FARMAKOTERAPI

OBAT ANTIEPILEPSI

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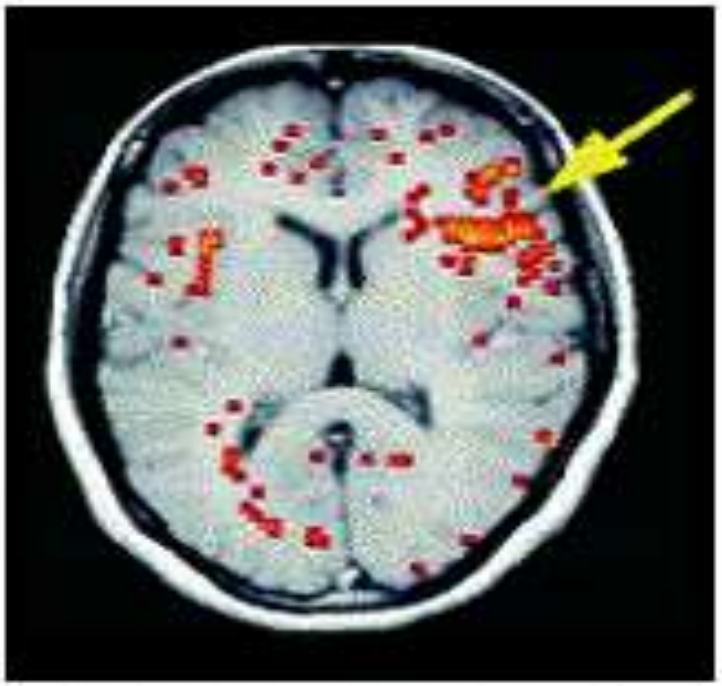
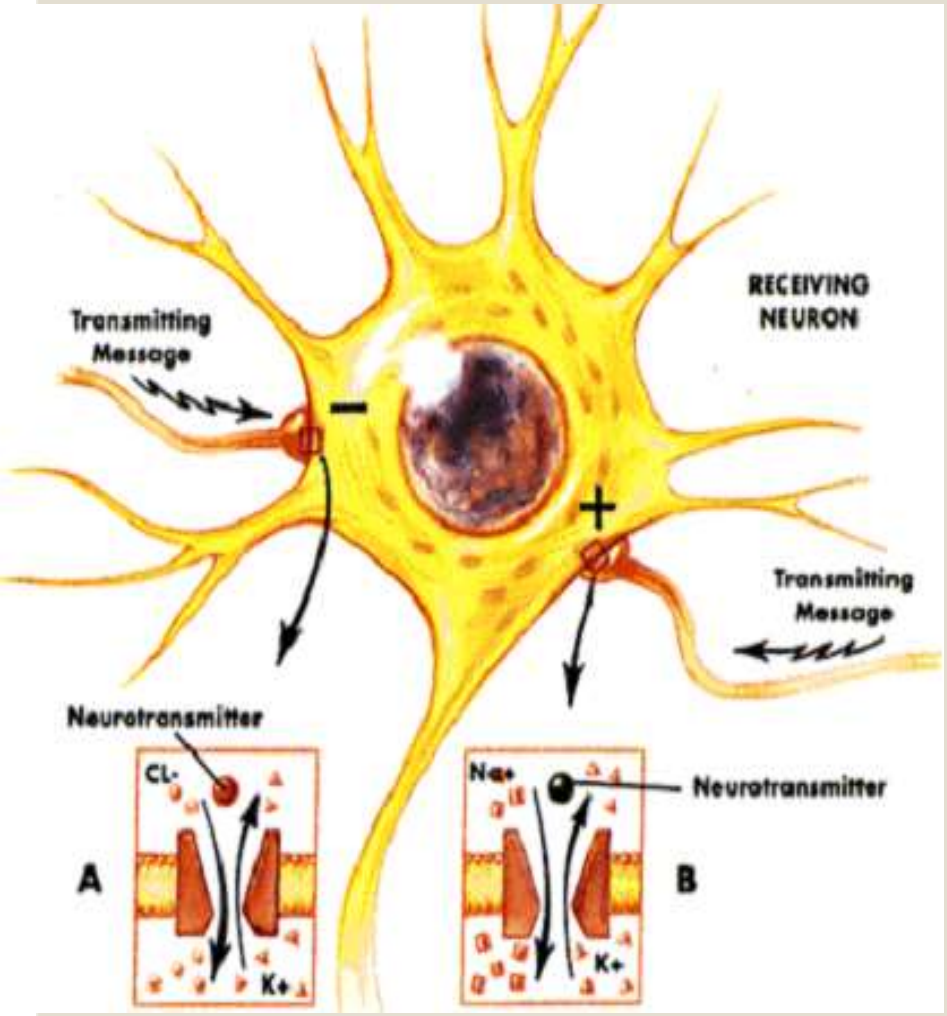
DEFINISI

- Epilepsi→ kejadian kejang /konvulsi /seizure yang terjadi spontan, episodik, berulang (kambuhan)
- Kejang /seizure : manifestasi klinis dari aktivitas neuron yang berlebihan di korteks serebral
- Manifestasi klinis kejang bervariasi tergantung daerah otak yang terlibat
- Fokus ektopik → neuron epileptik



Brain scan of a person with frontal lobe epilepsy. Arrow points to the focus of seizure activity. [Image reproduced with permission from Seeck et al. (1998) Electroenceph. Clin. Neurophys. 106, 508-512.]

SEIZURE



Kejang disebabkan krn :

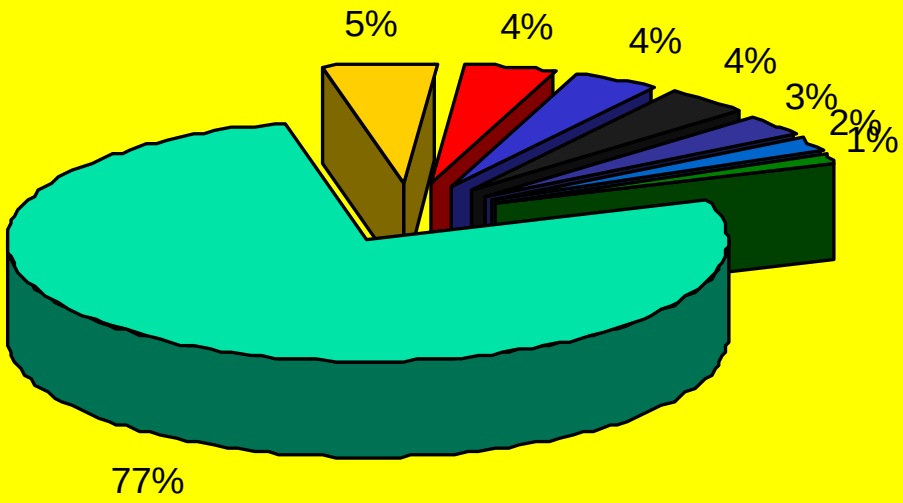
- Ketidakseimbangan antara pengaruh inhibisi (GABA) dan eksitatori pada otak (Glutamat)
- Me ↓ transmisi inhibitori : paska Tx dg antagonis GABA, penghentian pemberian agonis GABA (benzodiazepin, alkohol)
- Me ↑ transmisi eksitatori : meningkatnya glutamat atau aspartat

Penyebab seizure mnrt usia

Age Range	Major Causes
Infant	Birth injury, hypoxia/ischemia, congenital malformations, and congenital infection
Childhood	Febrile seizures, central nervous system infection, head trauma, birth injury, and idiopathic origin
Young adult	Head trauma, drugs, withdrawal from alcohol or sedatives, and idiopathic origin
Elderly	Strokes, brain tumor, cardiac arrest with hypoxia, and metabolic origin

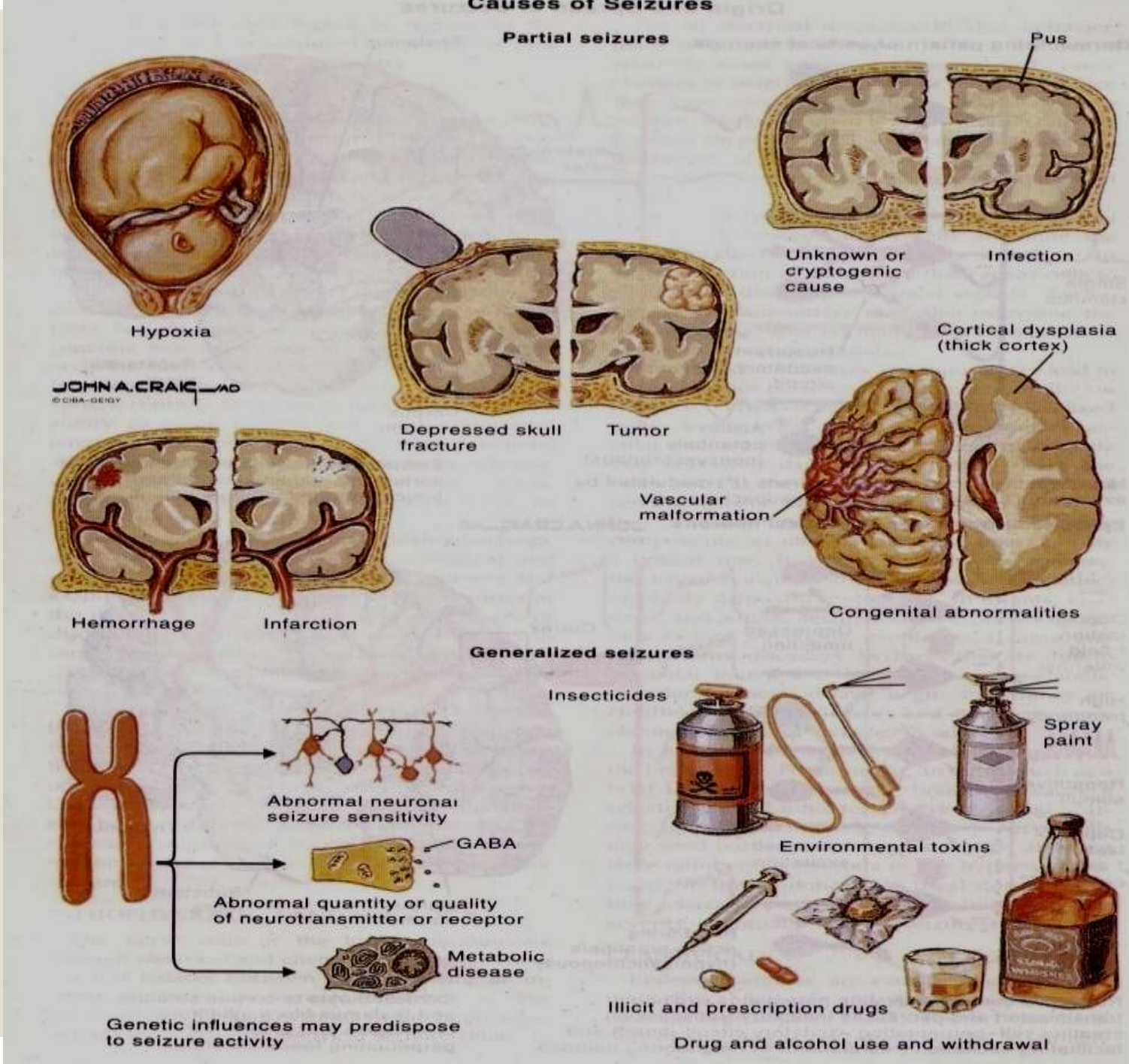
Etiologi Epilepsi

Symptomatic or Cryptogenic (23%)



Primary – Idiopathic (77%)

- Primary - Idiopathic
- Cerebrovascular
- CNS Neoplasma
- Congenital CNS Malformation
- Trauma
- CNS Infection
- Other known
- Birth asphyxia


Causes of Seizures
Partial seizures
Pus
Hypoxia
Unknown or cryptogenic cause
Infection
JOHN A. CRAIG M.D.
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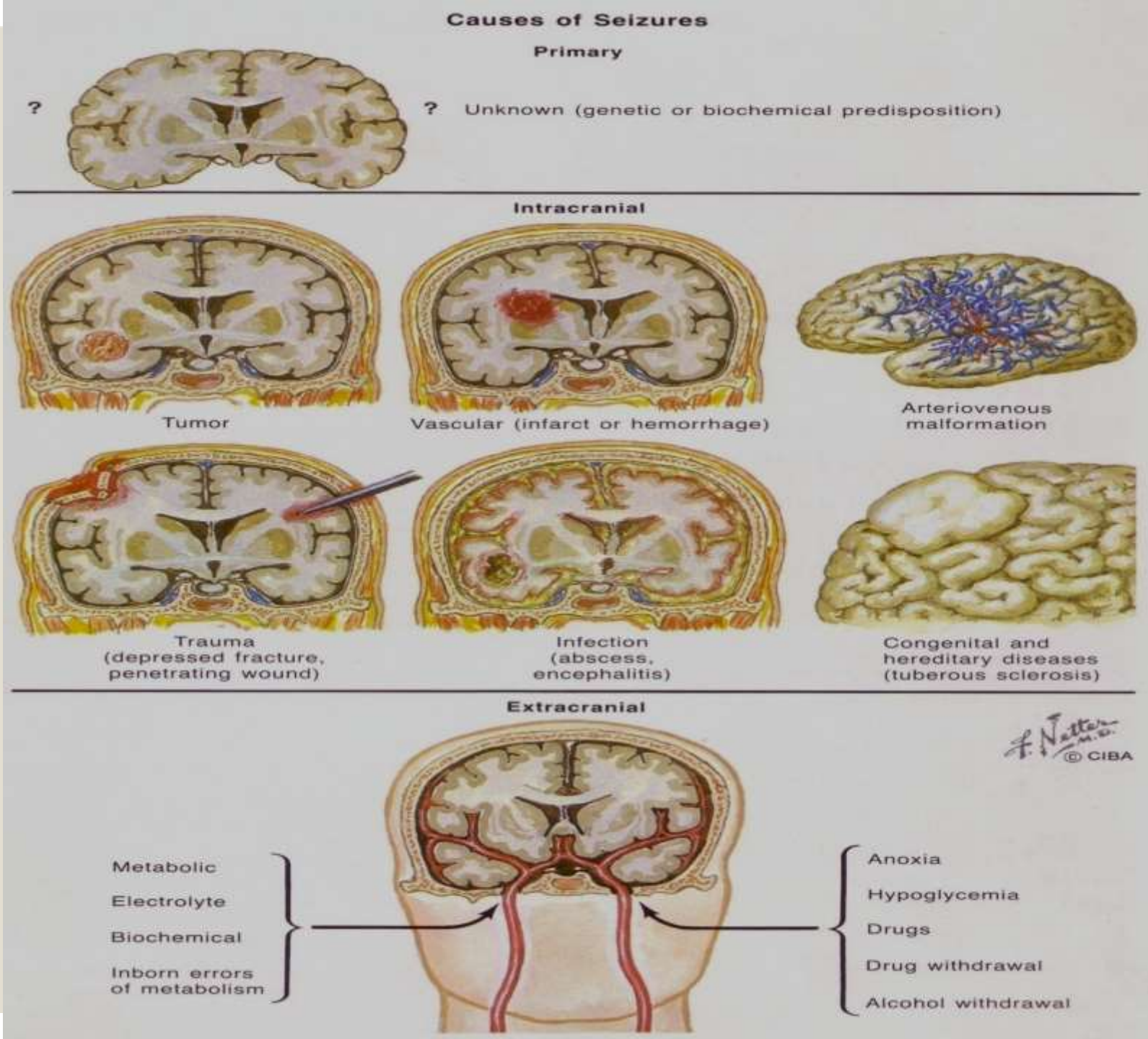
Depressed skull fracture
Tumor
Cortical dysplasia (thick cortex)
Vascular malformation
Hemorrhage
Infarction
Congenital abnormalities
Generalized seizures
Insecticides
Spray paint
Abnormal neuronal seizure sensitivity
GABA
Environmental toxins
Abnormal quantity or quality of neurotransmitter or receptor
Metabolic disease
Illicit and prescription drugs
Genetic influences may predispose to seizure activity
Drug and alcohol use and withdrawal


Causes of Seizures
Primary
?
?
Unknown (genetic or biochemical predisposition)
Intracranial
Tumor
Vascular (infarct or hemorrhage)
Arteriovenous malformation
Trauma (depressed fracture, penetrating wound)
Infection (abscess, encephalitis)
Congenital and hereditary diseases (tuberous sclerosis)
Extracranial
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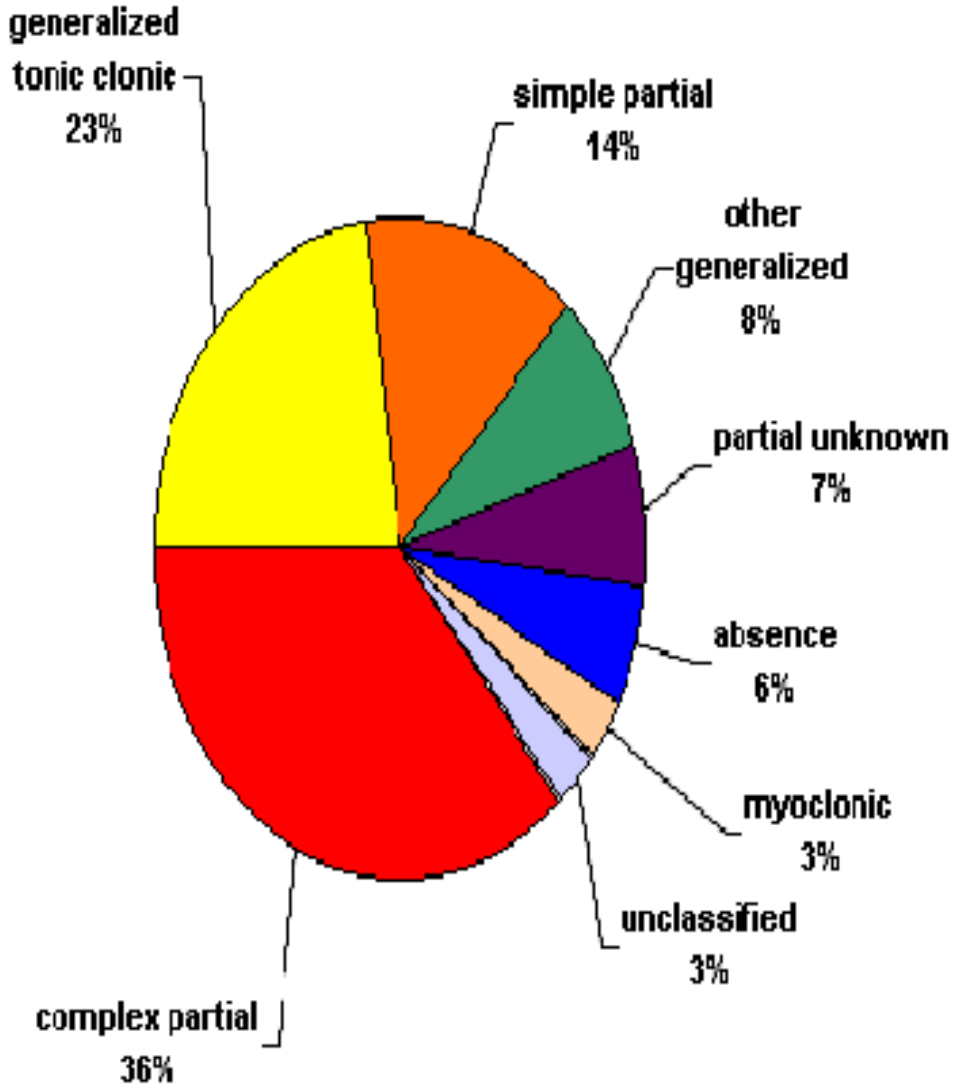
Metabolic
Electrolyte
Biochemical
Inborn errors of metabolism
Anoxia
Hypoglycemia
Drugs
Drug withdrawal
Alcohol withdrawal

