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Anticonvulsive drugs (antiepileptics)

Epilepsy

- brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition

- Seizures
  - manifestation of abnormal hypersynchronous or hyperexcitable discharges of cortical neurons
  - many causes, including a genetic predisposition for certain types of seizures, head trauma, stroke, brain tumors, alcohol or drug withdrawal, repeated episodes of metabolic insults, such as hypoglycemia

- Prevalence 0,5–1 %

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Factors lowering seizure threshold

- Sleep deprivation
- Alcohol withdrawal
- Television flicker
- Epileptogenic drugs
- Systemic infection
- Head trauma
- Recreational drugs
- Non-compliance
- Menstruation
- Dehydration
- Barbiturate withdrawal
- Benzodiazepine withdrawal
- Hyperventilation
- Flashing lights
- Diet and missed meals
- Stress
- Intense exercise

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Pharmacotherapy

- The goal to achieve a seizure-free status without adverse effects
- Monotherapy is desirable - avoids drug interactions
- Many of the older anticonvulsant agents have hepatic enzyme–inducing properties

- Main mechanism - to stabilize membrane of neuron and to decrease the excitability

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	Drug	International abbreviation	Date of introduction in market
First generation	Bromide	–	1857
	Phenobarbital	PB	1912
	Phenytoin	PHT	1960
	Primidone	PRM	1960
	Sulthiame	STM	1960
	Carbamazepine	CBZ	1965
	Valproate	VPA	1970
Second generation	Clobazam	CLB	1979
	Vigabatrin	VGB	1989
	Oxcarbazepine	OXC	1990
	Lamotrigine	LTG	1991
	Gabapentin	GBP	1994
	Felbamate	FBM	1994
	Topiramate	TPM	1995
	Tiagabine	TGB	1996
	Levetiracetam	LEV	2000
	Pregabalin	PGB	2005
	Zonisamide	ZNS	2007
	Stiripentol	STP	2007
	Rufinamide	RUF	2007
Third generation	Eslicarbazepine (acetate)	ESL	2010
	Lacosamide	LCM	2010
	Retigabine/ezogabine	RTG/EZG	2011
	Perampanel	PER	2012
	Everolimus	EVR	2017
	Brivaracetam	BRV	2018
	Cannabidiol	CBD	2019

An Pediatr (Barc). 2019;**91(6)**:415.e1---415.e10

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Mechanisms of action

- Classical
  - Enhancement of GABA mainly via GABA-A rc
  - Inhibition of sodium channel function
  - Inhibition of calcium channel function

- Mechanisms of newer drugs
  - Inhibition of glutamate release
  - Inhibition of GABA uptake
  - AMPA receptor antagonism
  - Synaptic vesicle protein SV2A

- (multiple mechanisms)

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GABA-ergic drugs

- barbiturates (phenobarbital), BZD
- vigabatrin – irreversible inhibition of GABA transaminase
- tiagabine – inhibitor of GABA transporter (increases extracellular GABA)
- stiripentol
  - increases GABA effect similarly as barbiturates and inhibits lactate dehydrogenase, which may reduce metabolic energy prodcution requiered to mainain the seizure, used as adjunctive treatment in children
- GABA-ergics may exacerbate absences

