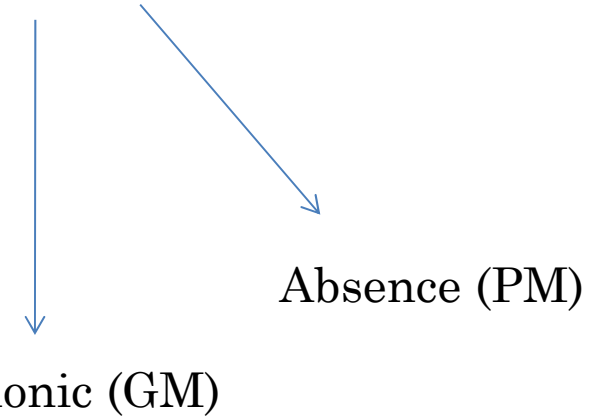
Antiepileptic drugs

Epilepsy classification

- Partial (60%) – Generalized (40%)
- Simple – Complex
  - Most common: Complex-partial



Other epilepsies: Atonic seizures, Infantile spasm, Lennox-Gastaut sy. (G), West sy. (G) etc.

Only 75% can be controlled by drugs!

Epilepsy classification

Classification	Characterization
Partial (Focal) Seizures	Arise in one cerebral hemisphere
Simple partial seizure	No alteration of consciousness
Complex partial seizure	Altered consciousness, automatisms, and behavioral changes
Secondarily generalized seizure	Focal seizure becomes generalized and is accompanied by loss of consciousness
Generalized Seizures	Arise in both cerebral hemispheres and are accompanied by loss of consciousness
Tonic-clonic *(grand mal)* seizure	Increased muscle tone is followed by spasms of muscle contraction and relaxation
Tonic seizure	Increased muscle tone
Clonic seizure	Spasms of muscle contraction and relaxation
Myoclonic seizure	Rhythmic, jerking spasms
Atonic seizure	Sudden loss of all muscle tone
Absence *(petit mal)* seizure	Brief loss of consciousness, with minor muscle twitches and eye blinking

Table 9.1 **Classification of epileptic seizures** as proposed by the International League Against Epilepsy