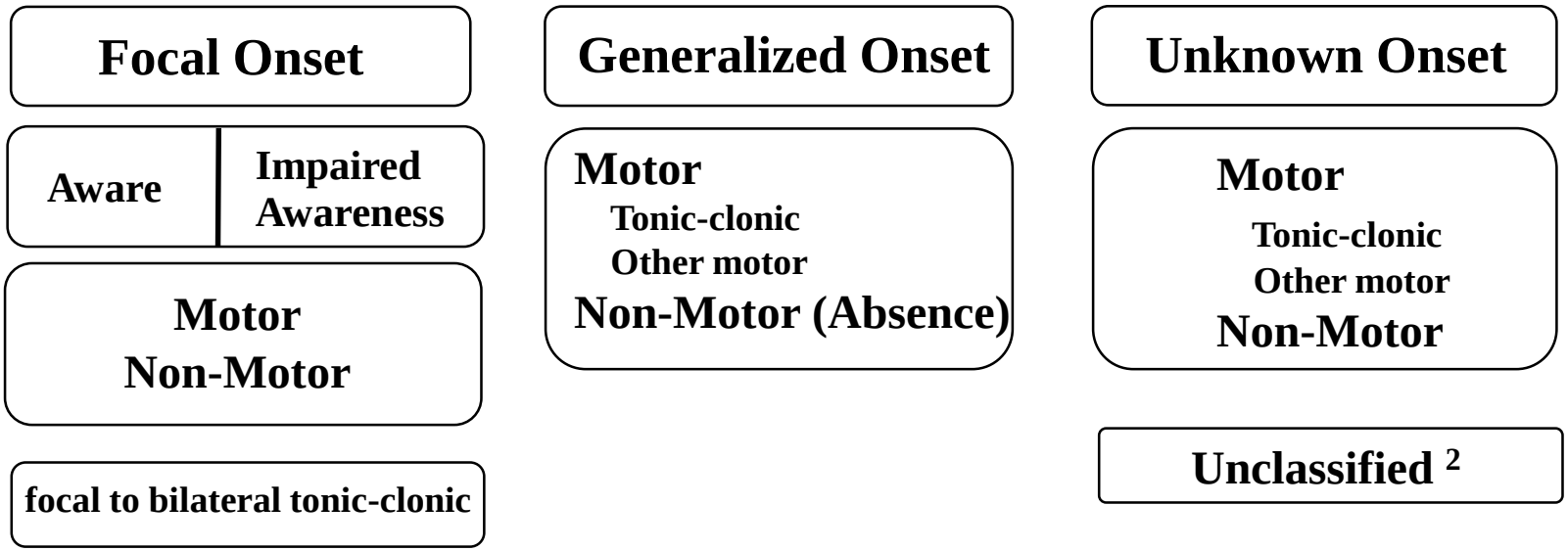
KLASIFIKASI EPILEPSI

Berdasarkan tanda klinik dan hasil EEG, kejang dibagi :

- Kejang umum (genelized seizure) : aktivasi terjadi pada kedua hemisfere otak secara bersama-sama
- Kejang parsial / focal : jika dimulai dari bagian tertentu di otak.



ILAE 2017 Classification of Seizure Types Basic Version [1]



[1] Definitions, other seizure types and descriptors are listed in the accompanying paper & glossary of terms

[2] Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi: 10.1111/epi.13671*

ILAE 2017 Classification of Seizure Types Expanded Version[1]

Focal Onset

Aware	Impaired Awareness

Motor Onset
- automatisms
- atonic[2]
- clonic
- epileptic spasms[2]
- hyperkinetic
- myoclonic
- tonic

Non-Motor Onset
- autonomic
- behavior arrest
- cognitive
- emotional
- sensory

focal to bilateral tonic-clonic

Generalized Onset

Motor
- tonic-clonic
- clonic
- tonic
- myoclonic
- myoclonic-tonic-clonic
- myoclonic-atonic
- atonic
- epileptic spasms[2]

Non-Motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown Onset

Motor
- tonic-clonic
- epileptic spasms

Non-Motor
- behavior arrest

Unclassified[3]

1 Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.

2 These could be focal or generalized, with or without alteration of awareness

3 Due to inadequate information or inability to place in other categories

From *Fisher et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia doi:*

MEKANISME SEIZURE PD EPILEPSI

- Neuron :

  Neuron epileptik mencetuskan letupan depolarisasi paroxysmal yg merubah potensial membran, berulang-ulang, IPSP hilang dan letupan depolarisasi abnormal menjalar ke sel sekitar

- Kanal ion :

  Terjadi defect pada transmisi sinap antar neuron

PRINSIP TERAPI EPILEPSI

- Mencegah penyebaran seizure ke neuron yang masih normal
- Meningkatkan nilai ambang neuron epileptik

Pd umumnya obat antikonvulsan dapat menghilangkan gejala (seizure)→50%, sebagian seizure dapat ditekan sehingga tidak menyebar

TATA LAKSANA EPILEPSI

- **Non – farmakologis**
  - cari dan hindari faktor pemicu (jika ada) : stress, OR, kopi, alkohol, sulit tidur, terlambat makan

- **Farmakologis :**
  - dengan obat antiepilepsi / antikonvulsi

Generasi I- Antiepileptic drug

Drug*	Presumed main mechanism of action	Approved use (FDA, EMA)	Main uses	Main limitations
Potassium bromide (1857)	GABA potentiation?	Generalized tonic-clonic seizures, myoclonic seizures	Focal and generalized seizures	Currently for adjunctive use only, not in wide use anymore, sedative
Phenobarbital (1912)	GABA potentiation	Partial and generalized convulsive seizures, sedation, anxiety disorders, sleep disorders	Focal and generalized seizures (intravenous); most cost effective treatment for epilepsy, particularly in low resource countries	Enzyme inducer, not useful in absence seizures, skin hypersensitivity. Less effective than carbamazepine or phenytoin for focal seizures in mostly new onset epilepsy
Phenytoin (1938)	Na^+ channel blocker	Partial and generalized convulsive seizures	First line drug (intravenous) for focal and generalized seizures with focal onset; similar efficacy to carbamazepine[42]	Enzyme inducer, non-linear pharmacokinetics. Not useful for absence or myoclonic seizures; skin hypersensitivity
Primidone (1954)	GABA potentiation	Partial and generalized convulsive seizures	Focal and generalized seizures	Enzyme inducer, not useful in absence seizures, sedative, skin hypersensitivity. Less effective than carbamazepine or phenytoin for focal seizures in new onset epilepsy
Ethosuximide (1958)	T-type Ca^{2+} channel blocker	Absence seizures	First line antiepileptic drug, no skin hypersensitivity. Use for absence seizures only. As effective as valproate for new onset absence seizures	Gastrointestinal adverse effects, insomnia, psychotic episodes

Generasi II –Antiepileptic drug

Drug*	Presumed main mechanism of action	Approved use (FDA, EMA)	Main uses	Main limitations
Diazepam (1963)	GABA potentiation	Convulsive disorders, status epilepticus, anxiety, alcohol withdrawal	Intravenous use, no clinical hepatotoxicity, no skin hypersensitivity, use for focal and generalized seizures	Currently for adjunctive use and emergency use only, sedative, substantial tolerance (loss of efficacy)
Carbamazepine (1964)	Na^+ channel blockade	Partial and generalized convulsive seizures, trigeminal pain, bipolar disorder	First line drug for focal and generalized seizures with focal onset; none of the newer drugs has currently been shown to be more efficacious than carbamazepine	Enzyme inducer, not useful for absence or myoclonic seizures, skin hypersensitivity
Valproate (1967)	Multiple (for example, GABA potentiation, glutamate (NMDA) inhibition, sodium channel and T-type calcium channel blockade)	Partial and generalized convulsive seizures, absence seizures, migraine prophylaxis, bipolar disorder	First line drug (used intravenously) for focal and generalized seizures; none of the newer drugs has cuurently been shown to be more efficacious than valproate; no skin hypersensitivity	Enzyme inhibitor, substantial teratogenicity, weight gain
Clonazepam (1968)	GABA potentiation	Lennox-Gastaut syndrome, myoclonic seizures, panic disorders	No clinical hepatotoxicity, use for focal and generalized seizures	Currently for adjunctive use only, sedative, substantial tolerance (loss of efficacy)
Clobazam (1975)	GABA potentiation	Lennox-Gastaut syndrome, anxiety disorders	No clinical hepatotoxicity. Use for focal and generalized seizures	Currently for adjunctive use only, sedative, substantial tolerance (loss of efficacy)

Generasi III- Antiepileptic drug (1)

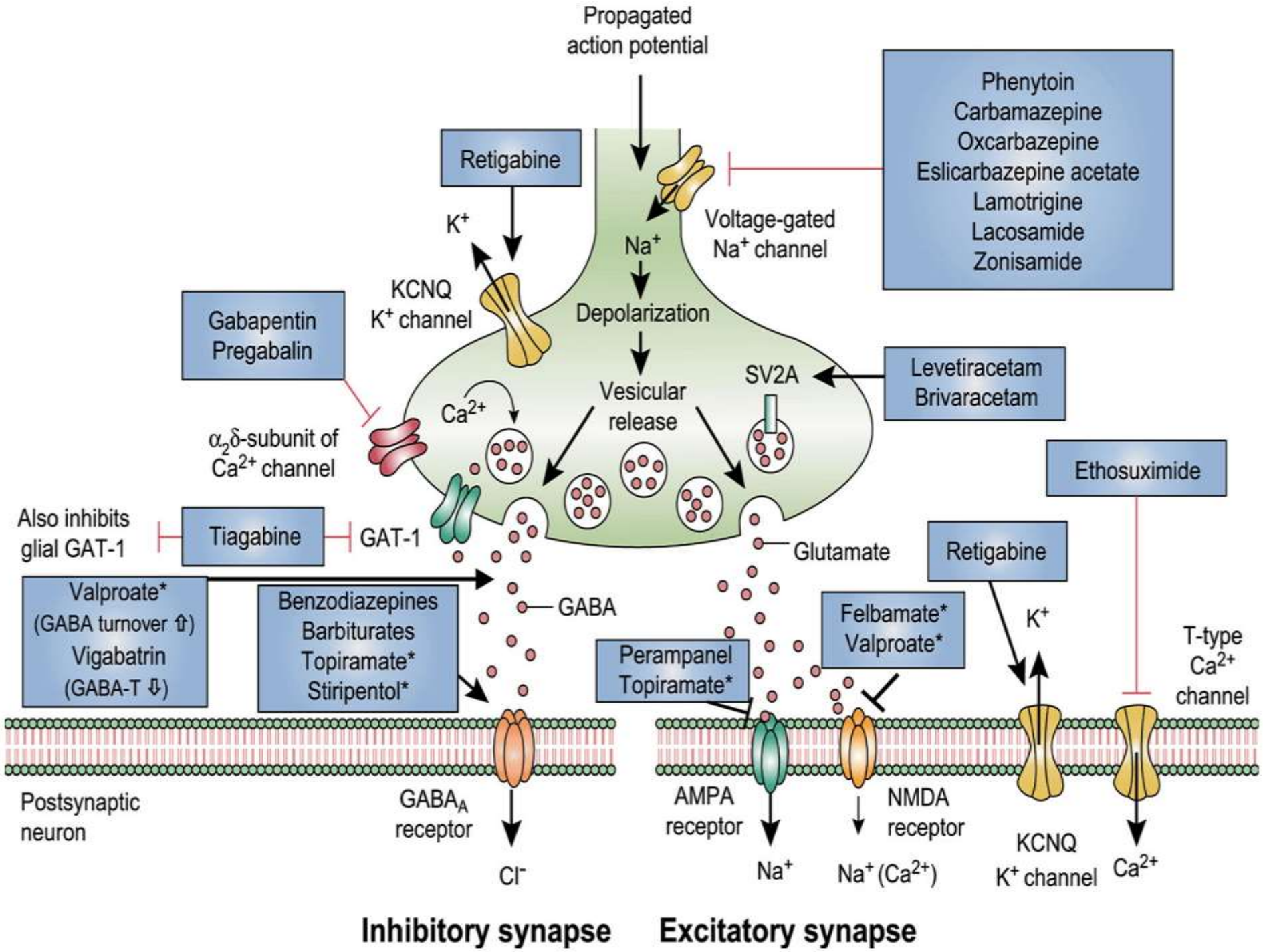
Drug*	Presumed main mechanism of action	Approved use (FDA, EMA)	Main uses	Main limitations
Vigabatrin (1989)	GABA potentiation	Infantile spasms, complex partial seizures (currently for adjunctive use only)	No clinical hepatotoxicity. Use for infantile spasms, focal and generalized seizures with focal onset	Not useful for absence or myoclonic seizures. Causes a visual field defect and weight gain. Not as efficacious as carbamazepine for focal seizures
Lamotrigine (1990)	Na^+ channel blocker	Partial and generalized convulsive seizures, Lennox-Gastaut syndrome, bipolar disorder	First line drug for focal and generalized seizures	Enzyme inducer, skin hypersensitivity. Not as effective as valproate for new onset absence seizures
Oxcarbazepine (1990)	Na^+ channel blocker	Partial seizures	First line drug for focal and generalized seizures with focal onset	Enzyme inducer, hyponatremia, skin hypersensitivity. Not useful for absence or myoclonic seizures
Gabapentin (1993)	Ca^{2+} blocker ($\alpha 2\delta$ subunit)	Partial and generalized convulsive seizures, postherpetic and diabetic neuralgia, restless leg syndrome	No clinical hepatotoxicity. Use for focal and generalized seizures with focal onset	Currently for adjunctive use only. Not useful for absence or myoclonic seizures and can cause weight gain. Not as effective as carbamazepine for new onset focal seizures
Topiramate (1995)	Multiple (GABA potentiation, glutamate (AMPA) inhibition, sodium and calcium channel blockade)	Partial and generalized convulsive seizures, Lennox-Gastaut syndrome, migraine prophylaxis	First line drug for focal and generalized seizures. No clinical hepatotoxicity	Cognitive side effects, kidney stones, speech problems, weight loss. Not as effective as carbamazepine for new onset focal seizures
Levetiracetam (2000)	SV2A modulation	Partial and generalized convulsive seizures, partial seizures, GTCS, juvenile myoclonic epilepsy	First line drug (intravenous) for focal and generalized seizures with focal onset and myoclonic seizures. No clinical hepatotoxicity. As efficacious as carbamazepine for new onset focal seizures	Not useful for absence or myoclonic seizures. Psychiatric side effects

Generasi III- Antiepileptic drug (2)

Drug*	Presumed main mechanism of action	Approved use (FDA, EMA)	Main uses	Main limitations
Zonisamide (2000)	Na^+ channel blocker	Partial seizures	First line drug for focal and generalized seizures. No clinical hepatotoxicity. Non-inferior to carbamazepine for new onset focal seizures	Cognitive side effects, kidney stones, sedative, weight loss
Stiripentol (2002)	GABA potentiation, Na^+ channel blocker	Dravet syndrome	Use for seizures in Dravet syndrome. No clinical hepatotoxicity	Currently for adjunctive use only
Pregabalin (2004)	Ca^{2+} blocker ($\alpha 2\delta$ subunit)	Partial seizures, neuropathic pain, generalized anxiety disorder, fibromyalgia	Use for focal and generalized seizures with focal onset. No clinical hepatotoxicity	Currently for adjunctive use only, not useful for absence or myoclonic seizures, weight gain
Rufinamide (2004)	Na^+ channel blockade	Lennox-Gastaut syndrome	Use for seizures in Lennox-Gastaut syndrome. No clinical hepatotoxicity	Currently for adjunctive use only
Lacosamide (2008)	Enhanced slow inactivation of voltage gated Na^+ channels	Partial seizures	Use (intravenous) for focal and generalized seizures with focal onset. No clinical hepatotoxicity	Currently for adjunctive use only
Eslicarbazepine acetate (2009)	Na^+ channel blocker	Partial seizures	Use for focal and generalized seizures with focal onset	Currently for adjunctive use only, enzyme inducer, hyponatremia
Perampanel (2012)	Glutamate (AMPA) antagonist	Partial seizures	Use for focal and generalized seizures with focal onset	Currently for adjunctive use only. Not useful for absence or myoclonic seizures

