spike frequency adaptation
		• ↓ AP bursts, focal firing, and seizure spread
		• stabilize neuronal membrane
Ca^{2+} channel blockers	ESM, VPA, LTG	• ↓ neurotransmitter release (N- & P-types)
		• ↓ slow-depolarization (T-type) and spike-wave discharges
$\alpha 2\delta$ ligands	GBP, PGB	• modulate neurotransmitter release
$GABA_A$ receptor allosteric modulators	BZDs, PB, FBM, TPM, CBZ, OxCBZ	• ↑ membrane hyperpolarization and seizure threshold • ↓ focal firing
		BZDs—attenuate spike-wave discharges
		PB, CBZ, OxCBZ—aggravate spike-wave discharges

GABA uptake inhibitors/ **GABA-transaminase inhibitors**	TGB, VGB	• ↑ extrasynaptic GABA levels and membrane hyperpolarization
		• ↓ focal firing
		• aggravate spike-wave discharges
NMDA receptor antagonists	FBM	• ↓ slow excitatory neurotransmission
		• ↓ excitatory amino acid neurotoxicity
		• delay epileptogenesis
AMPA/kainate receptor antagonists	PB, TPM	• ↓ fast excitatory neurotransmission and focal firing
Enhancers of HCN channel activity	LTG	• buffers large hyperpolarizing and depolarizing inputs • suppresses action potential initiation by dendritic inputs
SV2A protein ligand	LEV	• unknown; may decrease transmitter release
Inhibitors of brain carbonic anhydrase	ACZ, TPM, ZNS	• ↑ HCN-mediated currents • ↓ NMDA-mediated currents • ↑ GABA-mediated inhibition

Treatment

- **Pharmacotherapy**
- **Brain surgery**
- **Vagus Nerve Stimulation (VNS)**
- **Ketogenic diet (MCT Oil)**

Pharmacotherapy of Epilepsy

Pharmacotherapy of Epilepsy

Seizure disorder	Drugs
Tonic-clonic(Grand mal) Drug of Choice	Valproate Topiramte Lamotrigine Zonisamide
Alternatives:	Carbamazepine Phenobarbital Phenytoin ,Levetiracetam
Partial (simple or complex) Drug of choice	Carbamazepine ,Eslicarnbazepine,Oxcarbazepin Levetiracetam, Phenytoin, Lacosamide , Valproate
Alternatives:	Phenobarbital , Tiagabine, Felbamate Lamotringine (as adjunct or alone) Gabapentin , Prampanel, Pregaablin(as adjunct)

Pharmacotherapy of Epilepsy

Absence (petit mal) ***Drug of choice***	***Valproate*** ***Ethosuximide***
Alternatives:	***Clonazepam, Lamotrigine***
Myoclonic, Atonic ***Drug of choice***	***Valproate***
Alternatives:	***Clonazepam, Zonisamide, Levetiracetam,Topiramate,Lamotrigine***
Status Epilepticus ***Drug of choice***	***Lorazepam, Diazepam, i.v.*** ***or Phenytoin, Levetiracetam i.v. or Valproate***
Alternatives:	***Barbiturates, Propofol, Ketamin, Midazolam, : i.v***

FOCAL SEIZURES

- CARBAMAZEPINE
- OXCARBAZEPINE
- LACOSAMIDE
- PHENYTOIN
- MEPHENYTOIN
- ETHOTOIN
- PHENACEMIDE
- TIAGABINE
- RETIGABINE (EZOGABINE)

GENERALIZED ONSET SEIZURES

- **VALPROATE AND DIVALPROEX SODIUM (First Choice)**
- **TOPIRAMATE**
- **ZONISAMIDE**

GENERALIZED ABSENCE SEIZURES

- **ETHOSUXIMIDE**
- **TRIMETHADIONE**

MYOCLONIC SEIZURES

- **Valproate first choice (First Choice)**
- **Levetiracetam**
- **Zonisamide**
- **Topiramate**
- **Lamotrigine**