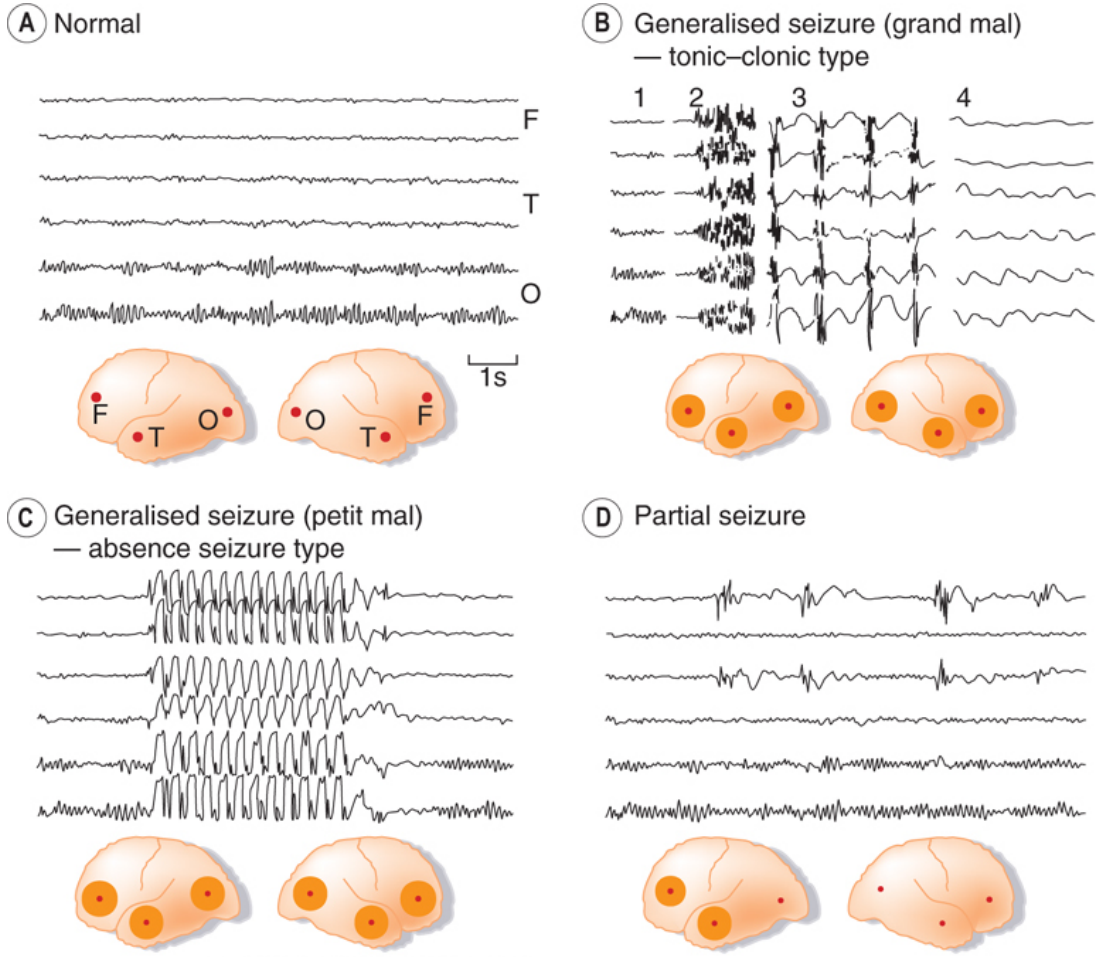
1.	Partial (focal, localized) seizures
1.1	*Simple partial seizures (without alteration of consciousness)*
1.1.1	with motor signs
	focal motor without Jacksonian march
	focal motor with Jacksonian march
	versive
	postural
	phonatory (vocalization without interruption of speech)
1.1.2	with somatosensory or special sensory symptoms (elementary hallucinations)
	somatosensory
	visual
	auditory
	olfactory
	gustatory
	vertiginous
1.1.3	with autonomic symptoms or signs
	epigastric sensations, diarrhea
	pallor
	sweating
	blushing
	gooseflesh
	pupillary dilatation
1.1.4	with mental symptoms and/or disturbances of higher cerebral function (almost always involving alteration of consciousness, i. e., more common in complex partial epilepsy)
	dysphasia
	dysmnesia (e. g., déjà vu)
	cognitive (twilight states, altered sense of time)
	affective (anxiety, agitation)
	illusions (e. g., dysmorphopsia)
	structured hallucinations
1.2	*Complex partial seizures (with disturbance of consciousness, sometimes beginning with simple manifestations only)*
1.2.1	simple partial onset, followed by disturbance of consciousness with simple partial features, followed by disturbance of consciousness with automatisms
1.2.2	with disturbance of consciousness at onset
	with isolated disturbance of consciousness
	with automatisms
1.3	*Partial seizures with secondary generalization to a tonic–clonic (GTC) seizure (synonymous terms: GTC seizures with partial or focal onset; secondarily generalized partial seizures)*
1.3.1	simple partial seizures with secondary generalization
1.3.2	complex partial seizures with secondary generalization
1.3.3	simple partial seizures that develop into complex partial seizures and then become secondarily generalized
2.	Generalized seizures
2.1	*Absence seizures*
	with isolated disturbance of consciousness
	with automatisms
	with mild clonic component
	with atonic component
	with tonic component
	with autonomic component
2.2	*Atypical absences*
	altered muscle tone may be more prominent; seizures may begin and end gradually, rather than abruptly
2.3	*Myoclonic seizures*
	single
	multiple
2.4	*Clonic seizures*
2.5	*Tonic seizures*
2.6	*Tonic–clonic seizures*
2.7	*Atonic seizures*
3.	Unclassifiable seizures