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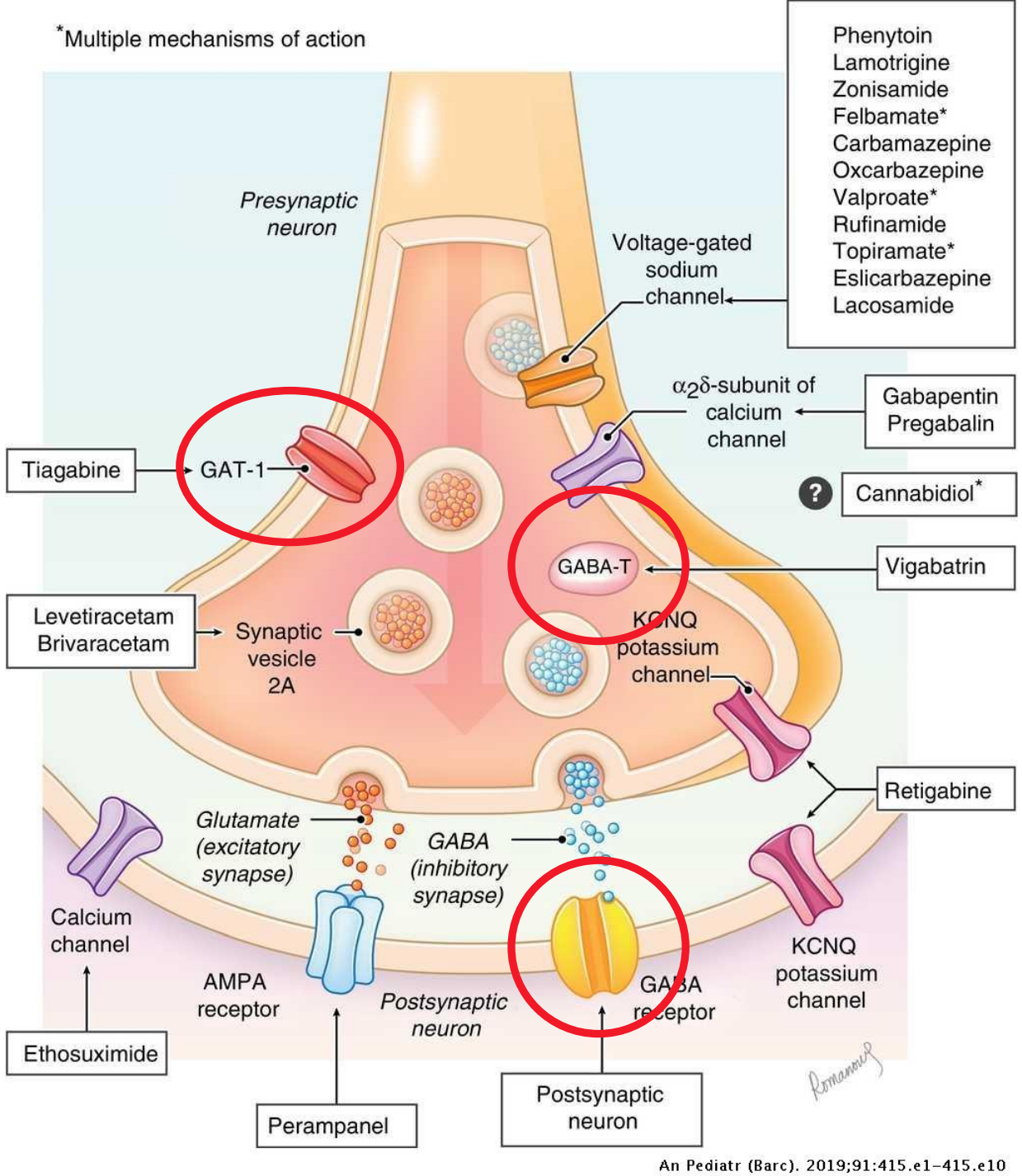

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Na^+ channel inhibitors

- carbamazepine
- lamotrigine
- phenytoin
- lacosamide

- Bind preferentially to inactivated channels and lower the number of functional channels able to generate action potential