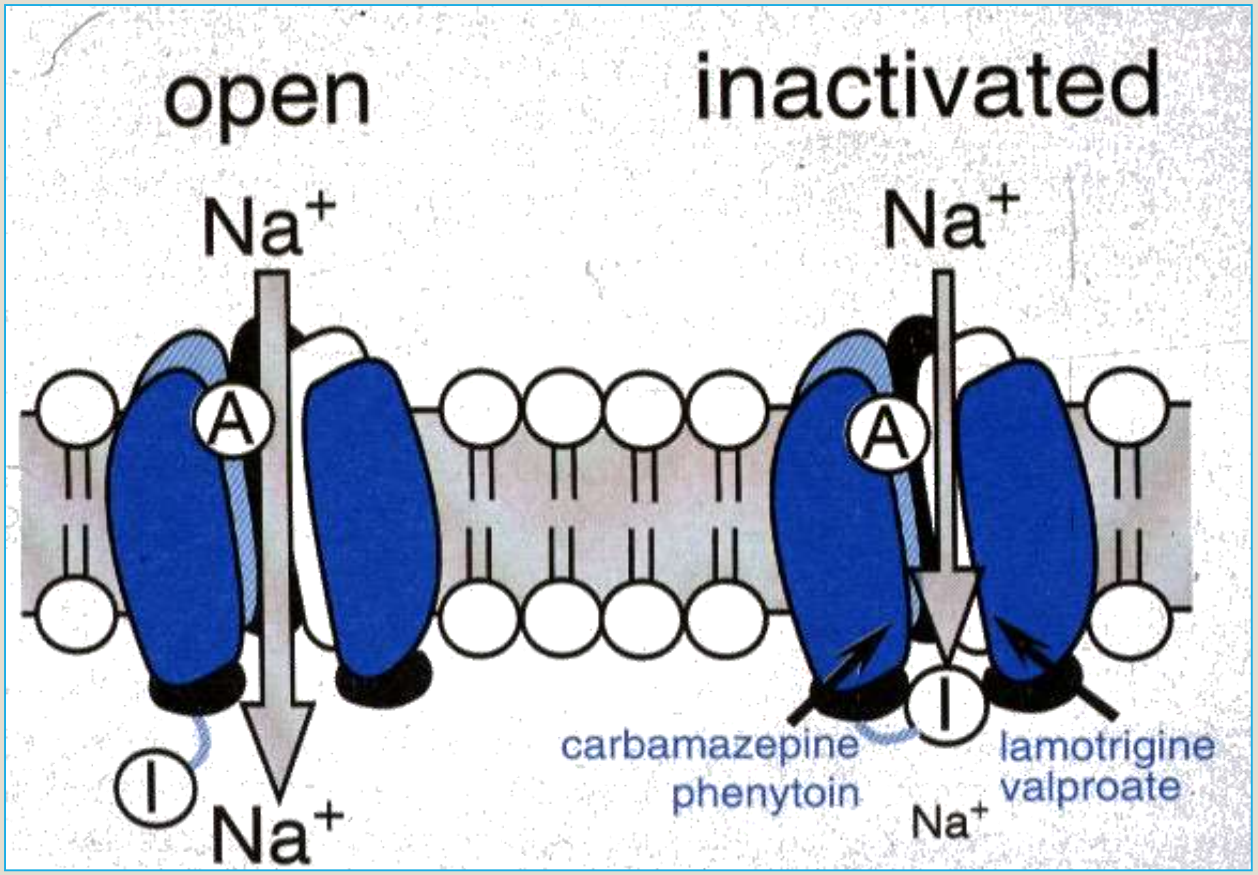
Prinsip Mekanisme kerja Antiepilepsi

- Me ↑ transmisi inhibitory GABA-ergik
  - a. increase GABA
  - c. release GABA ↑
  - d. increase post sinap GABA activity
  - f. inhibit re-uptake GABA (blok GAT-1)
  - g. GABA-Agonist
- Me ↓ transmisi glutamate
  - b. relase glutamate ↓
  - e. block AMPA receptor
- Stabilisation of neuron
  - h. inhibition Na channel - prolong the inactivated stage
  - i. block Ca channel
- Lain-lain
  - j. Activates K channel
  - k. Block SV A
  - l. CRMP-2 inhibitor


Propagated action potential
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Retigabine
K+
Na+
Voltage-gated Na+ channel
KCNQ K+ channel
Depolarization
Gabapentin
Pregabalin
Levetiracetam
Brivaracetam
SV2A
Ca2+
Vesicular release
α2δ-subunit of Ca2+ channel
Ethosuximide
Also inhibits glial GAT-1
Tiagabine
GAT-1
Glutamate
Retigabine
Valproate*
(GABA turnover ⇧)
Vigabatrin
(GABA-T ⇩)
Benzodiazepines
Barbiturates
Topiramate*
Stiripentol*
GABA
Felbamate*
Valproate*
K+
T-type Ca2+ channel
Perampanel
Topiramate*
Postsynaptic neuron
GABAA receptor
AMPA receptor
NMDA receptor
KCNQ K+ channel
Cl-
Na+
Na+ (Ca2+)
Ca2+
Inhibitory synapse
Excitatory synapse

DRUG		↑ GABA activity	↓ Glutamate Activity	Prolong inactivated Na^+ channels	Block T-Ca^{2+} Channels	Other
1.	Phenytoin			✓		
2.	Carbamazepine			✓		
3.	Valproate	✓ (a)		✓	✓	
4.	Lamotrigine		✓ (b)	✓		
5.	Ethosuximide				✓	
6.	Gabapentin	✓ (c)				
7.	Topiramate	✓ (d)	✓ (e)	✓		Activates K^+ Channel
8.	Tiagabine	✓ (f)				
9.	Phenobarbitone	✓ (g)				
10.	Primidone	✓ (g)				
11.	Benzodiazepines	✓ (g)				
12.	Felbamate		✓ (h)			
13.	Levetiracetam					Block SV_2A
14.	Zonisamide			✓	✓	
15.	Lacosamide			✓		CRMP-2 inhibitor
16.	Rufinamide			✓		
17.	Retigabine (Ezogabine)					K^+ channel opener

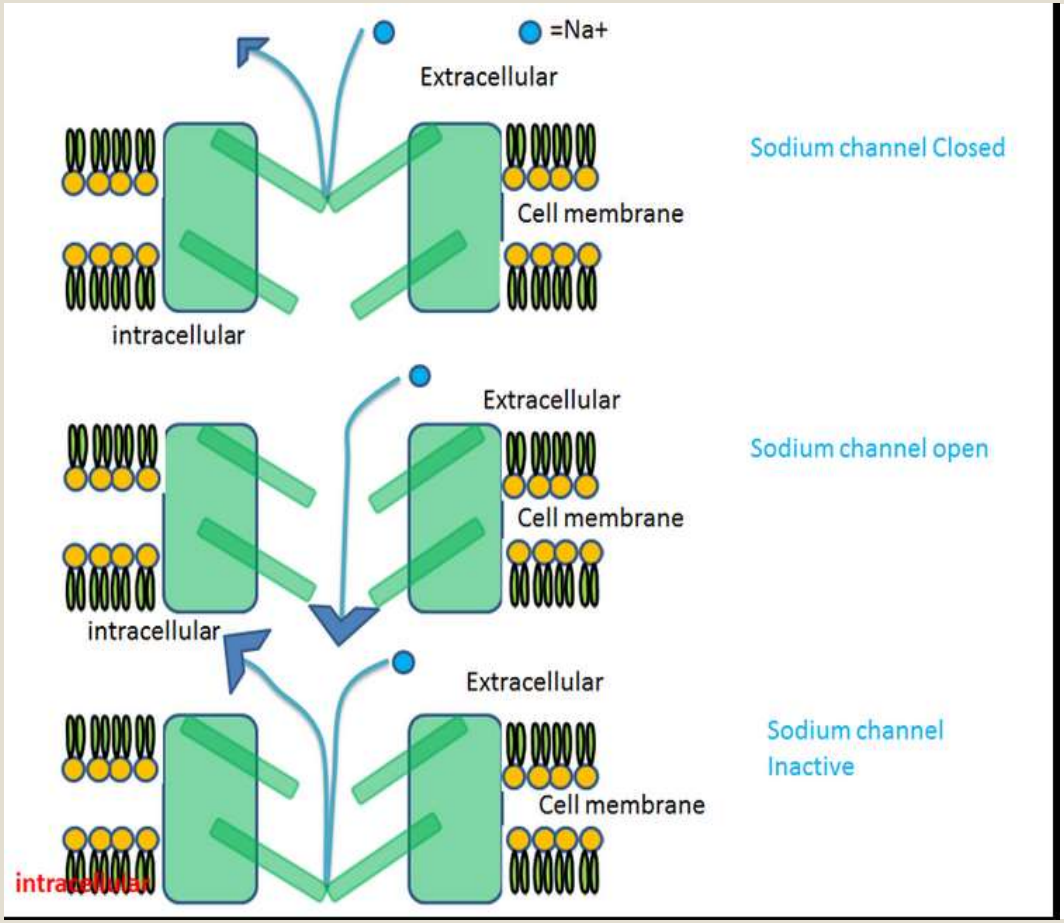
SODIUM CHANNEL BLOCKER



Na terhambat masuk → meningkatkan keadaan steady state-inactivation → tdk terj aksi potensial :

Fenitoin, Karbamazepin, Valproat,, Lamotrigin, Topiramat, Lacosamide

Phenytoin



Action of phenytoin on Na channel

(A) Resting state in which Na channel activation gate (A) is closed

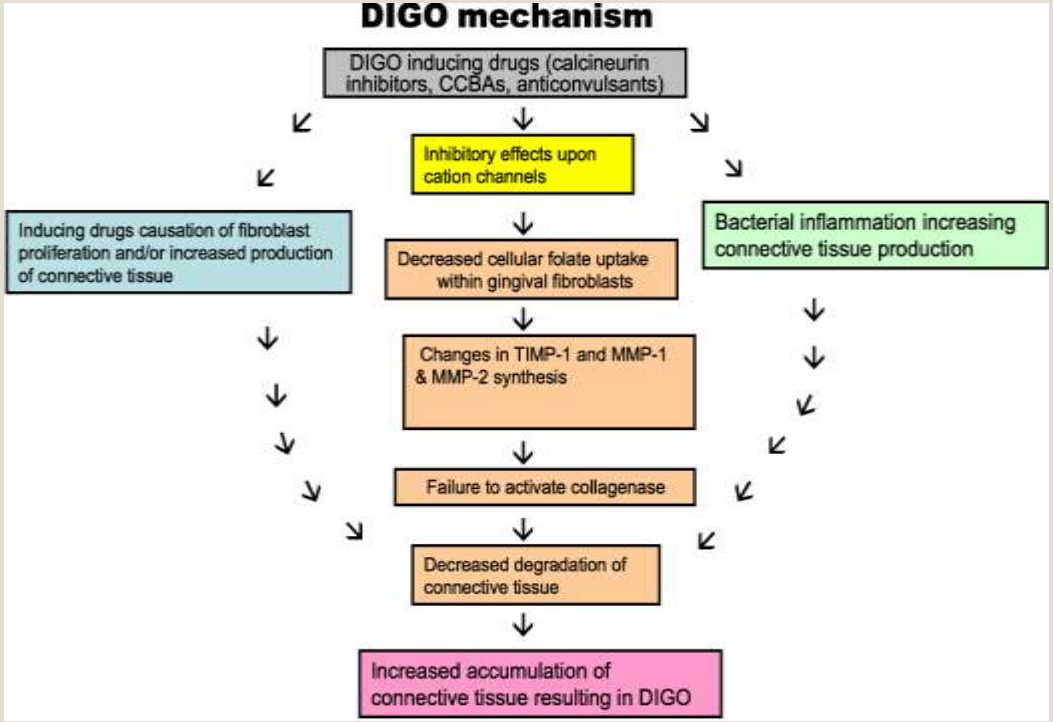
(B) Arrival of an action potential causes depolarization and opening of activation gate (A) and Na flows into the cell.

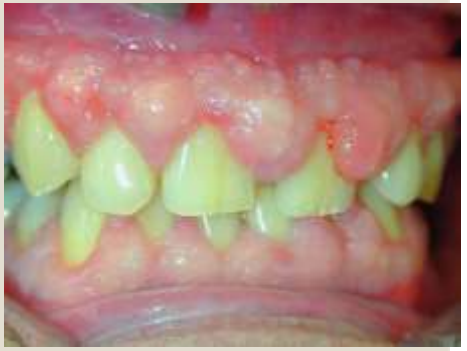
(C) When depolarization continues,an inactivation gate (B) moves into the cell.

Phenytoin prolongs the inactivated gate of the Na channel by preventing the reopening of inactivation gate(B).

Phenytoin (Drug induced gingivalovergrowth/hyperplasia)

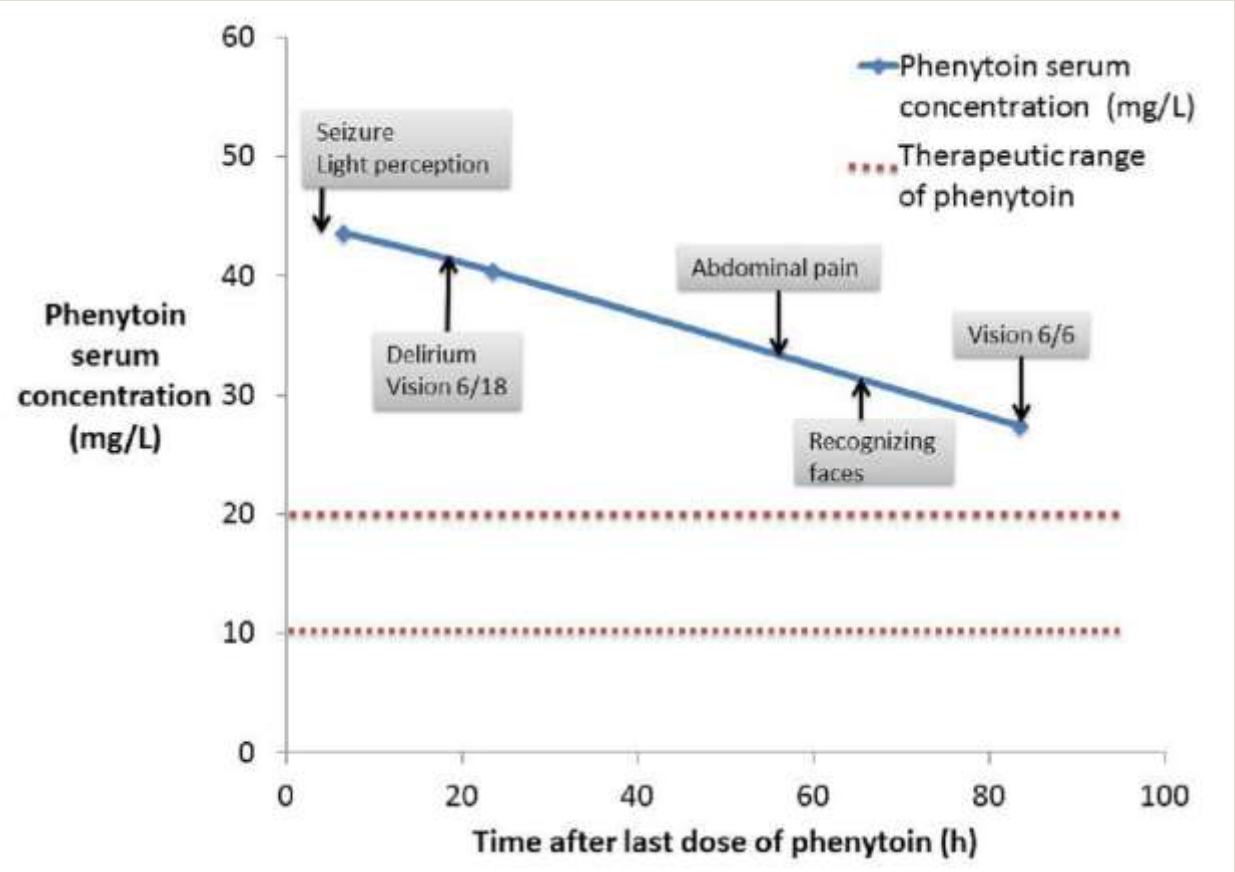
https://pul



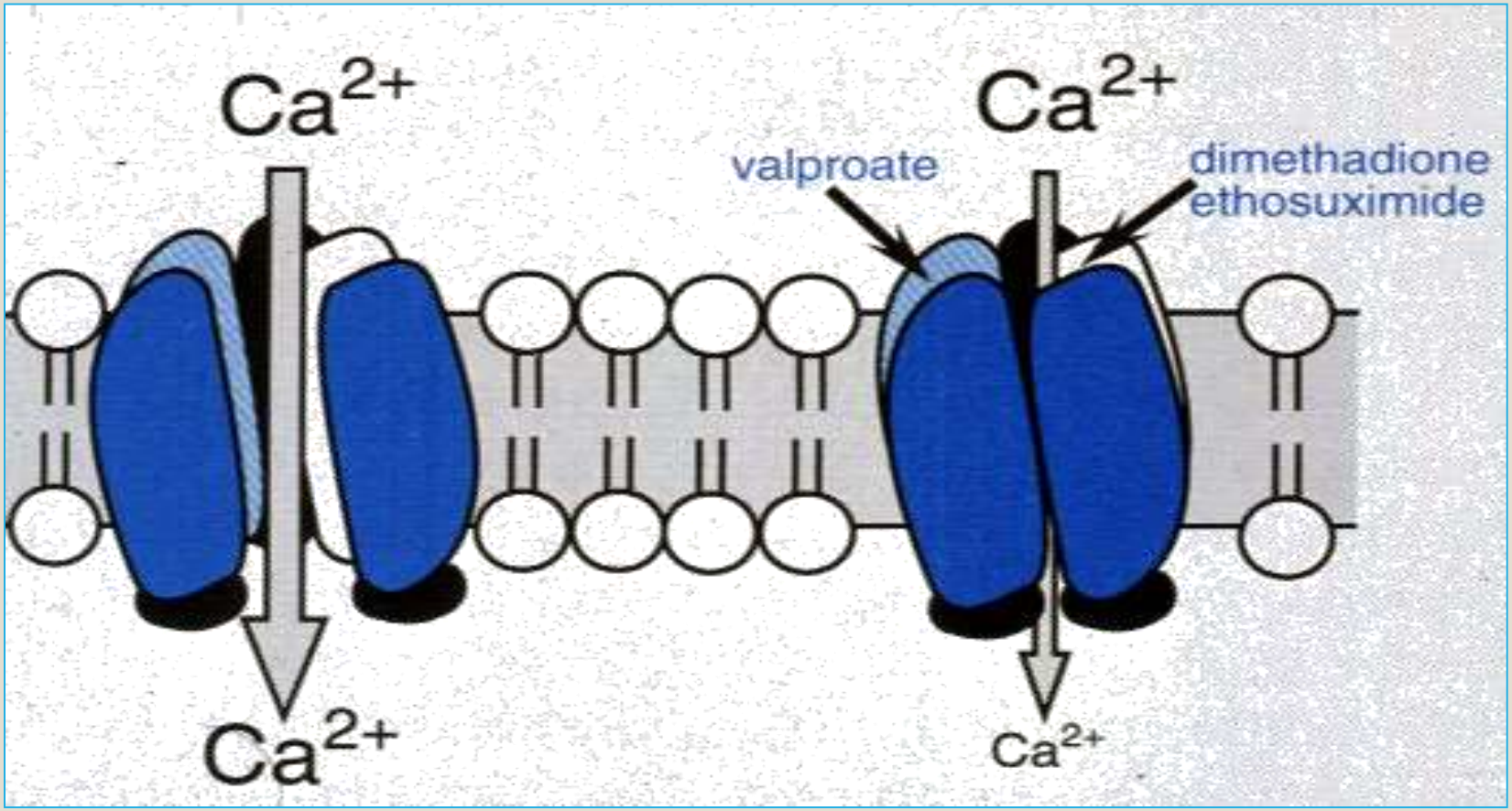


Oral Dis 2015 Jan;21(1):e51-61.
doi: 10.1111/odi.12264. Epub 2014 Aug 7.
Mechanism of drug-induced gingival overgrowth revisited: a unifying hypothesis
R S Brown [1], P R Arany