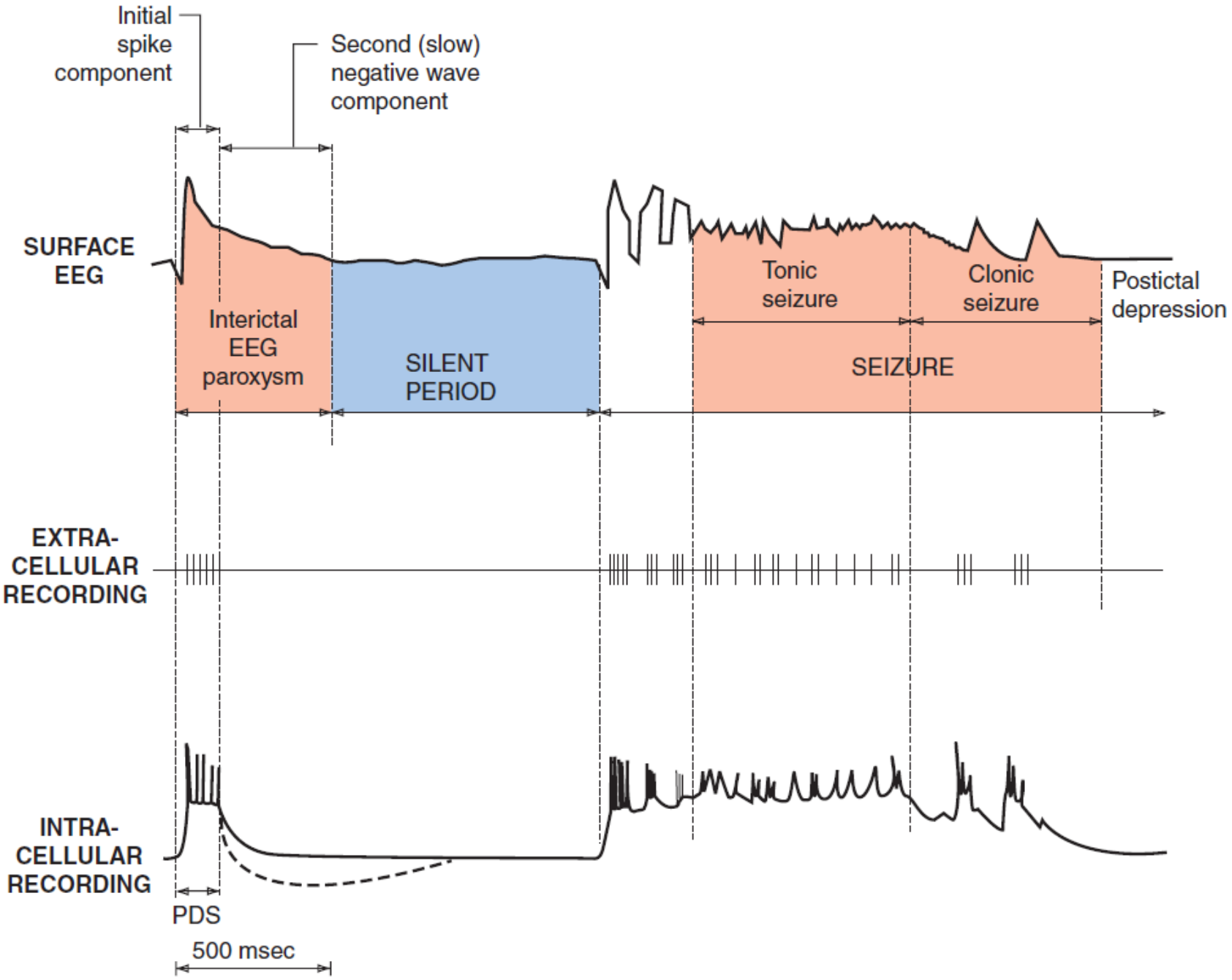
Epilepsy syndromes mainly or exclusivley affecting children