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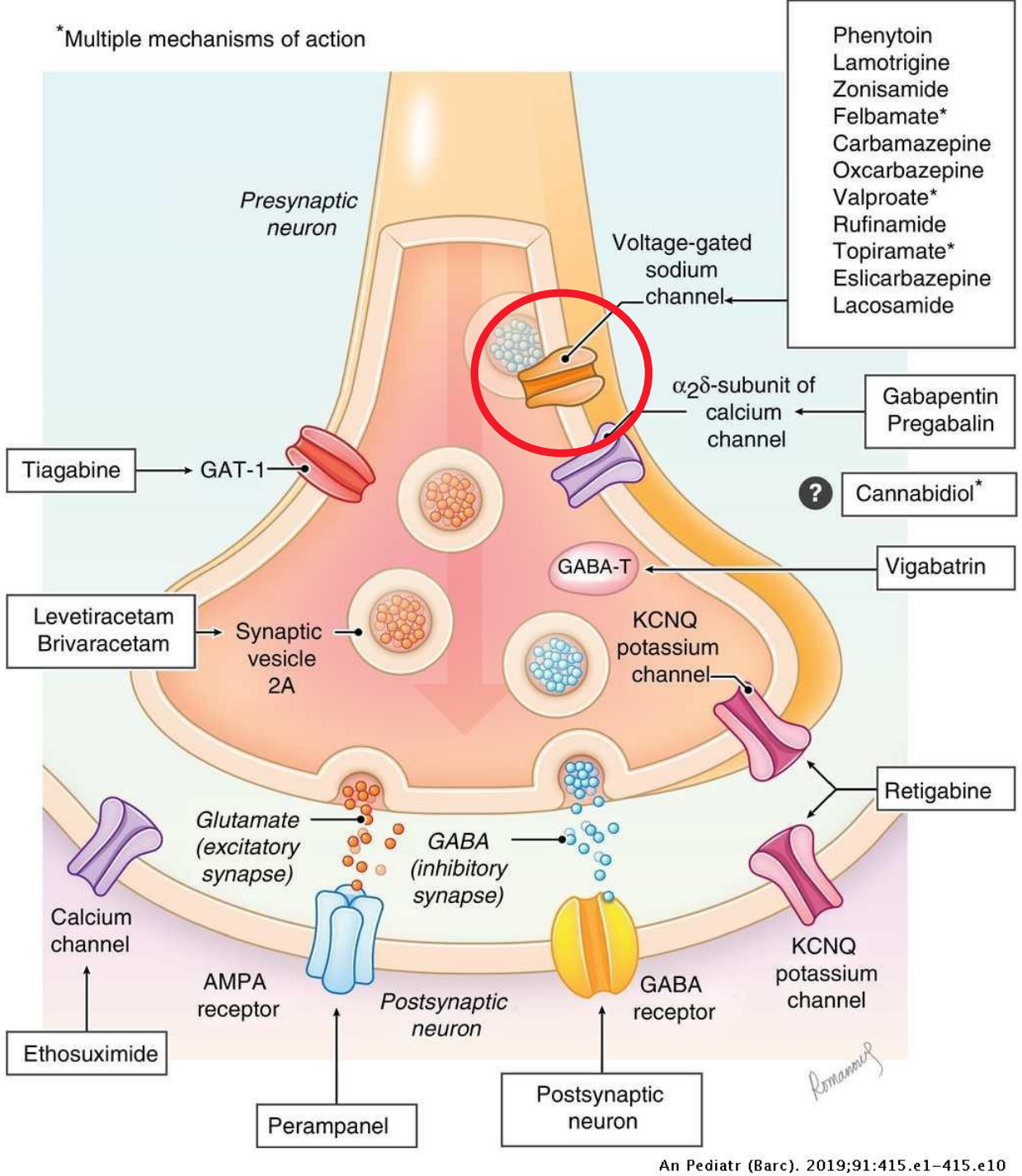

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Ca^{2+} channel inhibitors

- ethosuximide, valproate
  - Act primarily on T type channels in the thalamus, which are responsible for absences

- gabapentin, pregabalin
  - GABA analogues, act primarily on P/Q type channels
  - Lower trafficking of the channels to the membrane - reduce the calcium entry to the cell – reduce neurotransmitter release