Intoksikasi Fenitoin



CALCIUM CHANNEL BLOCKER

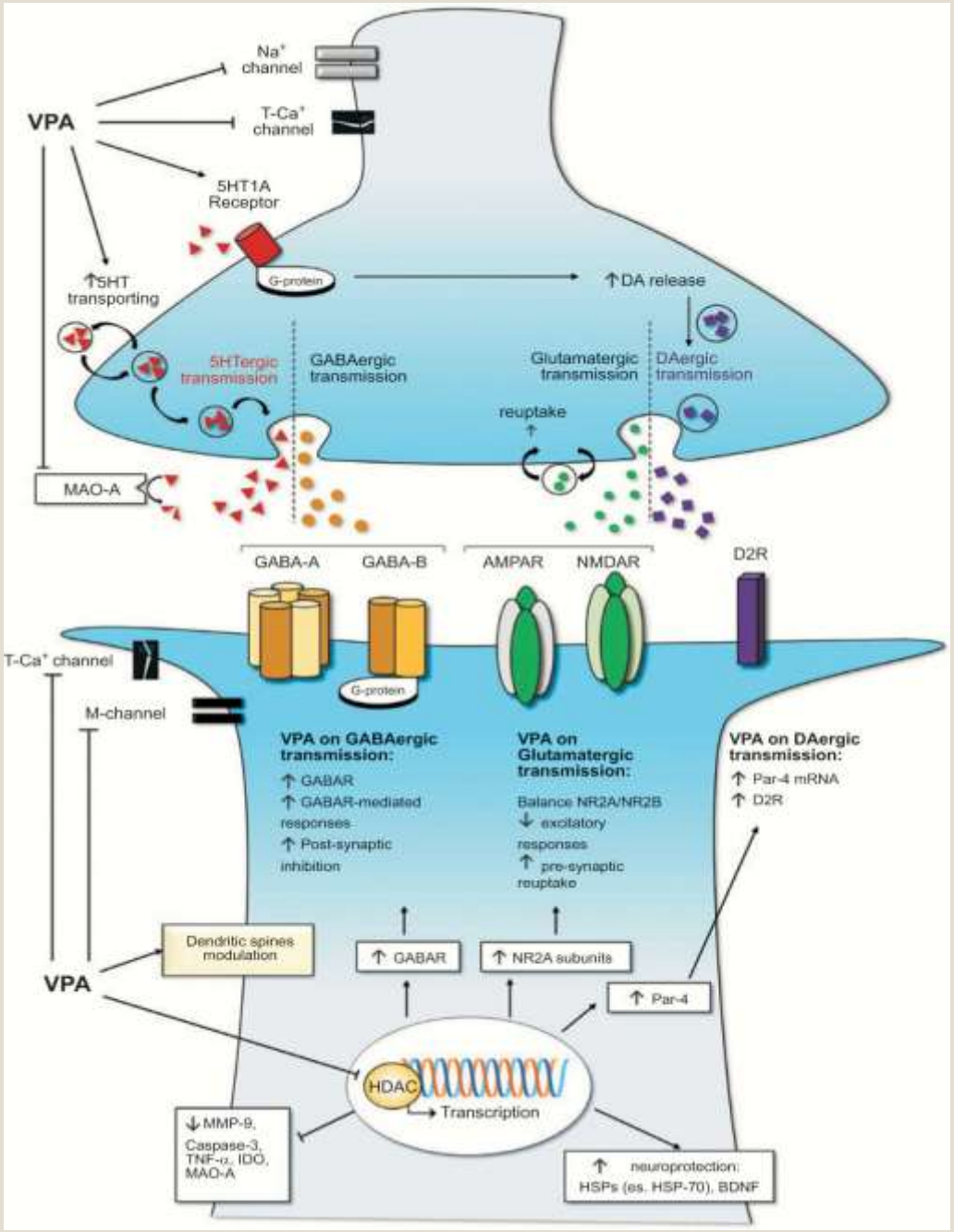


Blok kanal Ca →menurunkan ' the low-threshold calcium current (LTCC) ' atau ' T (transient) current'

Valproat, Ethosuximide, Dimethadione, Lamotrigin

Utk absence seizure, petit mall epilepsy

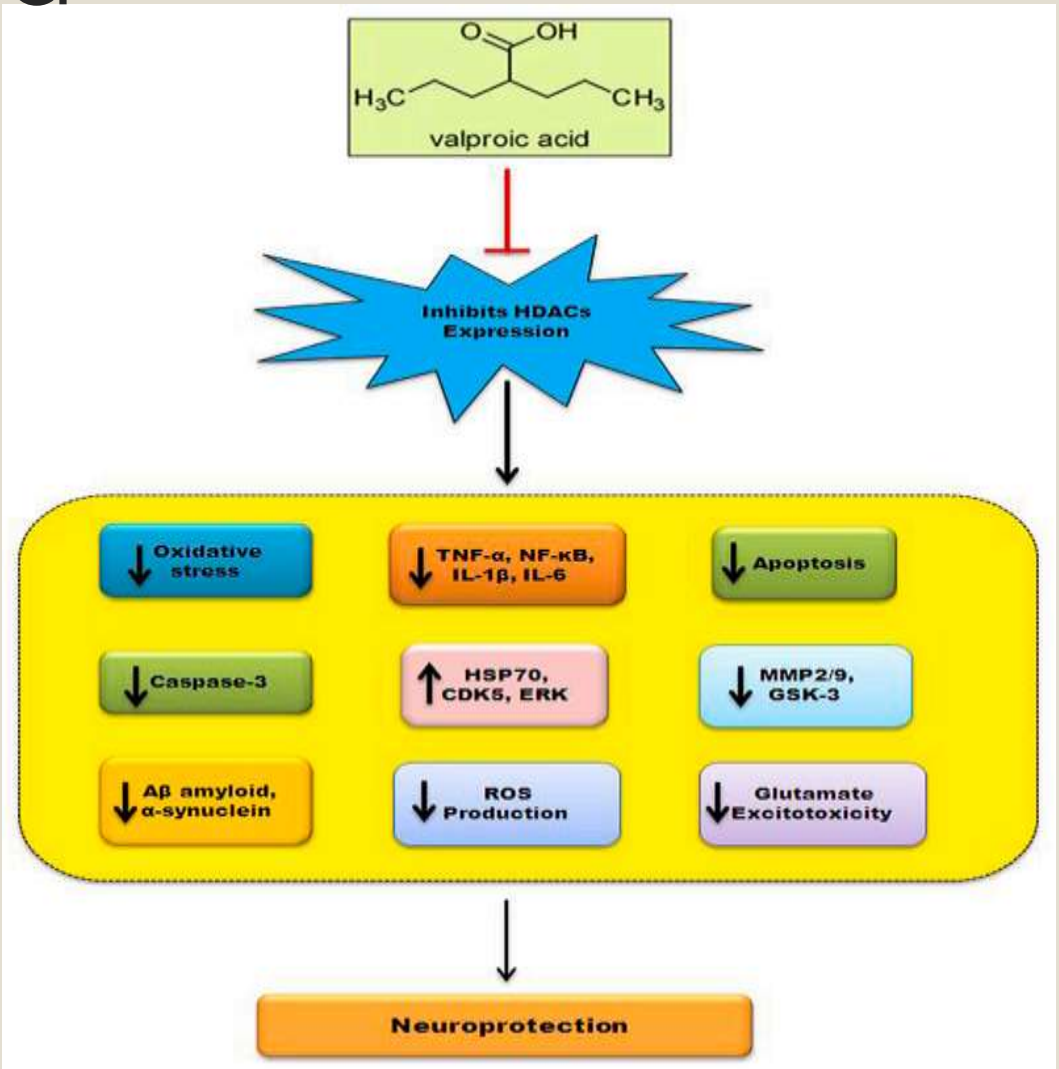
Valproic acid



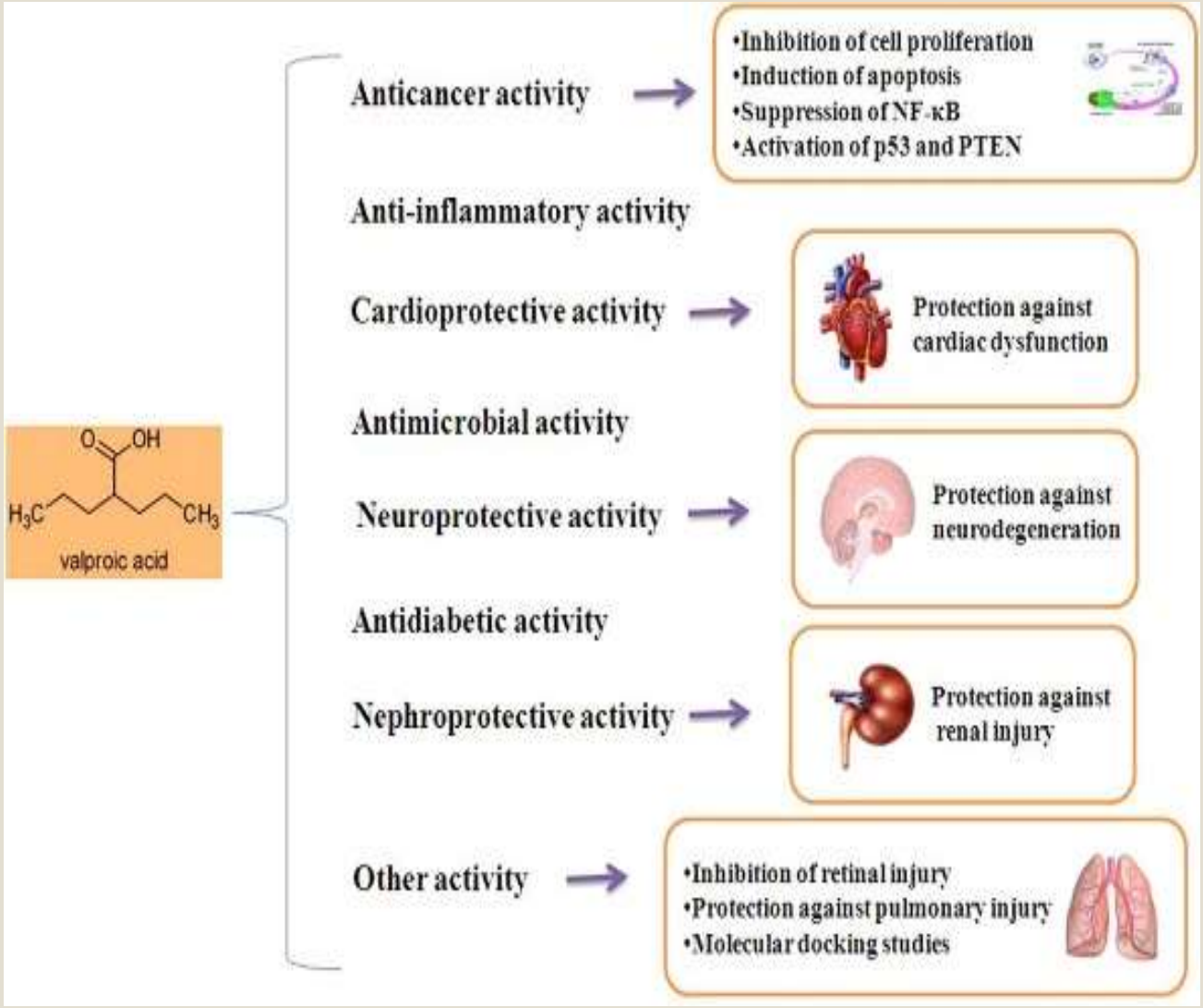
Valproic Acid and Epilepsy: From Molecular Mechanisms to Clinical Evidences
Author(s): Michele Romoli, Petra Mazzocchetti, Renato D'Alonzo, Sabrina Siliquini, Victoria Elisa Rinaldi, Alberto Verrotti, Paolo Calabresi and Cinzia Costa* Volume 17 , Issue 10 , 2019
Page: [926 - 946] **Pages:** 21
DOI: 10.2174/1570159X17666181227165722

Valproic acid (VPA)

- VPA blocks the action of histone deacetylases (HDACs) and leads to transcriptional activation of anti-apoptotic and neuronal surviving pathways like HSP70, AKT, CDK5, ERK, NF-κB, and suppression of caspase-3, TNF-a, IL-1β, IL-6, ROS, and many other factors which cause neuronal death.



Biomedicine & Pharmacotherapy 142 (2021) 112021


O
OH
H3C
CH3
valproic acid
Anticancer activity
•Inhibition of cell proliferation
•Induction of apoptosis
•Suppression of NF-κB
•Activation of p53 and PTEN
Anti-inflammatory activity
Cardioprotective activity
Protection against cardiac dysfunction
Antimicrobial activity
Neuroprotective activity
Protection against neurodegeneration
Antidiabetic activity
Nephroprotective activity
Protection against renal injury
Other activity
•Inhibition of retinal injury
•Protection against pulmonary injury
•Molecular docking studies

Me ↑ transmisi GABA

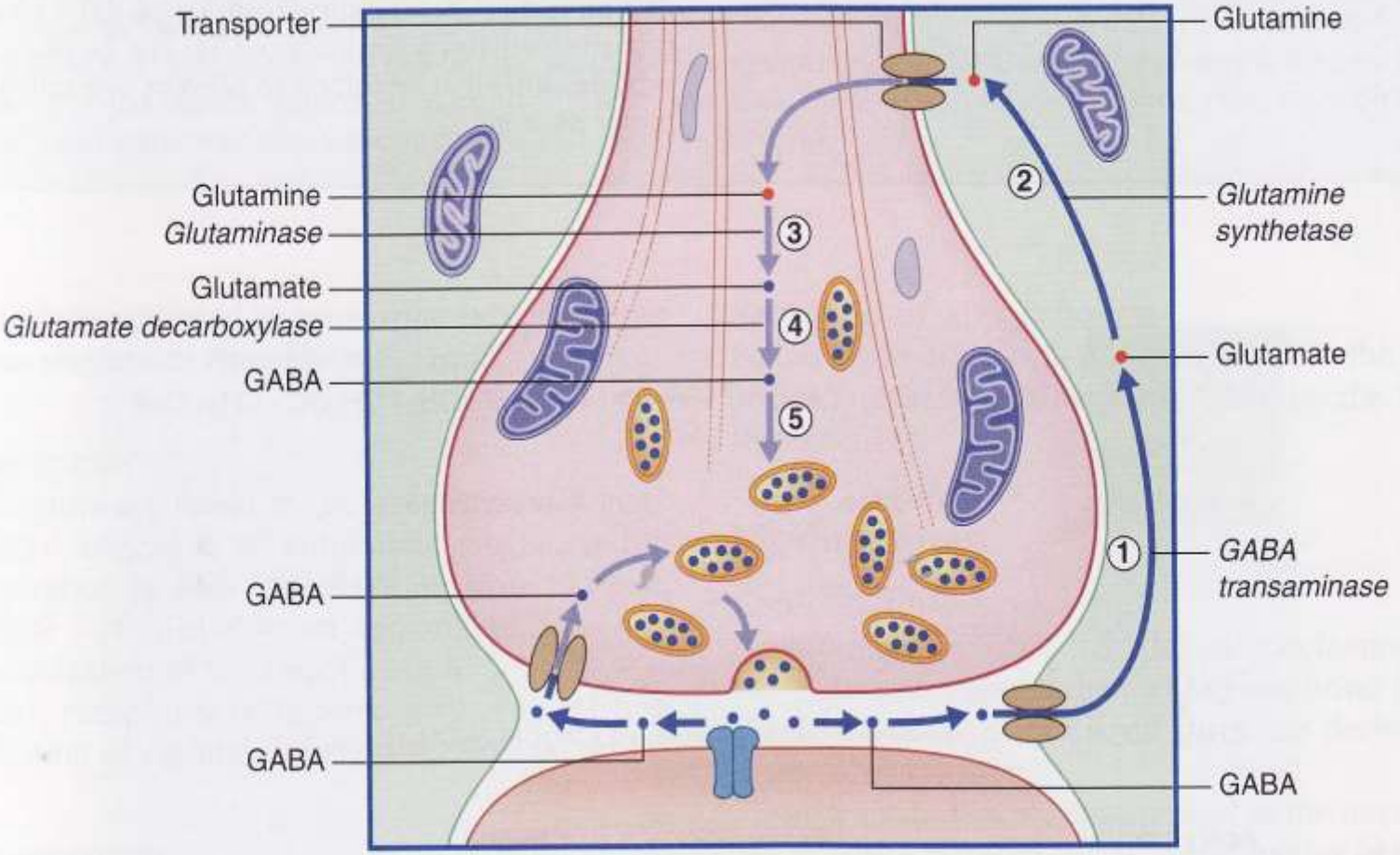
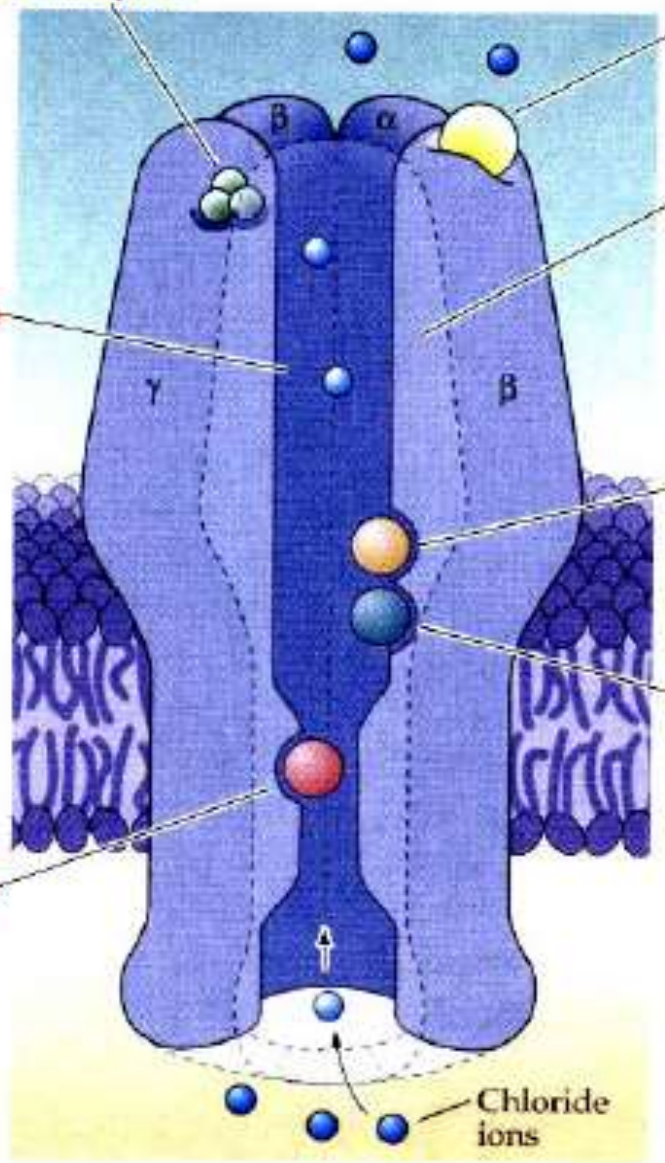