Syndrome	Age group	Features	Remarks
West syndrome (propulsive petit mal, infantile spasms, salaam spasms)	1st year of life	Rocking and nodding movements, twitching of the trunk, forward thrusting of the arms; seizures are very frequent	Often seen in brain-damaged, retarded children. Typical EEG finding: hypsarrhythmia
Febrile seizures	0–5 years	Generalized seizures in febrile children	Later development of true epilepsy is not uncommon
Myoclonic–astatic petit mal (Lennox–Gastaut syndrome)	0–8 years	Variable loss of muscle tone (ranging from nodding to collapse and falling), very brief unconsciousness; frequent seizures	More common in boys; seizures of this type often occur in association with tonic seizures
Typical absences	1–13 years	Very brief period of unconsciousness, rare falls, occasional minor motor phenomena (picking at clothes), vacant stare; many times a day, precipitated by hyperventilation	Sometimes found in association with grand mal seizures (mixed epilepsy); EEG typically shows 3 Hz spike-wave pattern (Fig. 9.3)
Myoclonic seizures (impulsive petit mal)	2nd decade and onward into adulthood	Irregular rocking twitches, more frequent on awakening, no loss of consciousness	Later often combined with grand mal seizures
Benign focal epilepsy of childhood and adolescence	1st and 2nd decades	Focal twitching, usually during sleep; patient is conscious during seizures that occur when he/she is awake; one-third also have generalized seizures	Multiple subtypes; typical EEG pattern with biphasic centro-temporal spikes; good prognosis for spontaneous recovery

EEG records in epilepsy

[**A**] Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. The α rhythm (10/s) can be seen in the occipital region. [**B**] Sections of EEG recorded during a generalised tonic-clonic (grand mal) seizure: 1, normal record; 2, onset of tonic phase; 3, clonic phase; 4, postconvulsive coma. [**C**] Generalised absence seizure (petit mal) showing sudden brief episode of 3/s 'spike and wave' discharge. [**D**] Partial seizure with synchronous abnormal discharges in left frontal and temporal regions.




Initial spike component
Second (slow) negative wave component
SURFACE EEG
Interictal EEG paroxysm
SILENT PERIOD
Tonic seizure
Clonic seizure
Postictal depression
SEIZURE
EXTRA-CELLULAR RECORDING
INTRA-CELLULAR RECORDING
PDS
500 msec