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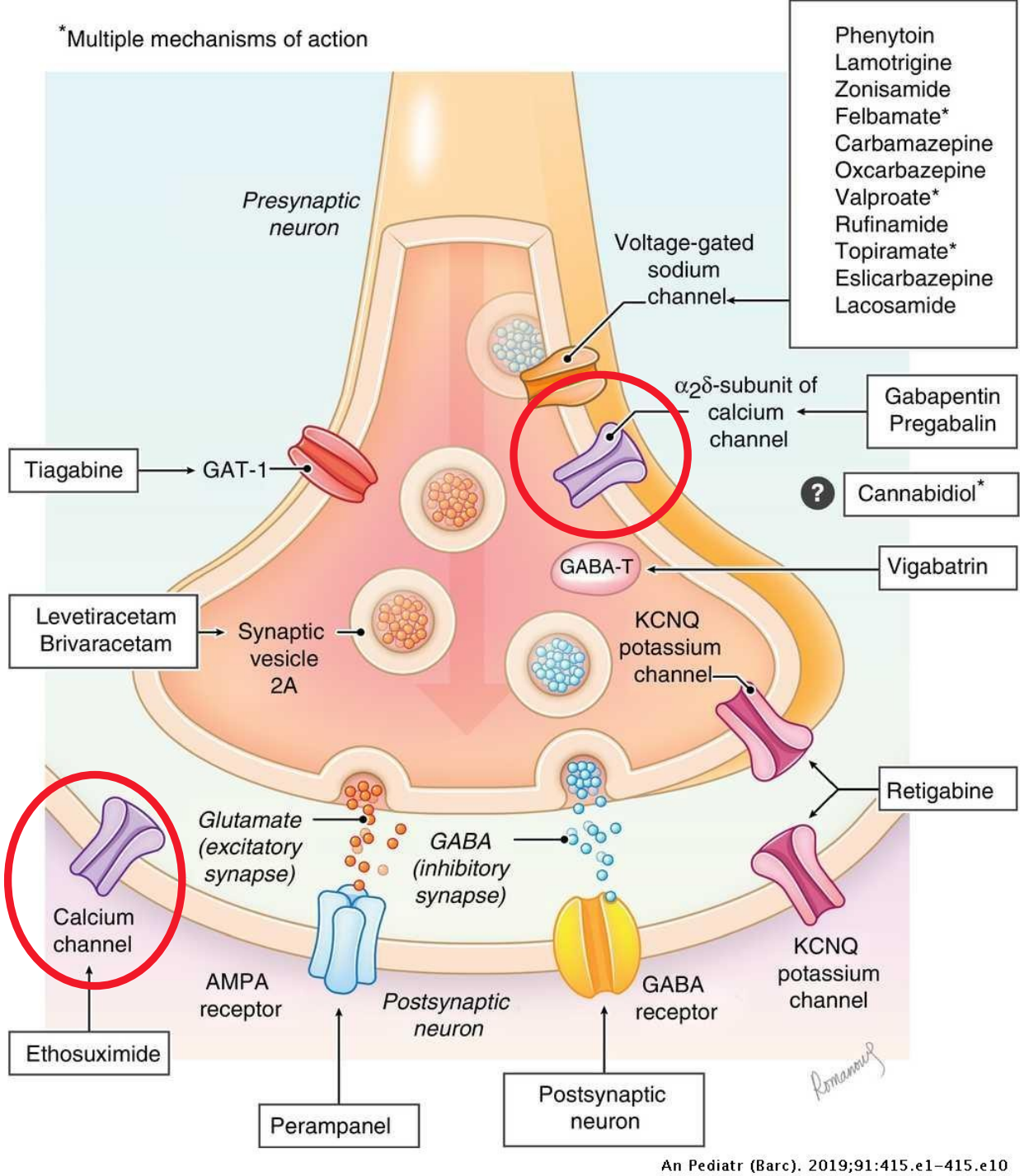