ATONIC SEIZURES
LENNOX-GASTAUT SYNDROME

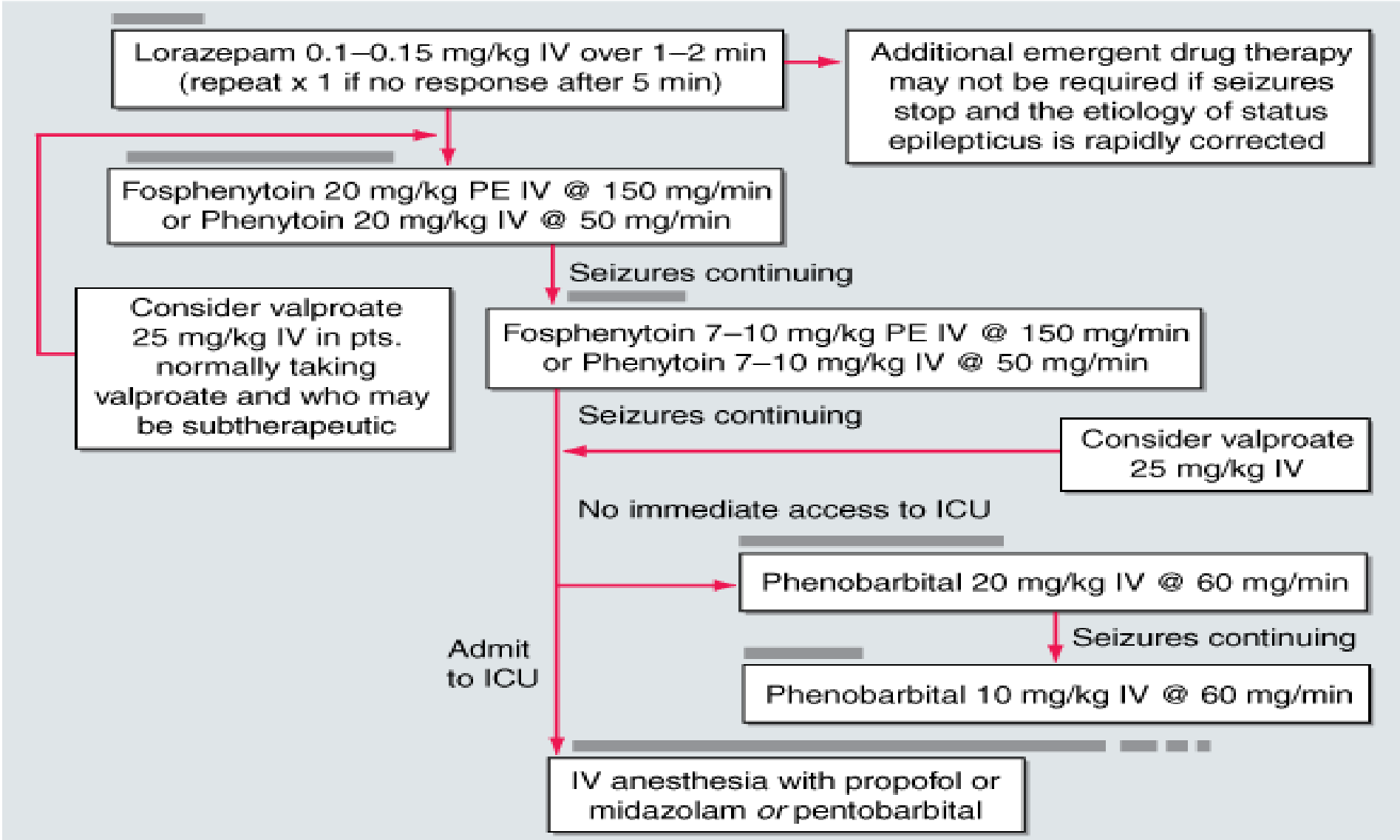
- **Clobazam**
- **Rufinamide**
- **Stiripentol**