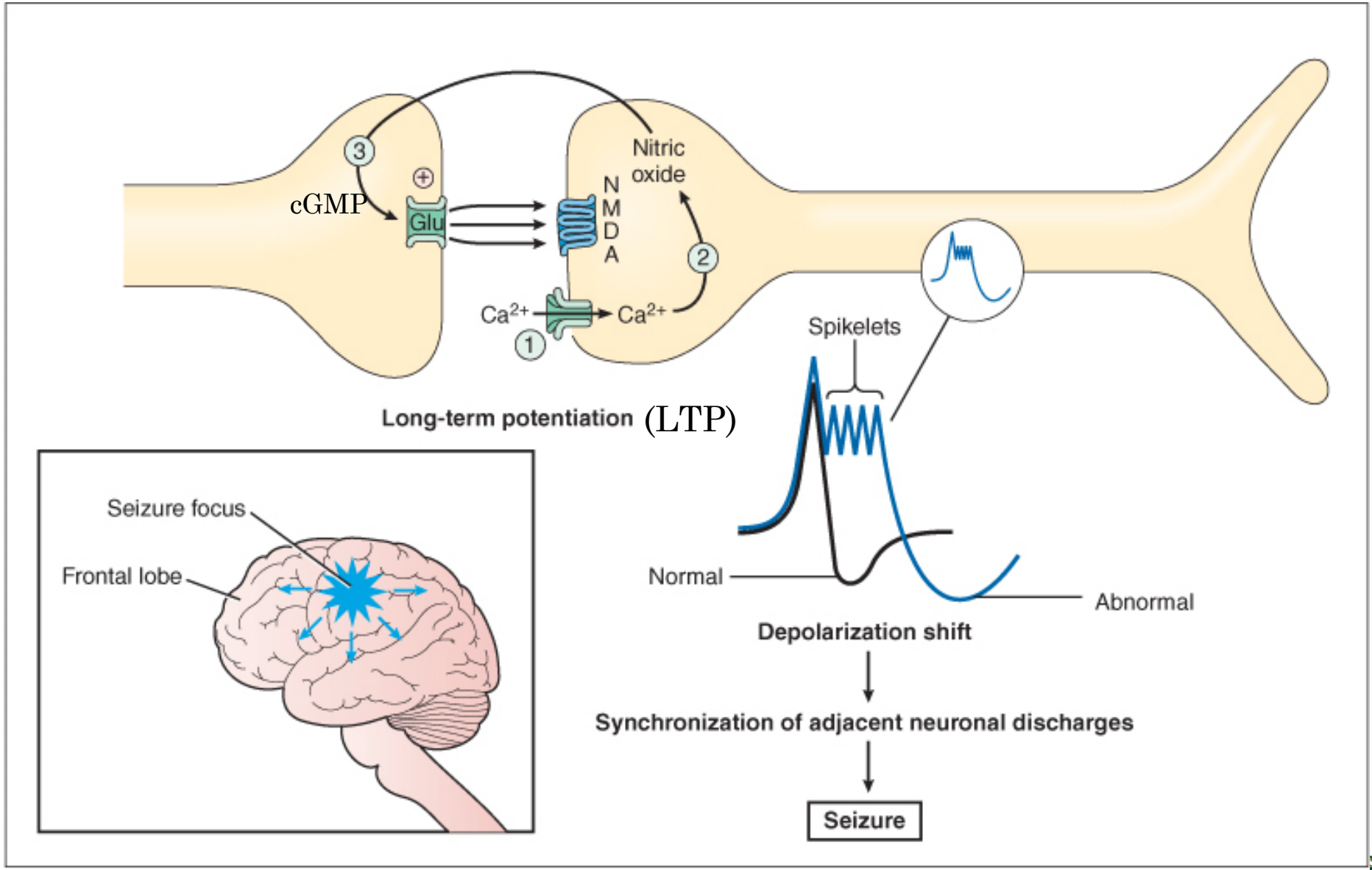
Etiology

- Symptomatic epilepsy
  - Structural lesions in the brain
    - Scar
    - Tumor
    - Congenital malformations
    - Degenerative disorders
  - Metabolic disturbances
    - Hypoglycemia
  - Toxic influences
    - Alcohol
    - Infections
- Idiopathic epilepsies
  - Genetic predisposition without any structural changes
- Cryptogenic epilepsies (symptomatic origin but their cause cannot yet be demonstrated)