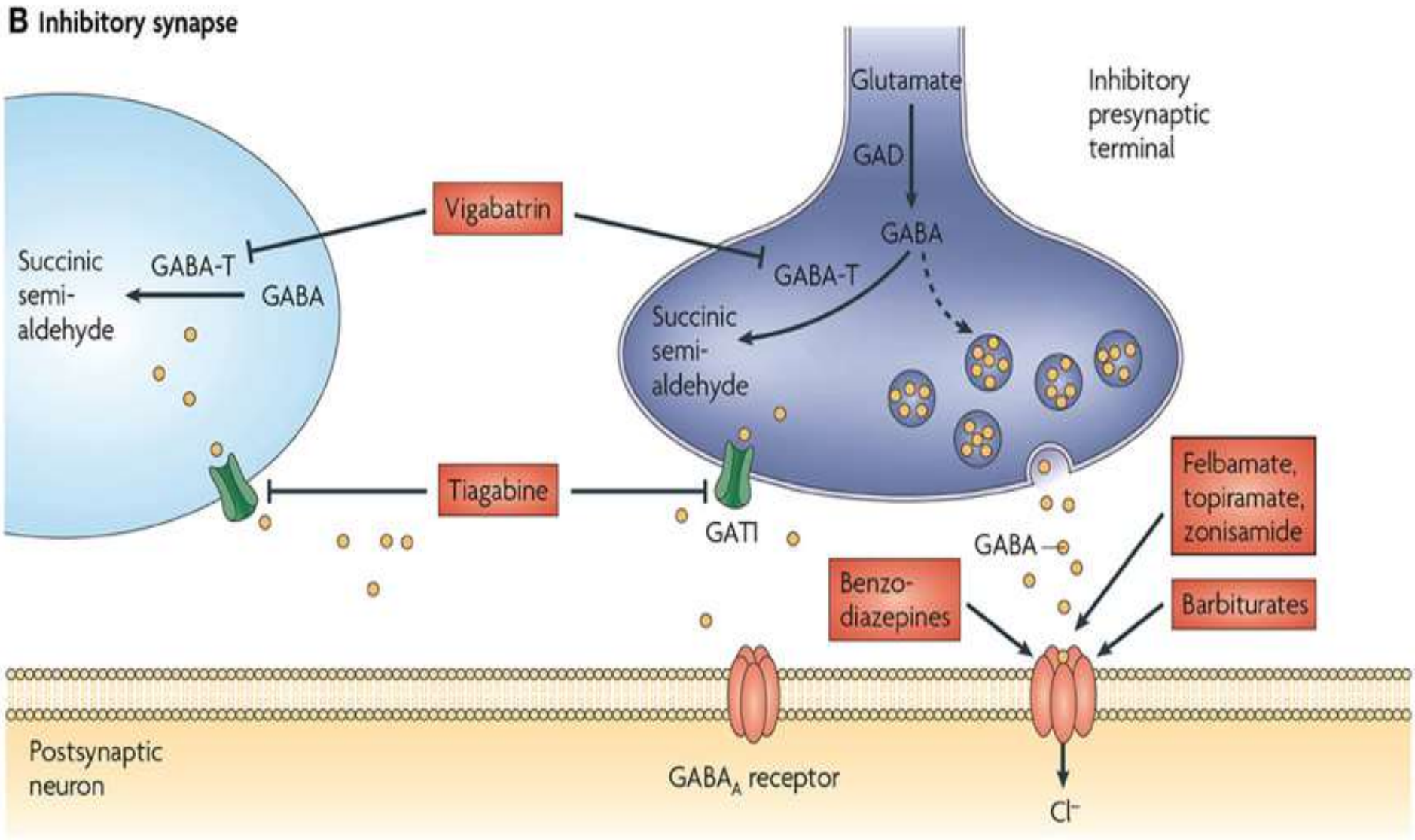
Figure 8.14 GABA reuptake and resynthesis. On the left, GABA molecules are being recycled intact. On the right, GABA is taken up by an astrocyte, then **(1)** GABA is converted to glutamate by GABA transaminase. **(2)** Glutamate is converted to glutamine by glutamine synthetase. **(3)** Glutamine is taken up by the axon and converted to glutamate by glutaminase. **(4)** Glutamate is converted to GABA by glutamate decarboxylase and **(5)** returned to a synaptic vesicle.

Ionotropic GABA Receptors



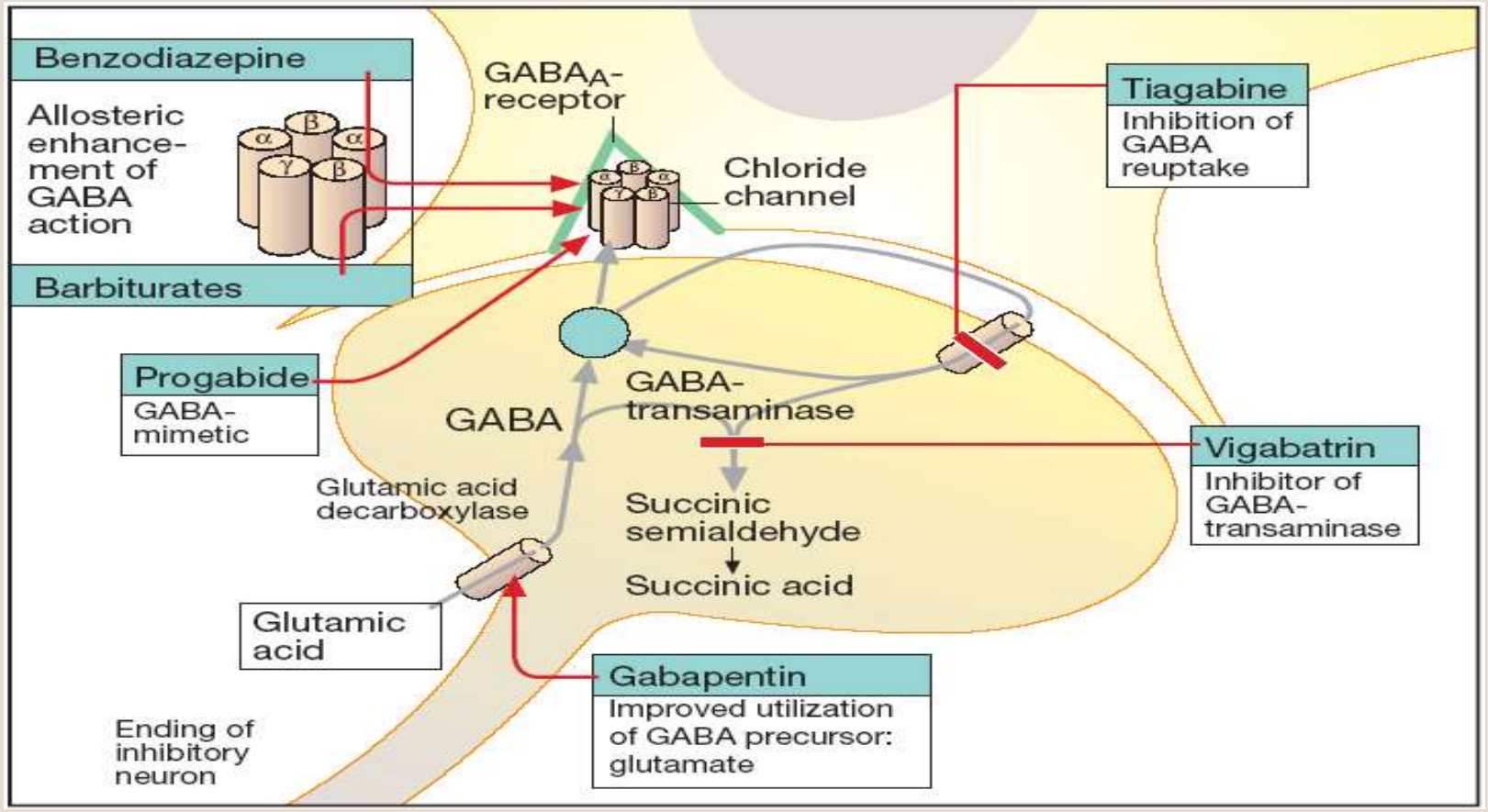
- Pentamers
- Inhibitory in action because the associated channels are permeable to negatively charged Cl^- ions
- Benzodiazepines are allosteric modulators to GABA neurotransmission

Me ↑ transmisi GABA

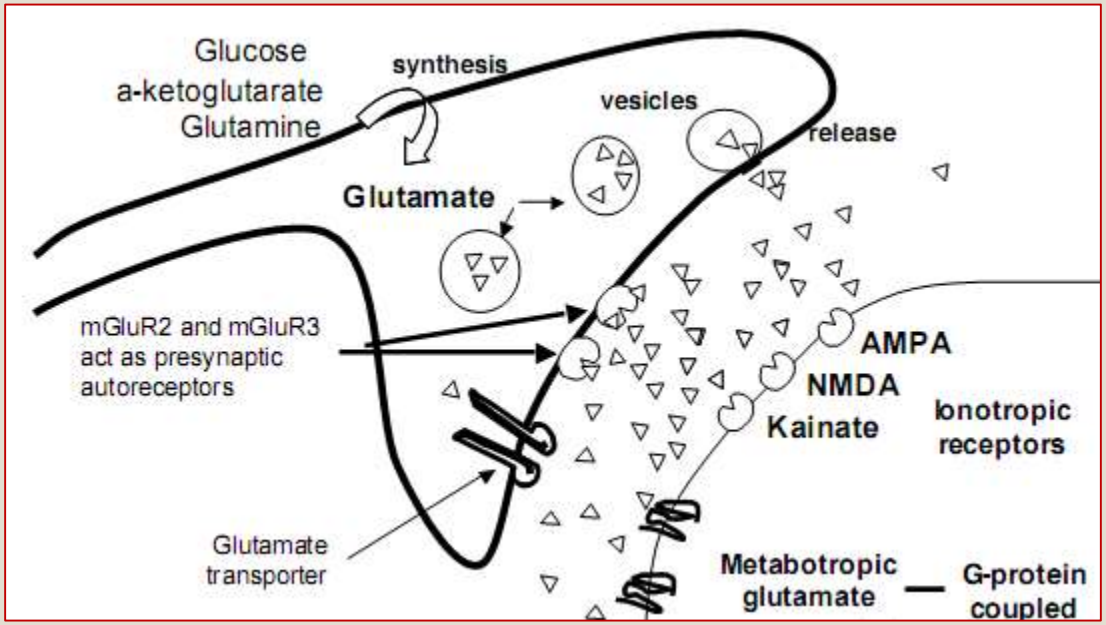


- Agonis GABA :
  - Phenobarbital : mengikat allosteric site GABA-barbiturat receptor → meningktkan aksi GABA-inhibitori : memperpanjang lama terbukanya kanal Cl → hiperpolarisasi,
  - Benzodiazepin : mengikat allosteric site GABA-benzodiazepine receptor → aktivasi R/ GABA : me ↑ frekuensi pembukaan kanal ion Cl → hiperpolarisasi
- Me ↑ kdr GABA dlm CSF, mungkin dg menstimuli release GABA dr non vesikuler pool , Analog GABA, agonis $GABA_B$, : Gabapentin
- Memfasilitasi glutamic acid decarboxylase (GAD), the enzyme responsible for GABA synthesis : Valproate
- menghambat re-uptake GABA ke neuron & glia → GABA di sinap lebih lama : Tiagabin
- Hambat enzim metab GABA-transaminase → konsentr GABA ↑(GABA-T) : Vigarabin, Valproate

Me ↑ transmisi GABA



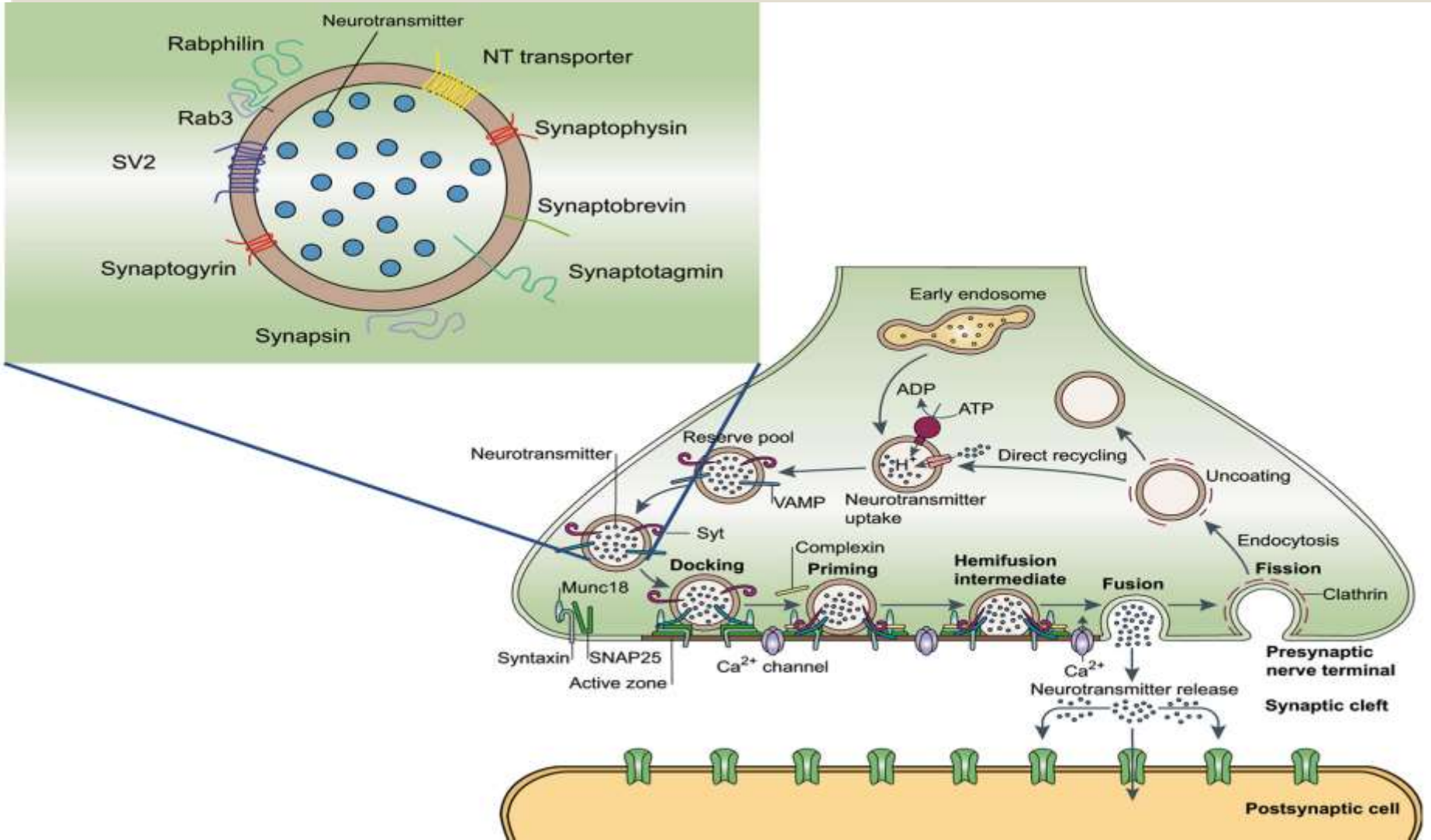
GLUTAMATE NEUROTRANSMISSION



MENGHAMBAT AKSI GLUTAMAT

- Blok R/ NMDA → aksi Glutamat-eksitatori terhambat Phenobarbital, Valproic
- menurunkan release glutamat di sinap : Lamotrigine
- Blok R/ kainate: Topiramate

Synaptic Vesicle Glycoprotein 2A



Levetiracetam

- **modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain.** reduce excitatory neurotransmitter release and enhance synaptic depression during trains of high-frequency activity