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Other mechanisms

- levetiracetam, brivaracetam
  - Bind to SV2A protein and probably have also other mechanisms
- perampanel, topiramate (multiple mechanisms)
  - AMPA antagonism
- rufinamide
  - Inhibition of GABA reuptake
- retigabine
  - Opens KCNQ/Kv7 potassium channels

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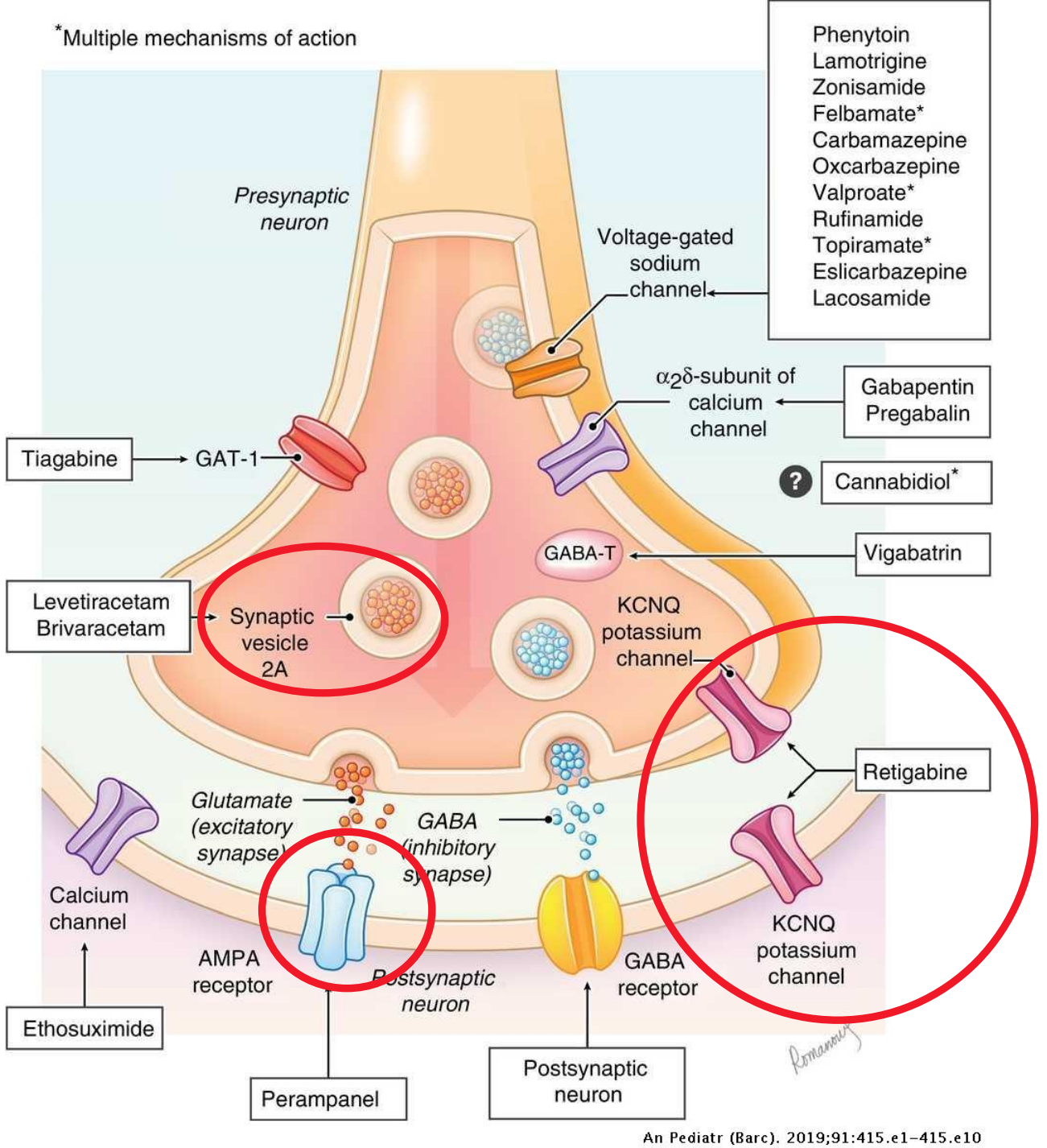