INFANTILE SPASMS

(WEST'S SYNDROME)

- **(ACTH)**
- **Prednisone or Hydrocortisone**
- **Vigabatrin (permanent loss of vision)**
- **Valproate,Topiramate, Zonisamide**
- **Benzodiazepine such as Clonazepam, Nitrazepam**

STATUS EPILEPTICUS



Pharmacokinetics

- **Carbamazepine, Oxcarbazepine, Eslicarbazepine acetate,Phenobarbital, Phenytoin, Primidone:**
  CYP450 and glucuronyl transferase strong inducers

  Contraceptives?
  Carbamazepine Dose?

- **Phenytoin, Tiagabine,Valproate, Diazepam perampanel:**
  Highly (>90%) bounding to plasma protens

Adverse Drug Reactions

- **Toxic Epidermal Necrolysis & steven jahnson:**

  Zonisamide, Lamotrigine, Phenytoin, Carbamazepine

- **Aplastic anemia:**

  Carbamazepine, Felbamate, Valproate, Phenytoin, Phenobarbital, Valproate sodium

ype, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
ODIUM CHANNEL BLOCKERS				
Carbamazepine	Sodium channel blocker	Rapidly absorbed orally, with bioavailability 75–85% • peak levels in 4–5 h • plasma protein binding 75% • extensively metabolized in liver, in part to active carbamazepine-10, 11-epoxide • $t_{1/2}$ of parent in adults initially 25–65 h, decreasing to 12–17 h with autoinduction	Focal and focal-to-bilateral tonic-clonic seizures; trigeminal neuralgia	*Toxicity:* Nausea, diplopia, ataxia, hyponatremia, headache • *Interactions:* Phenytoin, valproate, fluoxetine, verapamil, macrolide antibiotics, isoniazid, propoxyphene, danazol, phenobarbital, primidone, many others
Oxcarbazepine: Similar to carbamazepine; 100% bioavailability; 1-2 h $t_{1/2}$ but active metabolites with $t_{1/2}$ of 8-12 h; fewer interactions reported *Eslicarbazepine acetate: Similar to oxcarbazepine but shown to be effective when given once daily and may be more rapidly converted to the active metabolite*				
Lamotrigine	Sodium channel blocker	Nearly complete (~90%) absorption • peak levels in 1–3 h • protein binding 55% • extensively metabolized; no active metabolites • $t_{1/2}$ 8–35 h	Focal seizures, generalized tonic-clonic seizures, absence seizures, other generalized seizures; bipolar depression	*Toxicity:* Dizziness, headache, diplopia, rash • *Interactions:* Valproate, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, succinimides, sertraline, topiramate
Lacosamide	Sodium channel blocker, slow blocking kinetics	Complete absorption • peak levels in 1–2 h • protein binding <30% • no active metabolites • $t_{1/2}$ 12–14 h	Focal seizures	*Toxicity:* Dizziness, headache, nausea • small increase in PR interval • *Interactions:* Minimal
Phenytoin, fosphenytoin	Sodium channel blocker	Absorption is formulation dependent • highly bound to plasma proteins • no active metabolites • dose-dependent elimination, $t_{1/2}$ 12–36 h • fosphenytoin is for IV, IM routes	Focal seizures, tonic-clonic seizures	*Toxicity:* Diplopia, ataxia, gingival hyperplasia, hirsutism, neuropathy • *Interactions:* Phenobarbital, carbamazepine, isoniazid, felbamate, oxcarbazepine, topiramate, fluoxetine, fluconazole, digoxin, quinidine, cyclosporine, steroids, oral