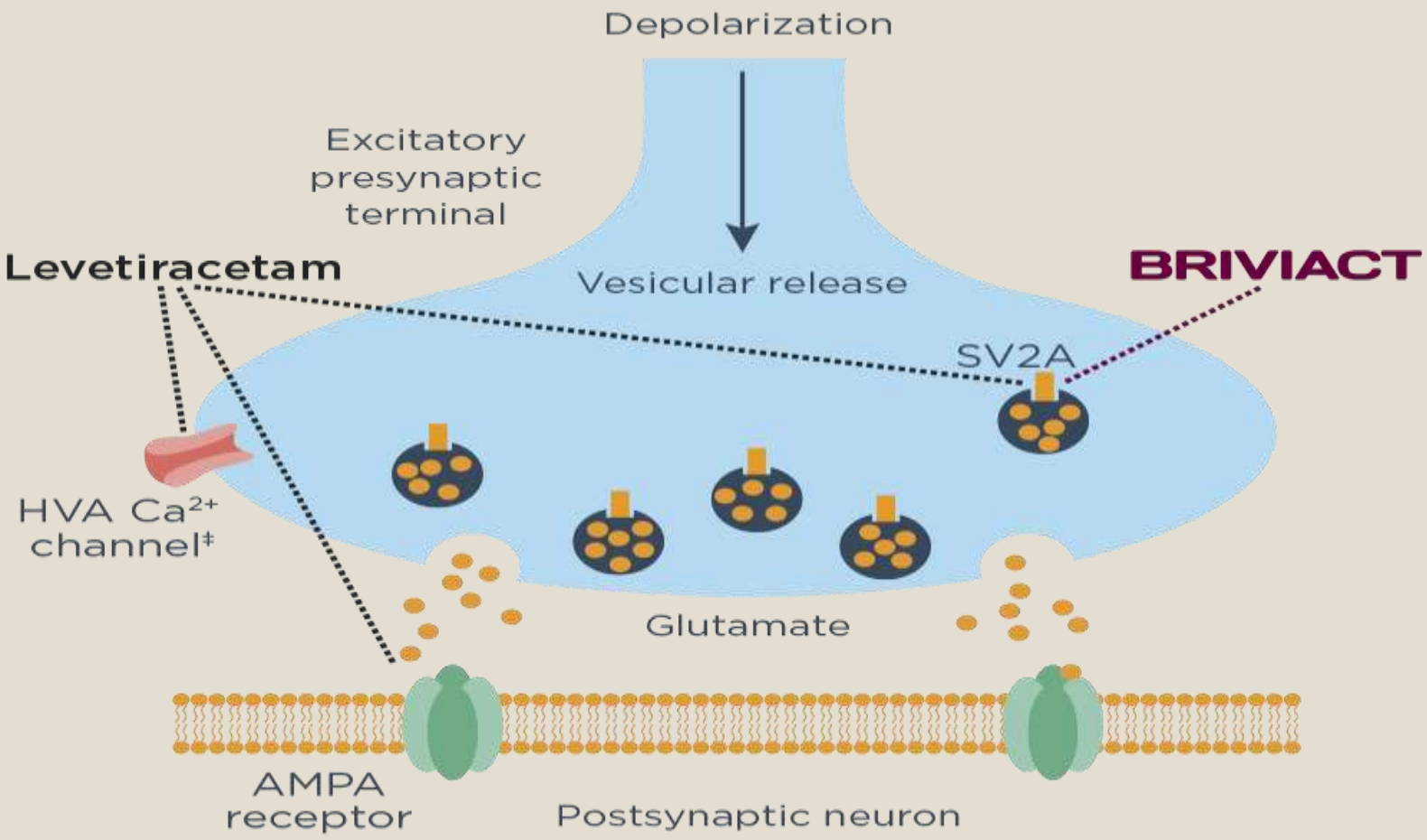
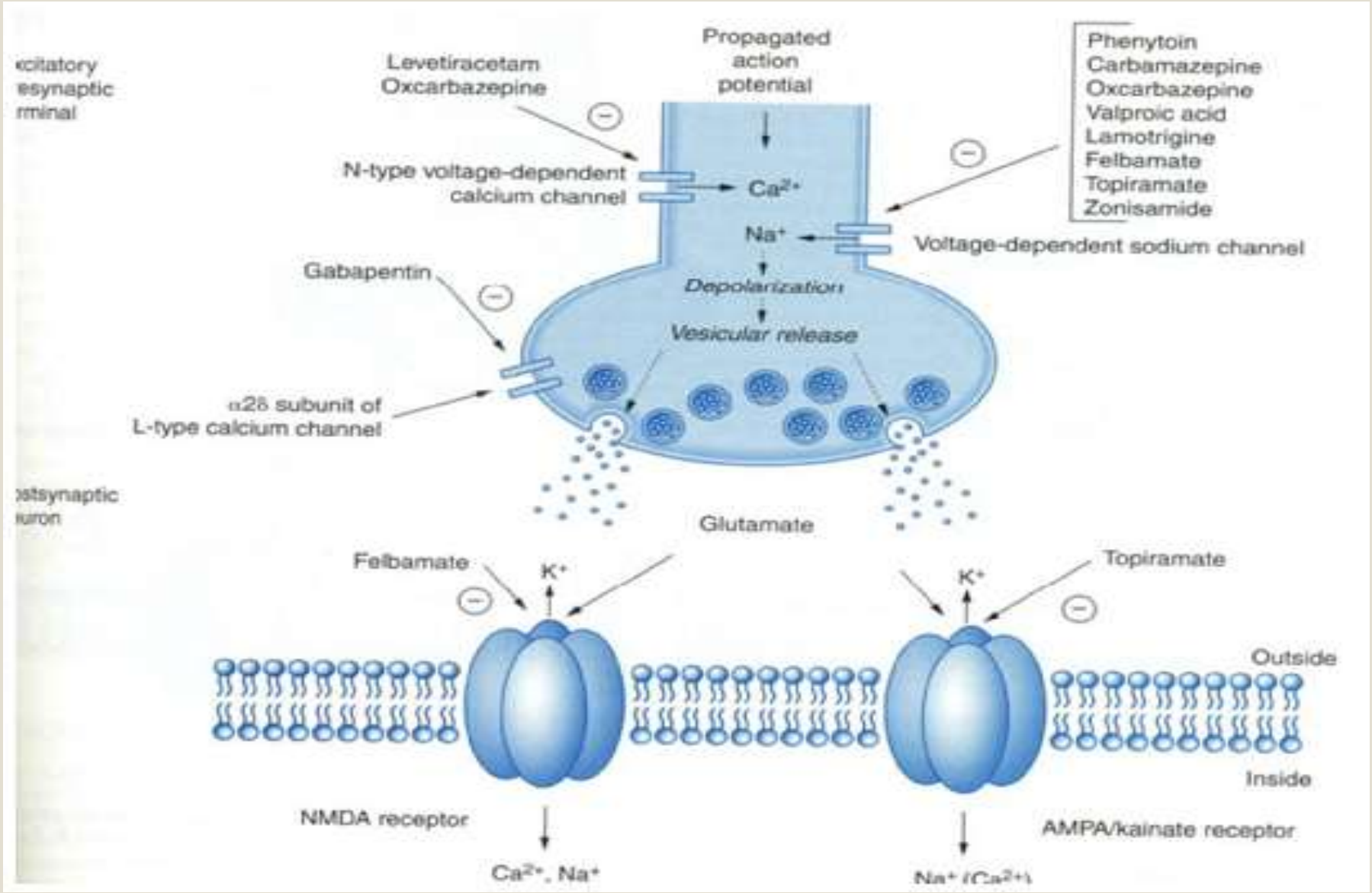
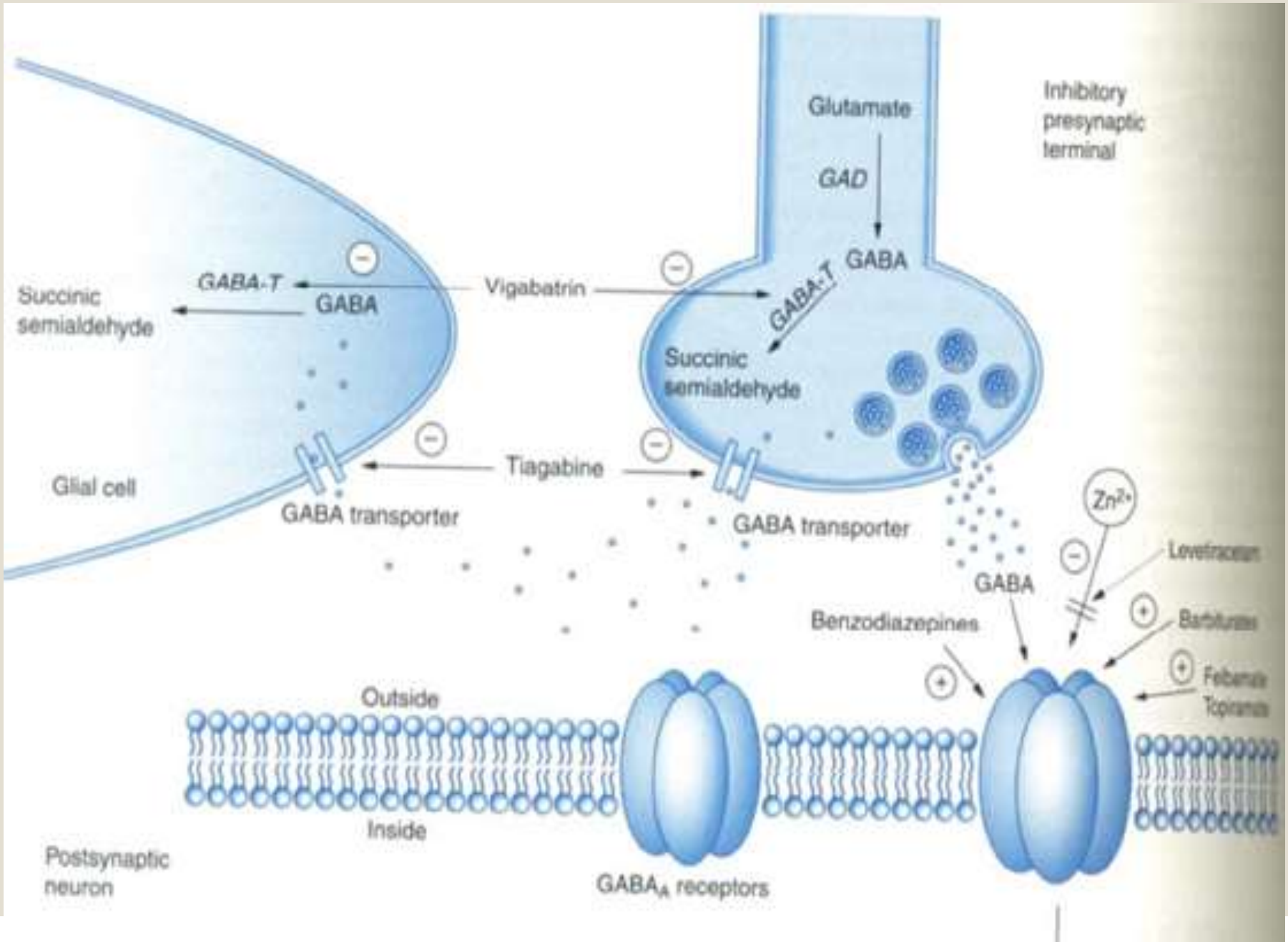


Table 3 Mechanisms of action of anticonvulsant drugs[a]

Drug	Blocks Na^+ channels	Blocks CA^{2+} channels	GABA agonist	Blocks NMDA	Blocks other glutamate
Phenobarbital			♦		
Phenytoin	♦				
Carbamazepine	♦				
Ethosuximide		♦			
Valproate	♦	♦			
Felbamate	♦		♦	♦	♦
Gabapentin			??		??
Lamotrigine	♦				♦
Topiramate	♦		♦		♦

[a]GABA, Gamma-aminobutyric acid; NMDA, N-methyl-D-aspartic acid.

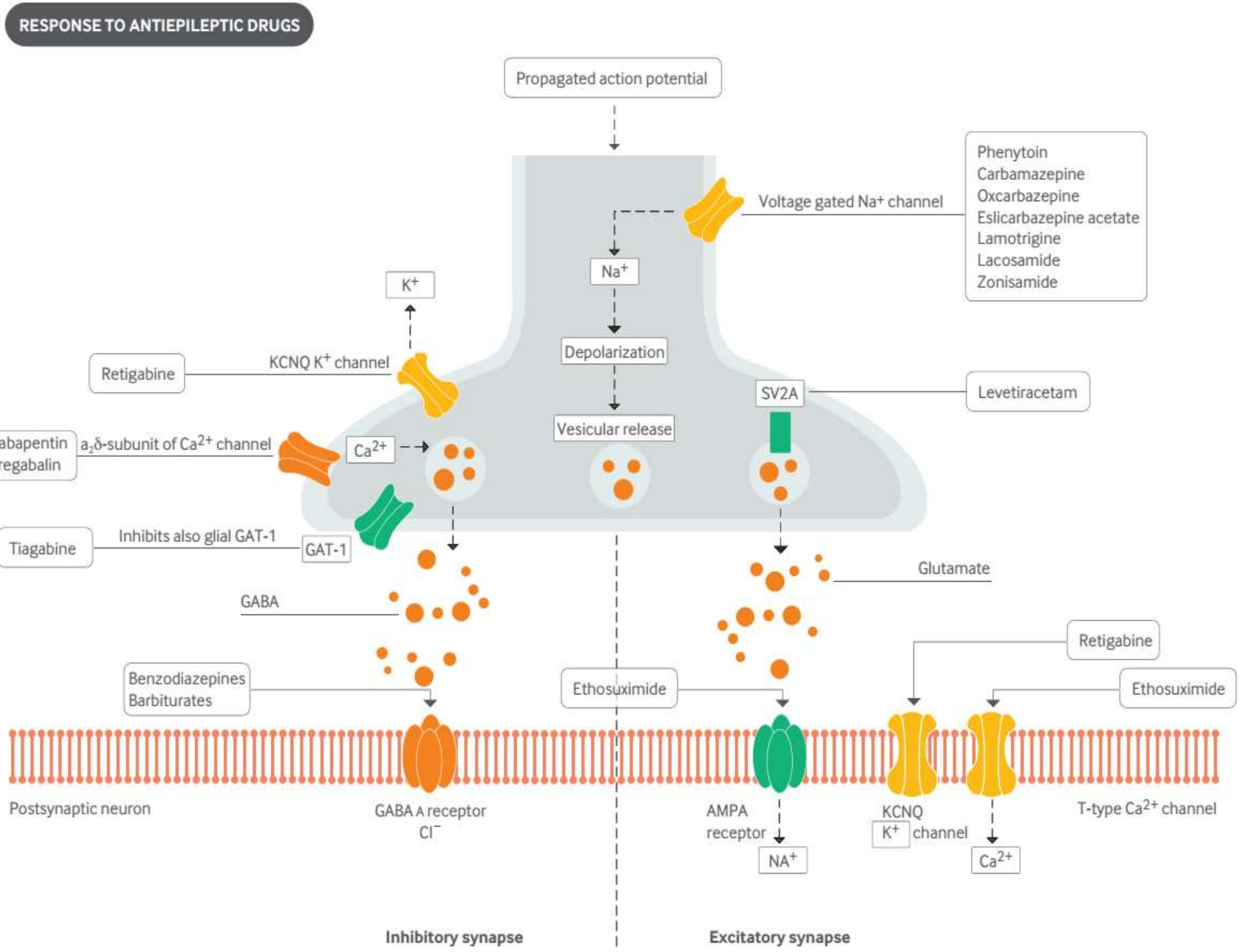

Propagated action potential
Levetiracetam
Oxcarbazepine
Phenytoin
Carbamazepine
Oxcarbazepine
Valproic acid
Lamotrigine
Felbamate
Topiramate
Zonisamide
N-type voltage-dependent calcium channel
Ca2+
Na+
Voltage-dependent sodium channel
Gabapentin
Depolarization
Vesicular release
α2δ subunit of L-type calcium channel
Glutamate
Felbamate
K+
K+
Topiramate
Outside
Inside
NMDA receptor
AMPA/kainate receptor
Ca2+, Na+


Inhibitory presynaptic terminal
Glutamate
GAD
GABA
GABA-T
Vigabatrin
GABA-T
Succinic semialdehyde
Succinic semialdehyde
GABA
Glial cell
Tiagabine
GABA transporter
GABA transporter
Zn^{2+}
Levetiracetam
GABA
Benzodiazepines
Barbiturates
Felbamate
Topiramate
Outside
Inside
Postsynaptic neuron
$GABA_A$ receptors

DOC bdsr klasifikasi epilepsi

	Kejang parsial	Kejang Umum (generalized seizures)		
		Tonic-clonic	Abscense	Myoclonic, atonic
Drug of choice	**Karbamazepin Fenitoin Valproat**	**Valproat Karbamazepin Fenitoin**	**Etosuksimid Valproat**	**Valproat**
Alternatives	Lamotrigin Gabapentin Topiramat Tiagabin Primidon Fenobarbital	Lamotrigin Topiramat Primidon Fenobarbital	Clonazepam Lamotrigin	Klonazepam Lamotrigin Topiramat Felbamat

Seizure Type	First-line	Second-line	Third-line
Generalized Seizures			
Absence (typical and atypical)	Valproate	Ethosuximide Lamotrigine	Levetiracetam Zonisamide
Myoclonic	Valproate	Topiramate Levetiracetam Lamotrigine Zonisamide	Clobazam Clonazepam Phenobarbital
Tonic-clonic	Phenobarbital Phenytoin Carbamazepine Valproate	Lamotrigine Oxcarbazepine	Topiramate Levetiracetam Zonisamide
Atonic	Valproate	Lamotrigine Topiramate	Felbamate
Partial Seizures			
Simple and complex partial with or without secondary generalization	Phenobarbital Phenytoin Carbamazepine	Valproate Oxcarbazepine Lamotrigine Topiramate Levetiracetam Zonisamide	Gabapentin Tiagabine Vigabatrin Felbamate


RESPONSE TO ANTIEPILEPTIC DRUGS
Propagated action potential
Voltage gated Na+ channel
Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lamotrigine
Lacosamide
Zonisamide
Na+
Depolarization
Vesicular release
K+
KCNQ K+ channel
Retigabine
SV2A
Levetiracetam
Gabapentin
Pregabalin
a2δ-subunit of Ca2+ channel
Ca2+
Tiagabine
Inhibits also glial GAT-1
GAT-1
GABA
Glutamate
Benzodiazepines
Barbiturates
Ethosuximide
Retigabine
Ethosuximide
Postsynaptic neuron
GABA A receptor
Cl−
AMPA
receptor
NA+
KCNQ
K+ channel
T-type Ca2+ channel
Ca2+
Inhibitory synapse
Excitatory synapse

Pemilihan OAE Berdasarkan Tipe Bangkitan

Tipe Bangkitan	Lini Pertama	Apabila tidak cocok terhadap lini pertama	OAE Tambahan dari OAE lini pertama	Apabila tidak cocok terhadap OAE tambahan dapat diganti	Dapat memperburuk bangkitan
Bangkitan Absans	Ethosuximide, Sodium Valproate	Lamotrigine	Kombinasi 2 dari 3 OAE : Ethosuximide, Lamotrigine, Sodium Valproate	clobazam, Clonazepam, Topiramate, Levetiracetam, Zonisamide.	Carbamazepine, Gabapentine, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabin, Vigabatrine
Bangkitan General Tonik Klonik	Sodium Valproate	Lamotrigine	Clobazam, Lamotrigine, Levetiracetam, Sodium Valproate, Topiramate		

Pemilihan OAE Berdasarkan Tipe Bangkitan

Tipe Bangkitan	Lini Pertama	Apabila tidak cocok terhadap lini pertama	OAE Tambahan dari OAE lini pertama	Apabila tidak cocok terhadap OAE tambahan dapat diganti	Dapat memperburuk bangkitan
Bangkitan Fokal	Carbamazepine, Lamotrigine	Levetiracetam, oxcarbazepine, Sodium Valproate	Carbamazepine ,Clobazam, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Sodium Valproate, Topiramate.	Eliscarbazepine acetate, Lacosamide, Phenobarbital, Phenytoin, Pregabalin, Tiagabine, vigabatrine, Zonisamide.	
Bangkitan Myoklonik	Sodium Valproate.	Levetiracetam, Topiramate.	Levetiracetam, Sodium valproate, Topiramate.	Clobazam, Clonazepam, Piracetam, Zonisamide.	Carbamazepine, Gabapentin, Oxcarbazepine, Phenytoin, Pregabalin, Tiagabine, Vigabatrine.