An Pediatr (Barc). 2019;**91(6)**:415.e1---415.e10

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Multiple mechanisms

- valproate
  - Inhibition of both sodium and calcium channels (T type), GABA transaminase
  - All types of seizures
- felbamate
  - Inhibition of both sodium and calcium channels, GABA-A and NMDA rc
  - Lennox-Gastaut sy
- topiramate
  - Inhibition of both sodium and calcium channels, GABA-A and AMPA rc
  - Lennox-Gastaut sy
- zonisamide
  - Inhibition of both sodium and calcium channels, GABA-A rc
  - Partial seizures

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Cannabidiol

- for adjuvant treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or with Dravet's syndrome (DS) in use together with clobazam in patients of the age 2 years and older
- for adjuvant treatment of attacks associated with tuberous sclerosis complex (TSC) in patients of the age 2 years and older

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Choice of anticonvulsant agent

- https://pathways.nice.org.uk/pathways/epilepsy#path=view%3A/pathways/epilepsy/anti-epileptic-drugs-to-offer-based-on-presenting-epilepsy-seizure-types.xml&content=view-node%3Anodes-absence-seizures

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All types of seizures

- All but absence
  - carbamazepine (oxcarbazepine, eslicarbazepine), phenytoin, phenobarbital (primidon)

- All
  - vigabatrin, lamotrigine, valproate

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Treatment of specific types of seizures

- Absence
  - ethosuximide or valproate
  - lamotrigine
- Partial (focal) seizures
  - carbamazepine or lamotrigine
  - valproate, levetiracetam, clobazam, gabapentin, topiramate
- Generalised tonic–clonic seizures
  - valproate, carbamazepine or lamotrigine
  - topiramate, levetiracetam
- Myoclonic seizures
  - valproate, topiramate, levetiracetam

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Status epilepticus

- Critical, life threatening condition, one seizure comes after another without recovery, lasts at least 30 min, fatal in 5-10% patients
  - Shall be distinguished from a series of seizures with recovery inbetween
- Causes – frontal lobe lesion (including stroke), head trauma, anticonvulsant discontinuation, alcohol withdrawal, metabolic disturbances, pregnancy
  - Requires inpatient treatment – energetically demanding condition, hypoglycaemia, lung edema, hyperthermia, excitotoxicity, ...
- lorazepam IV or midazolam IM or diazepam rectally

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Epilepsy resistant to monotherapy

- Consider combination therapy when:
  - Treatment with two first line AEDs has failed
  - The first well-tolerated drug substantially improves seizure control, but fails to produce seizure freedom at maximal dosage.
  - The choice of drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three AEDs.

- gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, zonisamide (alphabetical order) may be considered as adjunctive therapy dependent on patient and seizure type.

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DRUG RESISTENT EPILEPSY (DRE)