Type, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
BROAD SPECTRUM				
• Valproate	Unknown	Nearly complete (>90%) absorption • peak levels formulation dependent • highly (90%) bound to plasma proteins • extensively metabolized in liver • $t_{1/2}$ 5–16 h	Generalized tonic-clonic seizures, partial seizures, absence seizures, myoclonic seizures, other generalized seizure; migraine prophylaxis	*Toxicity:* Nausea, tremor, weight gain, hair loss, teratogenic, hepatotoxic • *Interactions:* Phenobarbital, phenytoin, carbamazepine, lamotrigine, felbamate, rifampin, ethosuximide, primidone
• Levetiracetam	SV2A ligand	Nearly complete (~95%) absorption • peak levels in 1–2 h • not bound to plasma proteins • minimal metabolism in blood to inactive metabolite; ~66% excreted unchanged in urine • $t_{1/2}$ 6–11 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures	*Toxicity:* Nervousness, dizziness, depression, seizures • *Interactions:* Rare
Brivaracetam: Similar to levetiracetam but interaction with carbamazepine				
• Topiramate	Multiple actions	Bioavailability ~80% • peak levels in 2–4 h • minimal (15%) plasma protein binding • variable metabolism; no active metabolites; 20–70% excreted unchanged in the urine • $t_{1/2}$ 20–30 h, but decreases with concomitant drugs	Focal seizures, primary generalized seizures, Lennox-Gastaut syndrome; migraine prophylaxis	*Toxicity:* Somnolence, cognitive slowing, confusion, paresthesias • *Interactions:* Phenytoin, carbamazepine, oral contraceptives, lamotrigine, lithium?
• Zonisamide	Unknown	Nearly complete (>90%) absorption • peak concentrations in 2–6 h • modest (40–60%) plasma protein binding • moderate (> 50%) metabolism in liver; 30% excreted unchanged in urine • $t_{1/2}$ 50–70 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures	*Toxicity:* Drowsiness, cognitive impairment, confusion, skin rashes • *Interactions:* Minimal
• Rufinamide	Sodium channel blocker and other mechanisms	Well absorbed orally • peak concentrations in 4–6 h • low (35%) plasma protein binding • $t_{1/2}$ 6–10 h • no active metabolites • mostly excreted in urine	Lennox-Gastaut syndrome; focal seizures	*Toxicity:* Somnolence, vomiting, pyrexia, diarrhea • *Interactions:* Not metabolized via P450 enzymes, but antiseizure drug interactions may be present

GABAPENTINOIDS				
• Gabapentin	α2δ ligand (Ca^{2+} channel and possibly other sites)	Bioavailability 50%, decreasing with increasing doses • peak concentrations in 2–3 h • not bound to plasma proteins • not metabolized; 100% excreted unchanged in urine • $t_{1/2}$ 5–9 h	Focal seizures; neuropathic pain; postherpetic neuralgia; anxiety	*Toxicity:* Somnolence, dizziness, ataxia • *Interactions:* Minimal
• Pregabalin	α2δ ligand (Ca^{2+} channel and possibly other sites)	Nearly complete (~90%) absorption • peak concentrations in 1–2 h • not bound to plasma proteins • not metabolized; 98% excreted unchanged in urine • $t_{1/2}$ 4.5–7 h	Focal seizures; neuropathic pain; postherpetic neuralgia; fibromyalgia; anxiety	*Toxicity:* Somnolence, dizziness, ataxia • *Interactions:* Minimal
BARBITURATES				
• Phenobarbital	Positive allosteric modulator of $GABA_A$ receptors • reduces excitatory synaptic responses	Nearly complete (>90%) absorption • peak concentrations in 0.5–4 h • modest (55%) plasma protein binding • extensively metabolized in liver; no active metabolites; 20–25% excreted unchanged in urine • $t_{1/2}$ 75–140 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures, neonatal seizures; sedation	*Toxicity:* Sedation, cognitive issues, ataxia, hyperactivity • *Interactions:* Valproate, carbamazepine, felbamate, phenytoin, cyclosporine, felodipine, lamotrigine, nifedipine, nimodipine, steroids, theophylline, verapamil, others
• Primidone	Sodium channel blocker-like but converted to phenobarbital	Nearly complete (>90%) absorption • minimal (10%) plasma protein binding • peak concentrations in 2–6 h • extensively metabolized in liver; 2 active metabolites (phenobarbital and phenylethylmalonamide); 65% excreted unchanged in urine • $t_{1/2}$ 10–25 h	Generalized tonic-clonic seizures, partial seizures	*Toxicity:* Sedation, cognitive issues, ataxia, hyperactivity • *Interactions:* Similar to phenobarbital