First line Drug

- **New onset partial epilepsies**
  Carbamazepine
  Gabapentin
  Lamotrigine
  Levetiracetam
  Oxcarbazepine
  Topiramate
  Valproate
- **New onset idiopathic generalized epilepsies**
  Lamotrigine
  Topiramate
  Valproate
- **Refractory partial epilepsy**
  Lacosamide
  Pregabalin
  Zonisamide
  Perampanel
  Clobazam
- **Refractory idiopathic generalized epilepsies**
  Clobazam
  Levetiracetam

Side Effect – Early Onset

Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
EARLY ONSET ADVERSE EVENTS																				
Somnolence	–	🔴	🟠	🟠	–	🟠	🟠	🟠	🟠	–	🟠	–	🔴	–	🔴	🟠	🔴	–	🟠	🔴
Dizziness	–	🔴	–	🟠	–	🟠	🟠	🟠	🟠	🔴	–	–	–	🔴	🔴	–	🔴	–	🟠	🟠
Seizure aggravation	🟠	🟠	🟠	–	–	🟠	–	–	–	–	🟠	–	–	🟠	🟠	–	–	–	🔴	
Gastrointestinal	🟠	–	–	🔴	🟠	🟢	–	🟢	–	🟠	–	–	–	–	–	–	–	🟠	–	🟠
Hypersensitivity (SJS/ TEN)	🟠	–	🟠	🟠	🟠	–	–	–	🟠	🟠	–	–	🟠	🟠	–	–	🟠	–	–	🟠
Rash	🟠	–	–	–	–	–	–	–	🟠	🟠	–	–	–	🟠	–	–	–	–	–	–

CLB=clobazam; CBZ=carbamazepine; ESL=eslicarbazepine; ETS=ethosuximide; FBM=felbamate; GBP=gabapentin; LEV=levetiracetam; LCM=lacosamide; LTG=lamotrigine; OXC=oxcarbazepine; PER=perampanel; PGB=pregabalin; PHB=phenobarbital; PHT=phenytoin; PRM=primidone; RTG=retigabine; ; TPM=topiramate; VPA=valproate; VGB=vigabatrin ZNS=zonisamide; SJS/TEN=Stevens-Johnson syndrome or toxic epidermal necrolysis. Key: – no increase, 🟢 low risk, 🟠 medium risk, 🔴 high risk

(Schmidt, 2014, drug treatment of epilepsy in adults)(

Side Effect - Late Onset (1)

Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
Encephalopathy														●				●	●	
Depression				●									●	●	●				●	
Behavioral problems								●				●	●	●	●		●		●	●
Psychotic episodes	●			●	●	●		●					●	●	●		●	●	●	
Leukopenia	●			●	●					●			●	●						
Aplastic anemia	●			●	●								●	●						
Thrombocytopenia					●													●		
Megaloblastic anemia	●												●	●						
Pancreatitis						●												●		
Liver failure					●													●		

CLB=clobazam; CBZ=carbamazepine; ESL=eslicarbazepine; ETS=ethosuximide; FBM=felbamate; GBP=gabapentin; LEV=levetiracetam; LCM=lacosamide; LTG=lamotrigine; OXC=oxcarbazepine; PER=perampanel; PGB=pregabalin; PHB=phenobarbital; PHT=phenytoin; PRM=primidone; RTG=retigabine; ; TPM=topiramate; VPA=valproate; VGB=vigabatrin; ZNS=zonisamide; SJS/TEN=Stevens-Johnson syndrome or toxic epidermal necrolysis. Key: – no increase, ● low risk, ● medium risk, ● high risk

Side Effect - Late Onset (2)

Adverse effect	CBZ	CLB	ESL	ETS	FBM	GBP	LCM	LEV	LTG	OXC	PGN	PER	PHB	PHT	TGB	RTG	TPM	VPA	VGB	ZNS
Nephrolithiasis																	🟢			🟠
Osteoporosis	🟢												🟠	🟠				🟢		
Hyponatremia	🟢		🟠							🟠										
Weight gain	🟠					🟠					🔴							🟠	🟠	
Weight loss					🔴												🟠			🟠
Cognition impaired	🟠	🟠	🟠										🔴	🟠			🟠			🟠
Teratogenicity																	🟠	🔴		
Retinal dysfunction																🔴		🔴		

CLB=clobazam; CBZ=carbamazepine; ESL=eslicarbazepine; ETS=ethosuximide; FBM=felbamate; GBP=gabapentin; LEV=levetiracetam; LCM=lacosamide; LTG=lamotrigine; OXC=oxcarbazepine; PER=perampanel; PGB=pregabalin; PHB=phenobarbital; PHT=phenytoin; PRM=primidone; RTG=retigabine; ; TPM=topiramate; VPA=valproate; VGB=vigabatrin; ZNS=zonisamide; SJS/TEN=Stevens-Johnson syndrome or toxic epidermal necrolysis. Key: – no increase, 🟢 low risk, 🟠 medium risk, 🔴 high risk

Table 2 Dosing and pharmacokinetics of anticonvulsant drugs

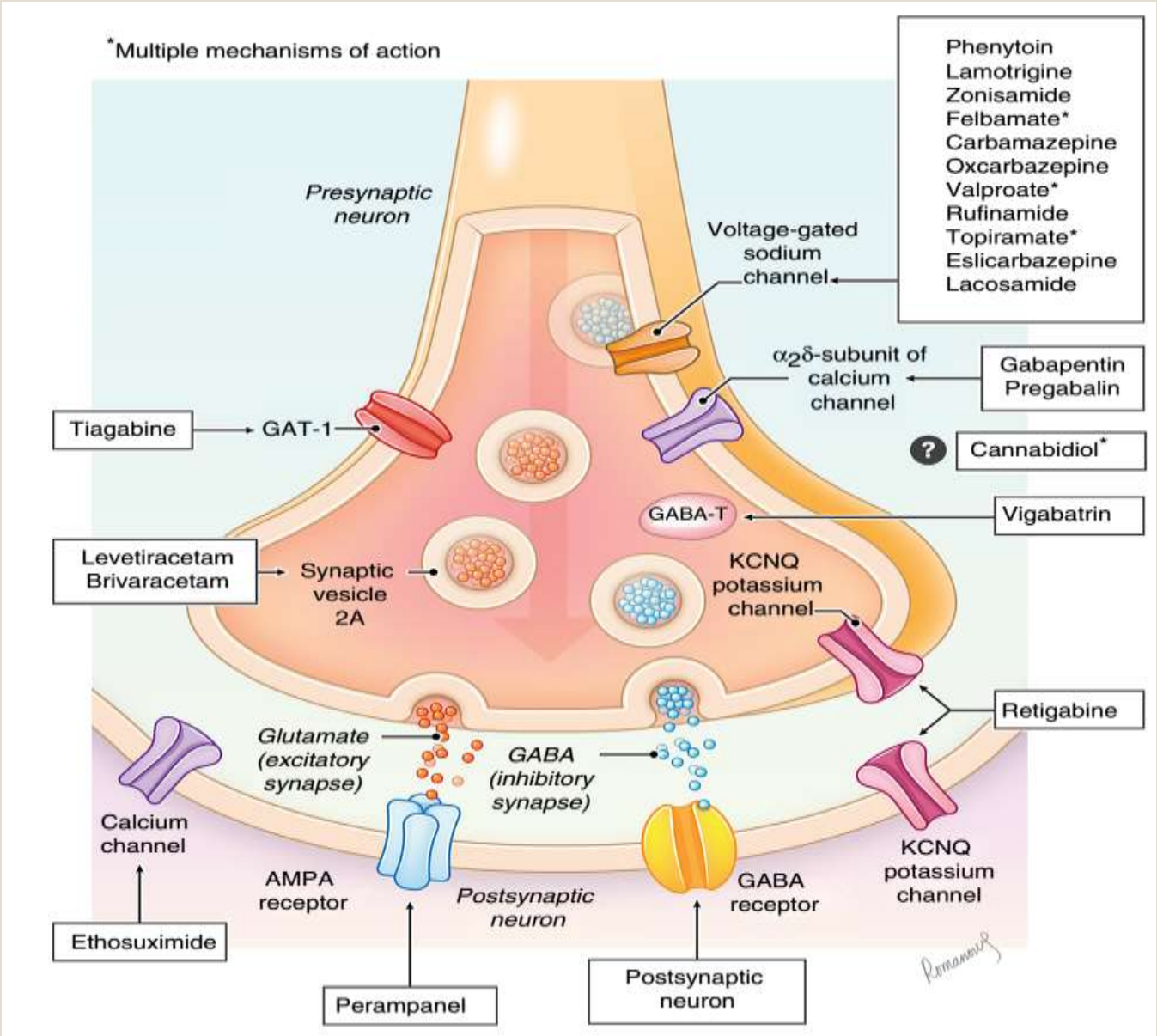
Drug	Usual adult dose 24 h (mg)	Half-life (h)	Usually effective plasma concentration (μg/mL)	Time to peak concentration (h)	Bound fraction (%)
Phenytoin	300–400	22	10–20	3–8	90–95
Carbamazepine	800–1600	8–22	8–12	4–8	75
Phenobarbital	90–180	100	15–40	2–8	45
Valproate	1000–3000	15–20	50–120	3–8	80–90
Ethosuximide	750–1500	60	40–100	3–7	<5
Felbamate	2400–3600	14–23	20–140		25
Gabapentin	1800–3600	5–7	>2[a]	2–3	<5
Lamotrigine	100–500	12–60[b]	1–4[a]	2–5	55
Topiramate	200–400	19–25[b]	NE[c]	2–4	9–17
Vigabatrin	1000–3000	5–7	NE	1–4	5
Tiagabine	32–56	5–13	NE	1	95

[a]Not established; coresponds to usual range in patients treated with recommended dose.

[b]Highly dependent on concurrently administered drugs.

[c]NE, Not established.

ANTIEPILEPTIC IN CHILD



Nuevos fármacos antiepilépticos
en Pediatría. An Pediatr (Barc). 2019;91:415.

Antiepileptic Drugs of Choice for Treatment of Generalized Seizures in Children

	GTC	Absence	Myoclonic	Tonic	Atonic
First Choice	Valproate	Ethosuximide Lamotrigine Valproate	Valproate	Lamotrigine Valproate	Lamotrigine valproate
Second choice	Carbamazepine Phenytoin Topiramate	Lavetiracetam Topiramate Zonisamide	Clonazepam Levetiracetam zonisamide	Phenytoin Topiramate Felbamate	Lamotrigine Topiramate Felbamate

Antiepileptic Drugs of Choice for Treatment of Focal Seizures in Children

First choice

Carbamazepine

Second choice

Valproate

Phenytoin

Phenobarbital

Lamotrigine

Alternative agent

Gabapentin

Lamotrigine

Oxcarbamazepine

topiramate

Prinsip Terapi dg Antiepilepsi

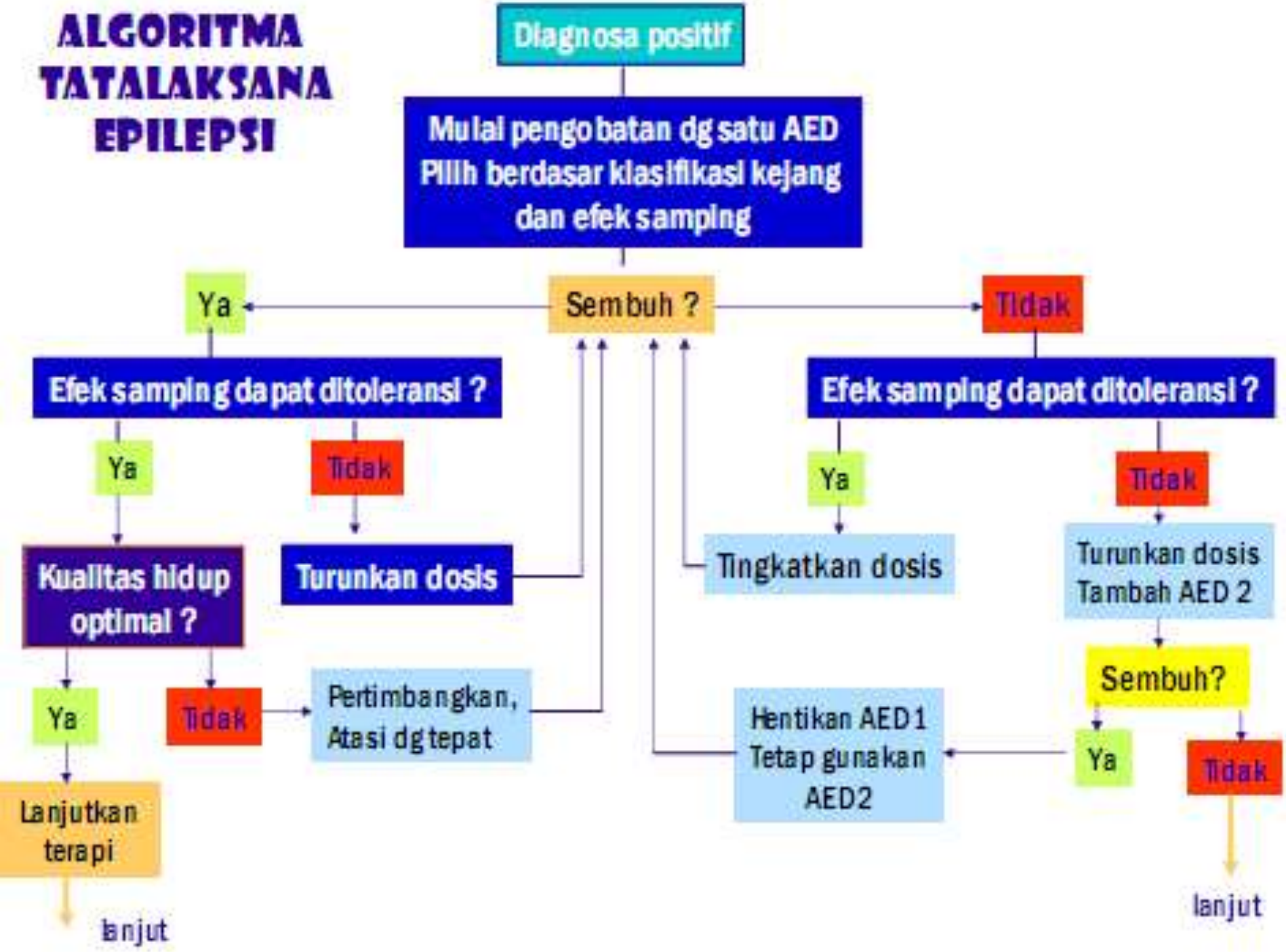
- monoterapi lebih baik → mengurangi potensi *adverse effect*, meningkatkan kepatuhan pasien, tidak terbukti bahwa politerapi lebih baik dari monoterapi
- hindari atau minimalkan penggunaan antiepilepsi sedatif → toleransi, efek pada intelegensia, memori, kemampuan motorik bisa menetap selama pengobatan
- jika mungkin, mulai terapi dgn satu antiepilepsi non-sedatif, jika gagal baru diberi sedatif atau politerapi
- berikan terapi sesuai dgn jenis epilepsinya

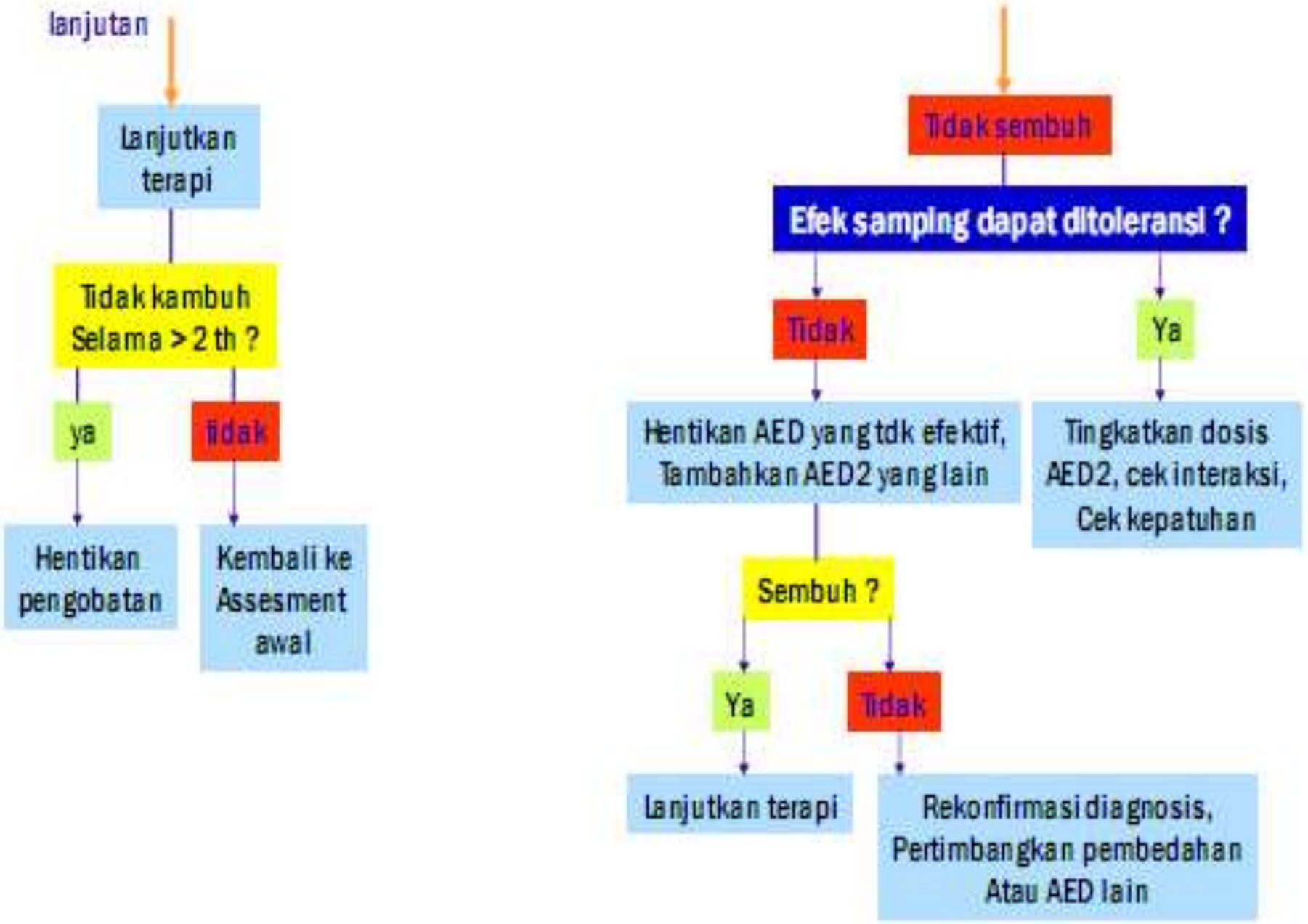
Prinsip Terapi dg Antiepilepsi

- mulai dengan dosis terkecil dan dapat ditingkatkan sesuai dg kondisi klinis pasien → penting : kepatuhan pasien
- ada variasi individual terhadap respon obat antiepilepsi → perlu pemantauan ketat dan penyesuaian dosis
- jika suatu obat gagal mencapai terapi yang diharapkan → pelan-pelan dihentikan dan diganti dengan obat lain (jgn politerapi)
- lakukan monitoring kadar obat dalam darah → jika mungkin, lakukan penyesuaian dosis dgn melihat juga kondisi klinis pasien