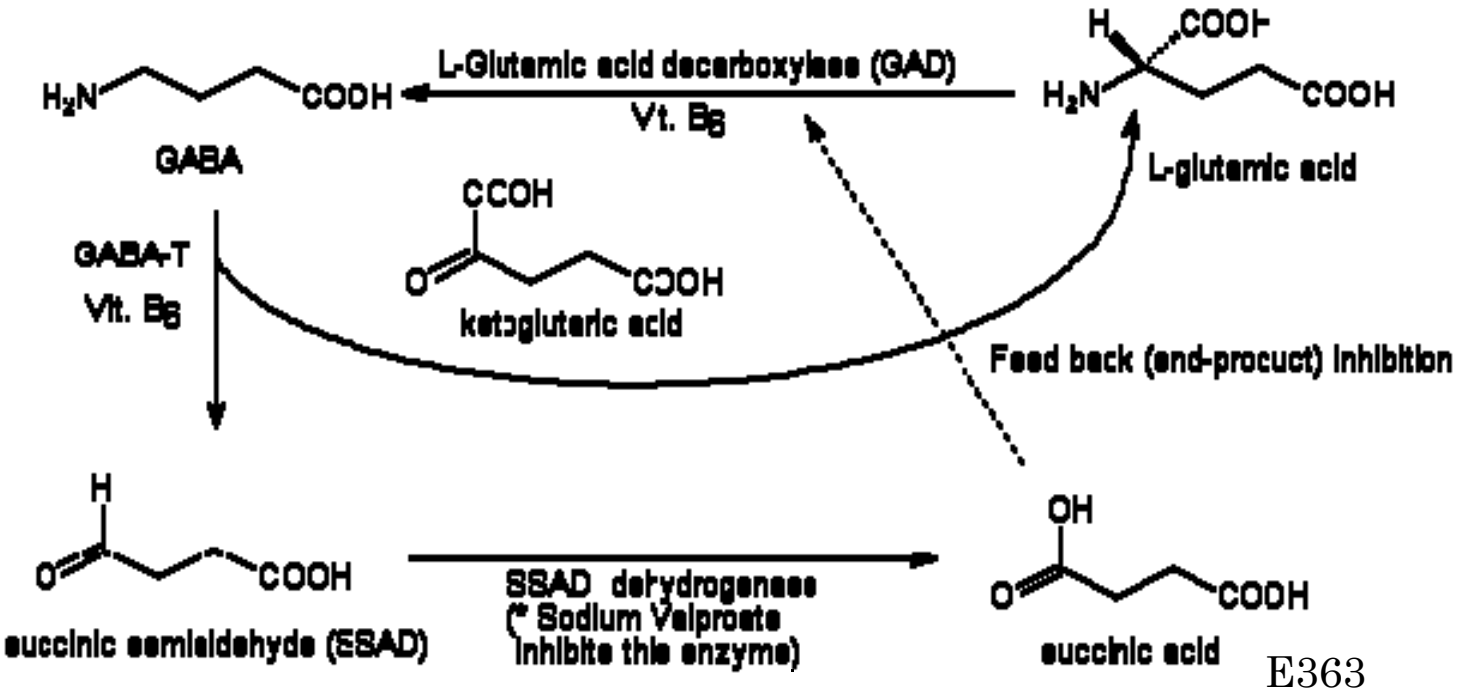
Precipitating factors can be:
Sleep deprivation
Medications
Alcohol withrawal
Strobe lighting
Hyperventilation
Fever

Animal models of epilepsy

- Aluminium oxide, Co slats, penicillin crystals
- Pentylenetetrazole (PTZ), Leptasol, Bicuculline
- Kindling model
- Kainate model
- MES
- Paroxismal Depolarizing Shift (PDS)
- Glutamate
- Neurotrophins (BDNF) (trkA)
- Pilocarpine
- Allylglycine (GAD inhibitor)