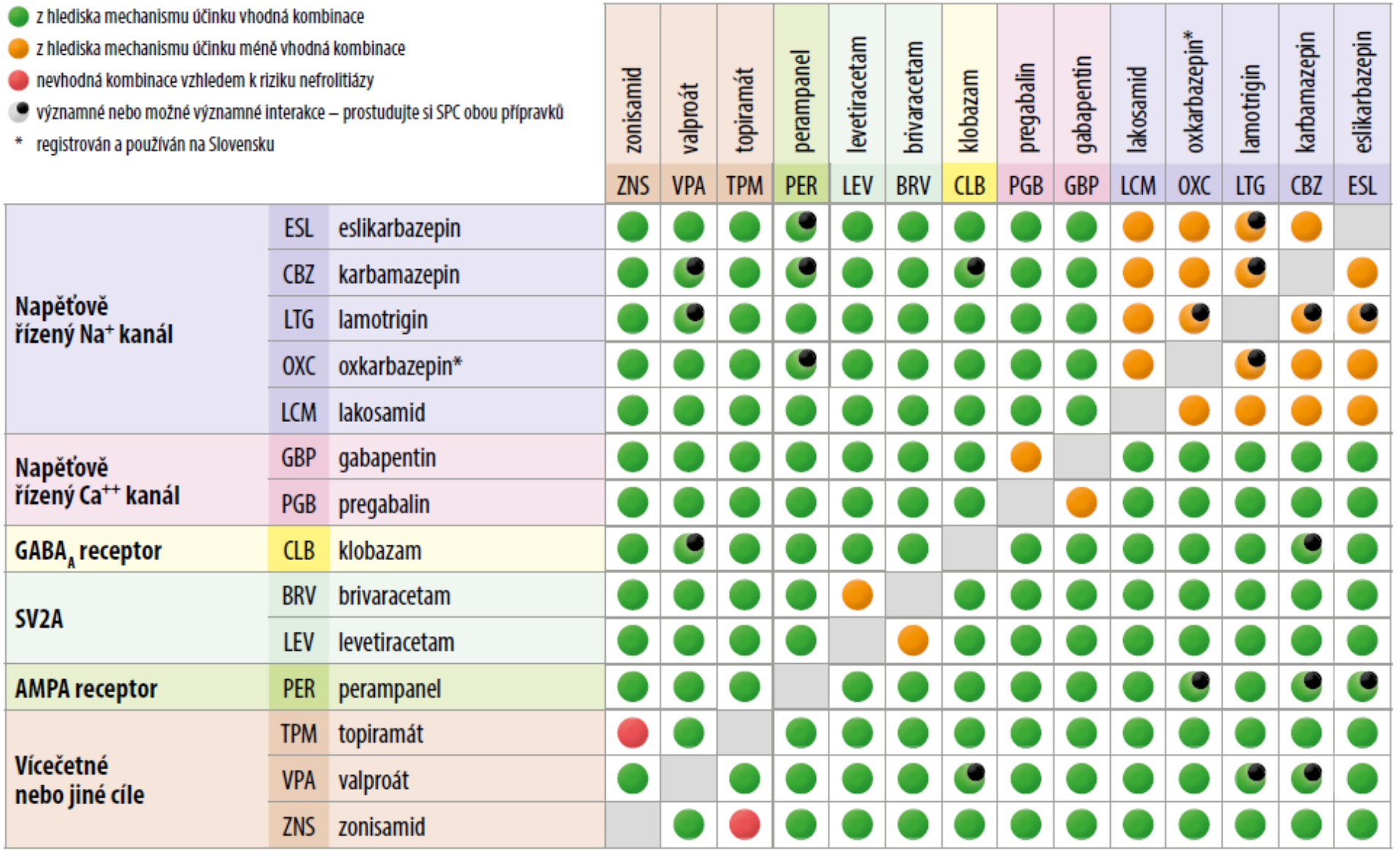
- ILAE - **DRE** non-satisfactory compensation of attacks after trying of two well-tolerated, correctly chosen and dosed antiepileptic drugs **(anti-seizure medication; ASM)** in the form of monotherapy **or combined treatment.**[1]

About 40 % of patients with epilepsy after treatment with two AE drugs do not achieve permanent and full control of attacks and therefore it belon to DRE defined by ILAE[1]

ILAE, Mezinárodní liga proti epilepsii.