Prinsip Terapi dg Antiepilepsi

ALGORITMA TATALAKSANA EPILEPSI




lanjutan
Lanjutkan terapi
Tidak kambuh Selama > 2 th ?
ya
tidak
Hentikan pengobatan
Kembali ke Assesment awal
Tidak sembuh
Efek samping dapat ditoleransi ?
Tidak
Ya
Hentikan AED yang tdk efektif, Tambahkan AED2 yang lain
Tingkatkan dosis AED2, cek interaksi, Cek kepatuhan
Sembuh ?
Ya
Tidak
Lanjutkan terapi
Rekonfirmasi diagnosis, Pertimbangkan pembedahan Atau AED lain

STATUS EPILEPTIKUS

- kejang umum yang terjadi selama 5 menit atau lebih atau kejadian kejang 2 kali atau lebih tanpa pemulihan kesadaran di antara dua kejadian tersebut
- Merupakan kondisi darurat yg memerlukan pengobatan yang tepat untuk meminimalkan kerusakan neurologik permanen maupun kematian

Penyebab Status Konvulsi

Tipe 1
(tidak ada lesi struktural)

- Infeksi
- Infeksi CNS
- Gangguan metabolik
- Turunnya level AED
- Alkohol
- Idiopatik

Tipe 2
(Ada lesi struktural)

- Anoksia/hipoksia
- Tumor CNS
- CVA
- Overdose obat
- Hemoragi
- Trauma

TATA LAKSANA STATUS KONVULSI

- Non-farmakologi:
  - Tanda-tanda vital dipantau
  - Pelihara ventilasi
  - Berikan oksigen
  - Cek gas darah utk memantau asidosis respiratory atau metabolik
  - Kadang terjadi hipoglikemi → berikan glukosa
- Farmakologi : dengan obat-obatan

Status epilepticus

Initial therapy (dalam 5 menit)	
Dewasa	Anak
Midazolam im Lorazepam iv Diazepam iv Phenobarbital iv } Sama efektifnya Bila belum terpasang iv line: midazolam im lebih superior	Lorazepam iv Diazepam iv } Sama efektifnya (Lv A) Diazepam rectal Midazolam im/nasal/buccal } (Lv B)

Kejadian depresi napas dan kardiovaskuler lebih tinggi pada status epilepticus untreated dibandingkan dengan pemberian initial therapy → PENTING !

American Epilepsy Society, 2016

Pasien epilepsi dengan riwayat status epilepticus memanjang/ berulang, disiapkan midazolam buccal/ diazepam rectal (NICE, 2012)

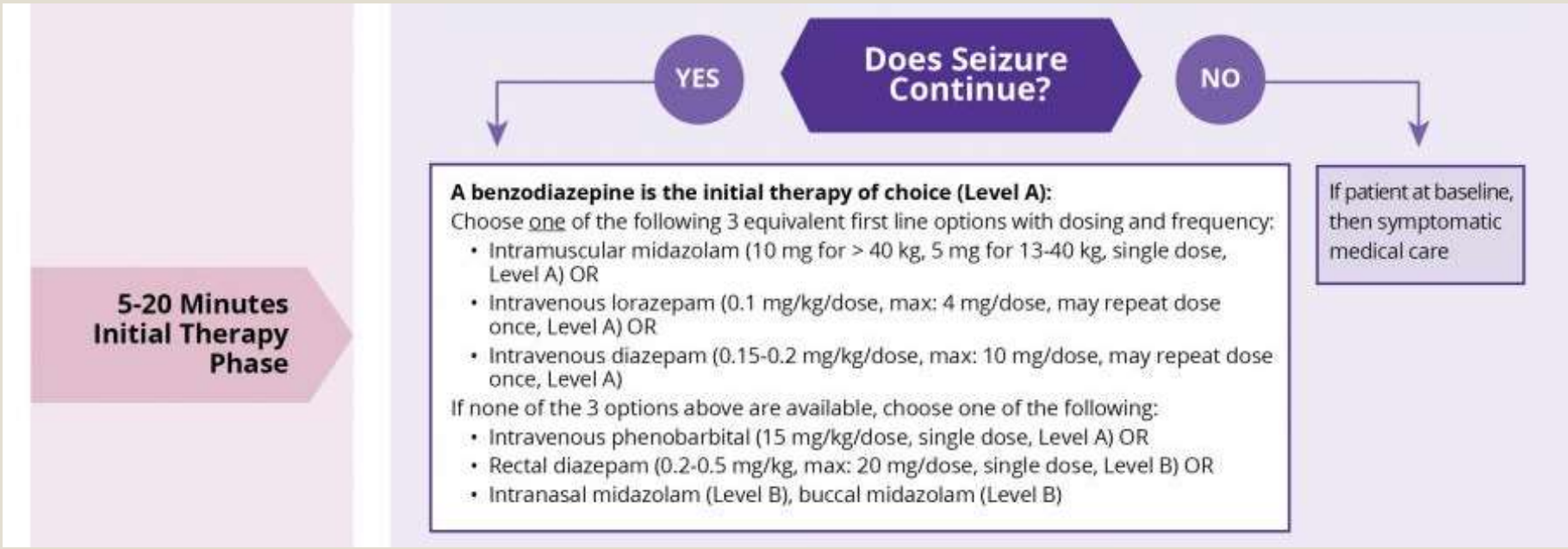
Algoritma status epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016

Time Line	Interventions for emergency department, in-patient setting, or prehospital setting with trained paramedics
0-5 Minutes Stabilization Phase	1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam) 2. Time seizure from its onset, monitor vital signs 3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed 4. Initiate ECG monitoring 5. Collect finger stick blood glucose. If glucose < 60 mg/dl then Adults: 100 mg thiamine IV then 50 ml D50W IV Children ≥ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W IV 6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

	Prehospital
0-10 menit	Prehospital → primary survey Diazepam supp 10-20 mg, dapat diulang 15 menit

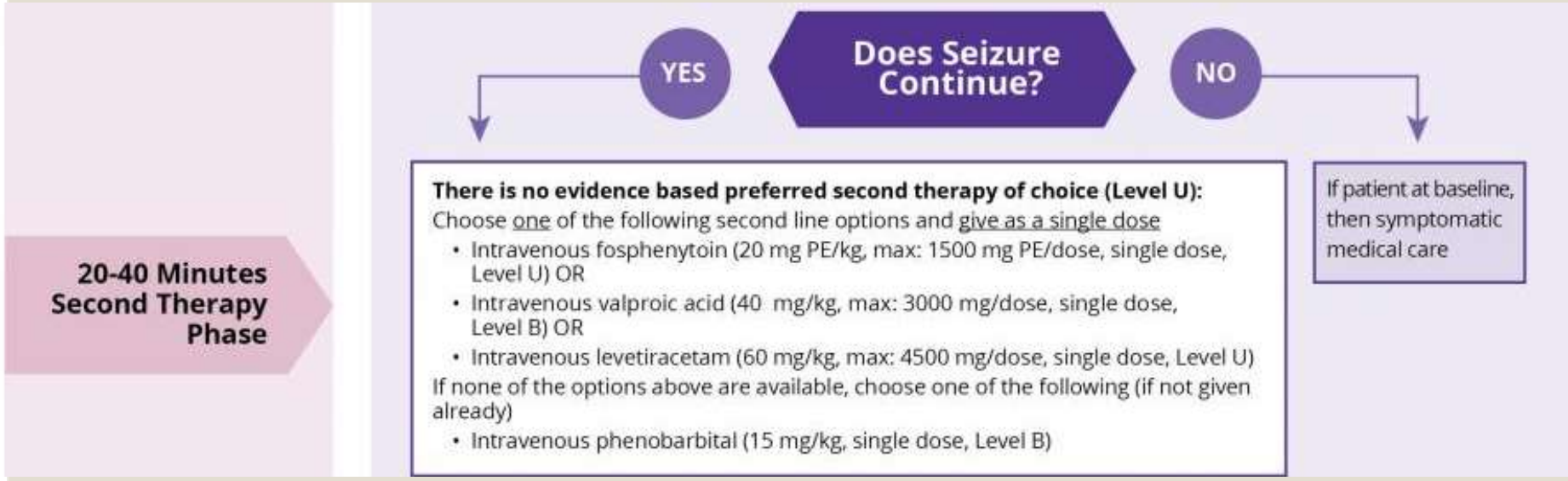
PERDOSSI, 2014



Midazolam im 10 mg (single dose)
Diazepam iv (0,15-2 mg/kg BB, max 10 mg) (may repeat once)

SE Dini	
0-30 menit	Diazepam iv (0,15-2 mg/kg BB, max 10 mg) (may repeat once) OAE yang rutin dikonsumsi diberikan

PERDOSSI, 2014



Phenytoin 15-18 mg/kg, kecepatan maksimal 50 mg/menit

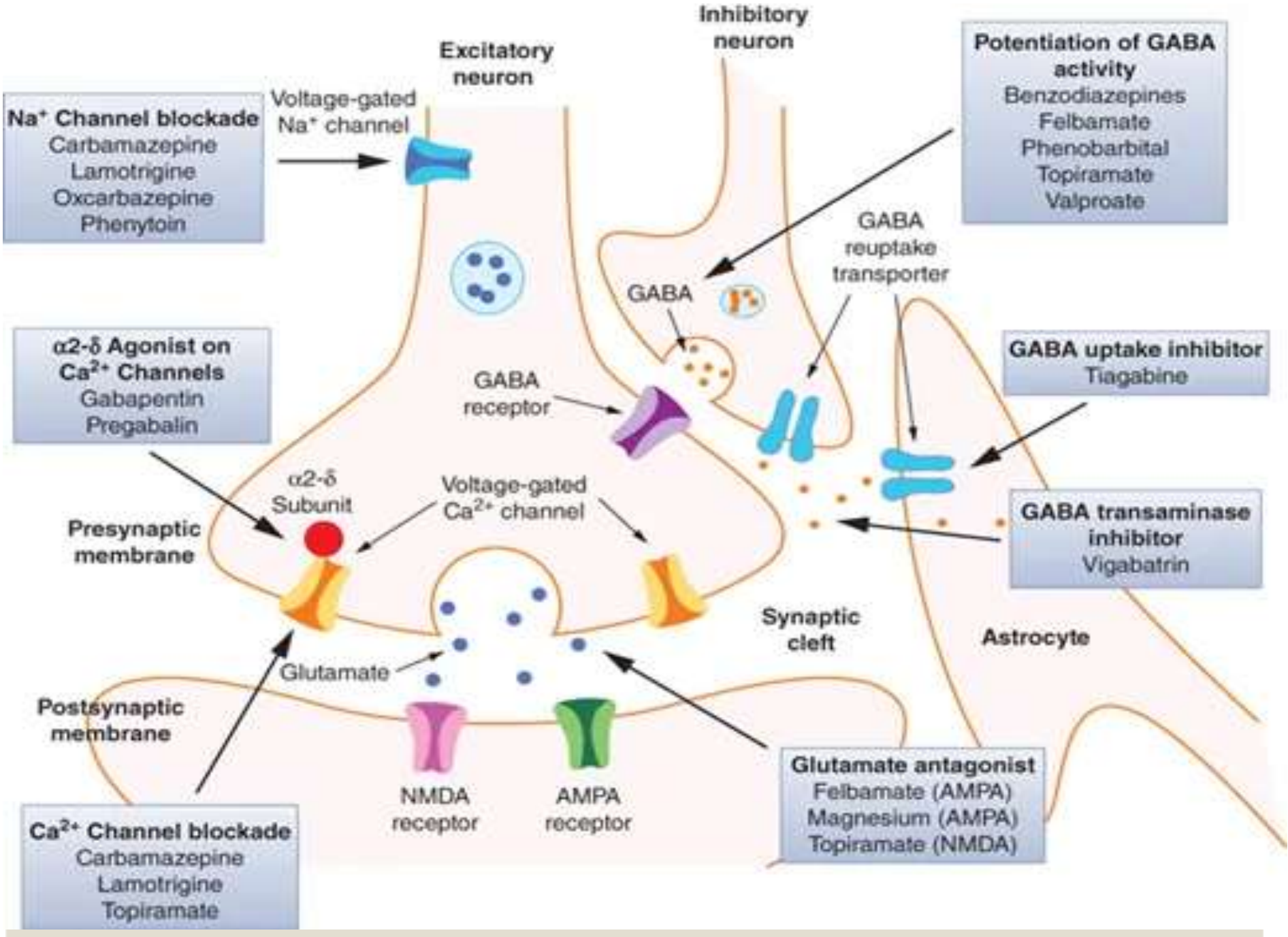
1 ampul = 100 mg (50 kg → 8 ampul, minimal dalam 16 menit)

SE Menetap	
0-60 menit	Phenytoin 15-18 mg/kg, kecepatan maksimal 50 mg/menit Atau Phenobarbital 10-15 mg/kg iv kecepatan 100 mg/menit

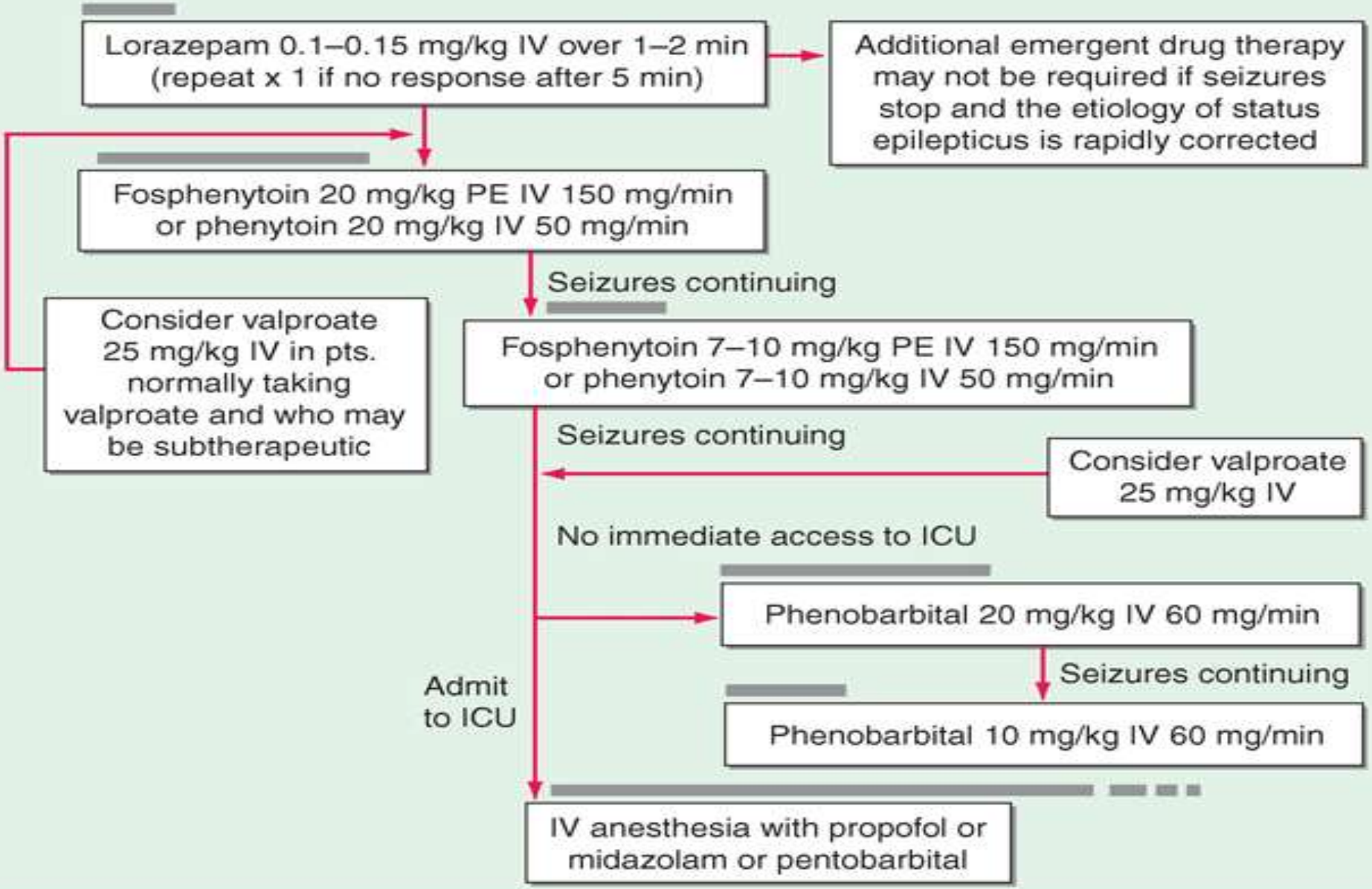
PERDOSSI, 2014

SE Refrakter	ICU
30-90 menit	Konsul Anestesi Terapi: Propofol, midazolam, thiopental → dipertahankan 12-24 jam sampai bangkitan klinis/elektrografis terakhir, tappering off

PERDOSSI, 2014


Inhibitory neuron
Excitatory neuron
Potentiation of GABA activity
Benzodiazepines
Felbamate
Phenobarbital
Topiramate
Valproate
Na+ Channel blockade
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
Voltage-gated Na+ channel
GABA reuptake transporter
GABA
α2-δ Agonist on Ca2+ Channels
Gabapentin
Pregabalin
GABA receptor
GABA uptake inhibitor
Tiagabine
α2-δ Subunit
Voltage-gated Ca2+ channel
Presynaptic membrane
GABA transaminase inhibitor
Vigabatrin
Synaptic cleft
Astrocyte
Glutamate
Postsynaptic membrane
NMDA receptor
AMPA receptor
Glutamate antagonist
Felbamate (AMPA)
Magnesium (AMPA)
Topiramate (NMDA)
Ca2+ Channel blockade
Carbamazepine
Lamotrigine
Topiramate

Treatment of Generalized Tonic-Clonic Status Epilepticus in Adults



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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