Biosynthesis and Metabolism of GABA



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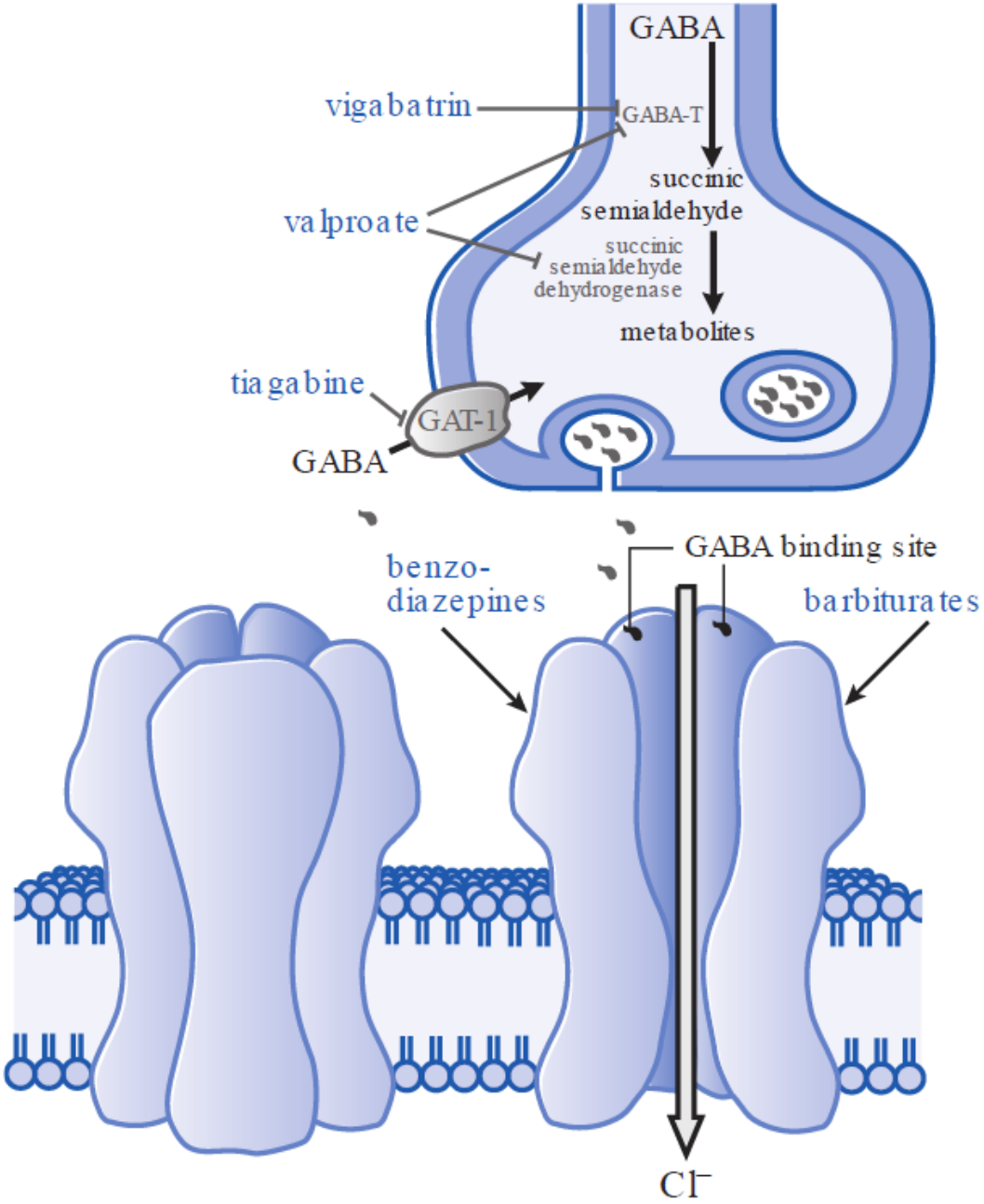
Possible points of modulation

- $GABA_A$ receptor function enhancement (phenobarbital, BZDs)
- GABA transaminase inhibitors (vigabatrin)
- GABA uptake (GAT-1) inhibitor (tiagabin)
- SSAD inhibitor (valproic acid)
- $GABA_A$ receptor agonist (gabapentin(?))