Type, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
ABSENCE SEIZURE-SPECIFIC				
• Ethosuximide	Inhibit low-threshold calcium channels (T-type)	Nearly complete (>90%) absorption • peak concentrations in 3–7 h • not bound to plasma proteins • extensively metabolized in liver; no active metabolites; 20% excreted unchanged in urine • $t_{1/2}$ 20–60 h	Absence seizures	*Toxicity:* Nausea, headache, dizziness, lethargy • *Interactions:* Valproate, phenobarbital, phenytoin, carbamazepine, rifampicin
BENZODIAZEPINES				
• Diazepam	Positive allosteric modulator of $GABA_A$ receptors	Nearly complete (>90%) oral or rectal absorption • peak concentrations in 1–1.5 h • IV for status epilepticus • highly (95–98%) bound to plasma proteins • extensively metabolized to several active metabolites • $t_{1/2}$ of active metabolite N-desmethyldiazepam up to 100 h	Status epilepticus, seizure clusters; sedation, anxiety, muscle relaxation (muscle spasms, spasticity), acute alcohol withdrawal	*Toxicity:* Sedation • *Interactions:* Additive with sedative-hypnotics
• Clonazepam	Positive allosteric modulator of $GABA_A$ receptors	Bioavailability >80% • peak concentrations in 1–4 h • highly (86%) bound to plasma proteins • extensively metabolized in liver; no active metabolites • $t_{1/2}$ 12–56 h	Absence seizures, myoclonic seizures, infantile spasms	*Toxicity:* Similar to diazepam • *Interactions:* Additive with sedative-hypnotics

- *Lorazepam: Similar to diazepam*
- *Clobazam: Indications include absence seizures, myoclonic seizures, infantile spasms*

BREASTFEEDING

- **Penetration in milk:**
- **Primidone, Levetiracetam, Gabapentin, Lamotrigine (18.3%) & Topiramate**

- **High Protein Binding: Valproate,Phenobarbital, Phenytoin, & Carbamazepine**

Withdrawal Effects syndromes: Absence more than Tonic clonic

Benzodiazeoines, Phenobarbital (Sedation)

Teratogenicity of AEDs

- No antiseizure drug is known to be completely safe for the developing fetus
- Dose dependent
- Monotherapy
- Valproate Sodium: First-trimester (3-fold increased risk- spina bifida %6–9)
- Phenobarbital: cardiac defects
- Topiramate: First trimester (10-fold increase in oral clefts risk %1.4)

Teratogenicity of AEDs

- **Topiramate: First trimester (10-fold increase in oral clefts risk %1.4)**
- **Lamotrigine or levetiracetam: safer with regard to cognition**

Nonepileptic Uses of AEDs

- **Neuropathic Pain: Pregabaline, Gabapentin**
- **Bipolar Disorder: Lamotrigine,Carbamazepine, Topiramate, Valproate**
- **Migraine: Valproic acid, Topiramate**
- **Trigeminal Neuralgia: Carbamzepine, Valproate, Phenytoin**
- **Bedsores: Phenytoin**
- **Antiarryhtmic: Phenytoin**

DRUGS IN DEVELOPMENT

- Staccato (Aerosol Inhaled), Alprazolam, Intranasal midazolam: For acute repetitive seizures
- Allopregnanolone, Ganaxolone:
  For status epilepticus:
- Cannabidiol, Annabidivarin Cenobamate:
  For focal seizures
- Fenfluramine, stiripentol:
  For Dravet's syndrome
- http://www.epilepsy.com/etp/pipeline_new_therapies