1. Kwan P, *et al. Epilepsia* 2010;51:1069–1077; 2. Chen Z, *et al. JAMA Neurol* 2018;75:279–286.

Combinations



- suitable combination (with respect to MoA)
- less suitable combination (with respect to MoA)
- non-suitable combination (with respect to risk of nephrolithiasis)
- significant or potentially significant interactions (check SmPC)

Other uses on antiepileptic drugs

- Bipolar disorder (valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate)
- Prophylaxis of migraine (valproate, gabapentin, topiramate)
- Anxiety disorders (gabapentin, pregabalin)
- Neuropathic pain (gabapentin, pregabalin, carbamazepine, lamotrigine)

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Drug-drug interactions

- Drug-drug interactions are common among anticonvulsants as well as between anticonvulsants and other drugs
- Mostly pharmacokinetic

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Interactions of anticonvulsant drugs

Table 4 - Main drug interactions between AEDs

Conventional AEDs effects on the new drugs					
Drugs	**Gabapentine**	**Lamotrigine**	**Topiramate**	**Oxcarbamazepine**	**Vigabatrine**
Phenytoin	None	Reduced serum level	Reduced serum level	Reduced serum level	None
Carbamazepine	None	Reduced serum level	Reduced serum level	Reduced serum level	None
Valproate	None	Increased serum level	None	None	None
Phenobarbital	None	Reduced serum level	Reduced serum level	Reduced serum level	None

AEDs effect on conventional drugs				
Drugs	**Phenytoin**	**Carbamazepine**	**Valproate**	**Phenobarbitall**
Gabapentine	None	None	None	None
Lamotrigine	None	None	Reduction of 25% in the serum level	None
Topiramate	Serum level might be increased	None	None	None
Oxcarbamazepine	Serum level might be increased	None	None	Mild increase in the serum level
Vigabatrine	Reduction in the serum level (±20%)	None	None	None

Modified from French & Gidal.[21]

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Anticonvulsants in specific populations

- Neonates, children, elderly patients
- Slowed hepatic metabolism
- Decreased renal clearance
- Decreased volumes of distribution
- Women on contraceptive agents
- Pregnant women - folic acid, at least 0.4mg/day, TDM, many drugs are teratogenic
- Patients with hepatic or renal insufficiency
  - Gabapentin, pregabalin, levetiracetam, and lacosamide excreted mostly renal clearance - their doses can be adjusted for renal insufficiency ; useful in patients with hepatic failure
  - Lamotrigine metabolized by glucuronidation - also might be used in hepatic insufficiency.

Generic substitution

- Changing the formulation or brand of AED is NOT recommended because different preparations may vary in bioavailability or have different pharmacokinetic profiles and, thus, increased potential for reduced effect or excessive side effects.

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Exam questions

- **gabapentin** – GABA analogue, without affinity to GABA rcp., without effects on metabolism of GABA
  - bonding to voltage gated Ca^{2+} channels
  - used for therapy of partial attacks
  - way of application: p.o.
  - low interaction potential
  - relatively safe, few AE
  - other use: peripheral neuropathic pain (diabetic neuropathy, postherpetic neuralgia), preemptive analgesia

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Exam questions

- **carbamazepine** – inhibition of Na^+ channels
  - used for therapy of generalized attacks, mixed attacks, ineffective in absences
  - way of administration: p.o. (both conventional tbl. and tbl. with prolonged effect)
  - teratogenic!
  - risk of severe skin toxicity (mainly in people of Chinese or Thai origin – pharmacogenetic background)
  - high interaction potential (with inhibitors of CYP3A4 $\rightarrow\uparrow\uparrow$ AE)
  - other use: mania and prophylactic treatment of bipolar affective disorder, treatment of neuropathic pain and neuralgias (neuralgia of trigeminal nerve, diabetic neuropathy, treatment of abstinence syndrome in alcoholics

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Exam questions

- **valproate (valproic acid)** – inhibition of sodium and calcium channels of T type, GABA transaminase
  - suitable for therapy of many types of attacks (epilepsy in children, adolescents; affects both tonic-clonic seizures and absences), suitable for therapy of pharmaco-resistant epilepsy
  - non-sedative
  - way of administration: p.o. (with prolonged effect), injections
  - high interaction potential
  - high teratogenic!!!
  - about 10% of patients – hair impairment, hepatotoxic
  - other possible use: bipolar affective disorder, prophylaxis of migraine

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