Enhanced GABA synaptic transmission

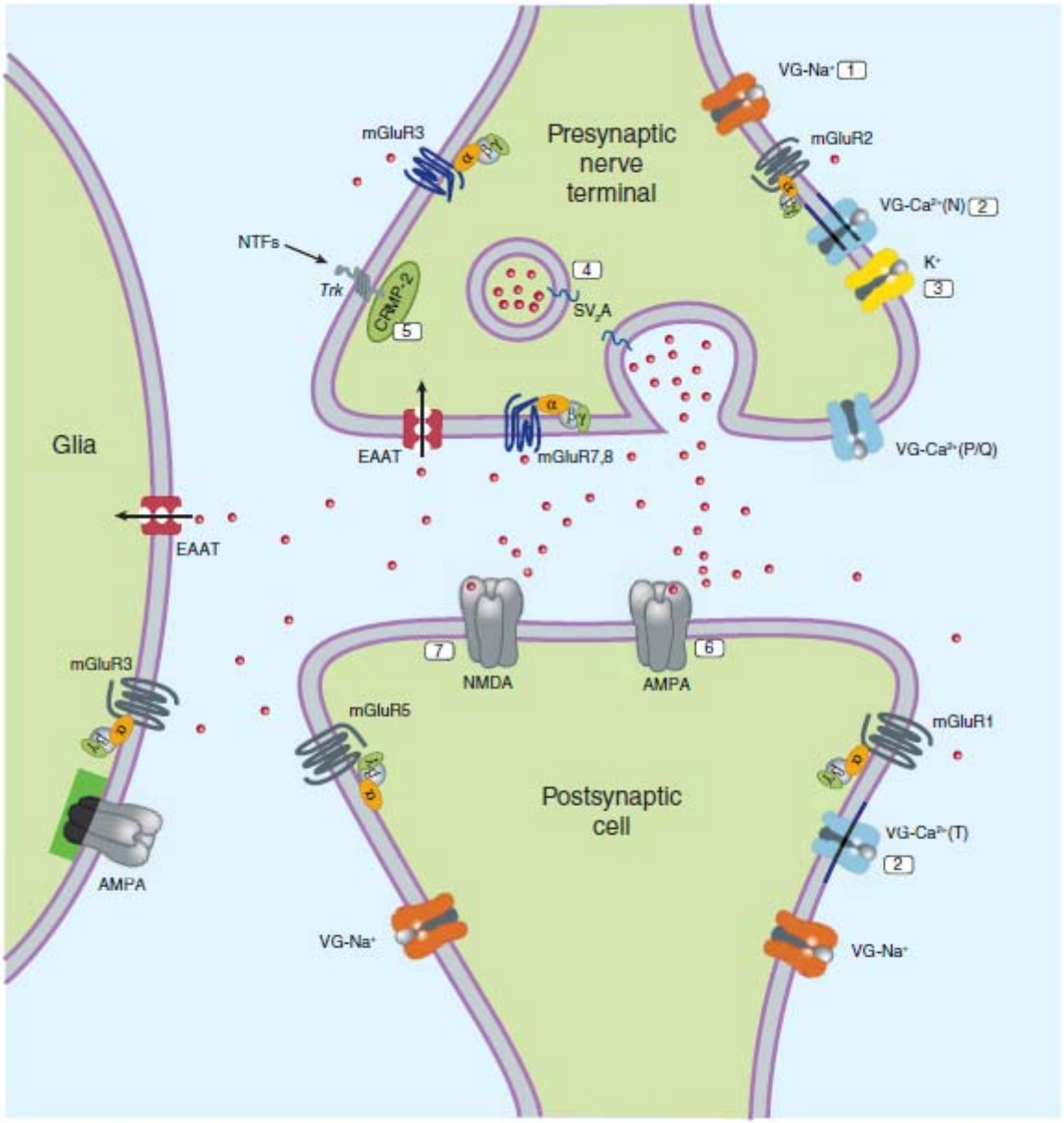


FIGURE 24–1 Molecular targets for antiseizure drugs at the excitatory, glutamatergic synapse. Presynaptic targets diminishing glutamate release include 1, voltage-gated (VG) Na^+ channels (phenytoin, carbamazepine, lamotrigine, and lacosamide); 2, VG-Ca^{2+} channels (ethosuximide, lamotrigine, gabapentin, and pregabalin); 3, K^+ channels (retigabine); synaptic vesicle proteins, 4, SV_2A (levetiracetam); and 5, CRMP-2, collapsin-response mediator protein-2. Postsynaptic targets include 6, AMPA receptors (blocked by phenobarbital, topiramate, lamotrigine, and perampanel) and 7, NMDA receptors (blocked by felbamate). EAAT, excitatory amino acid transporter; NTFs, neurotrophic factors; SV_2A, synaptic vesicular proteins. Red dots represent glutamate.

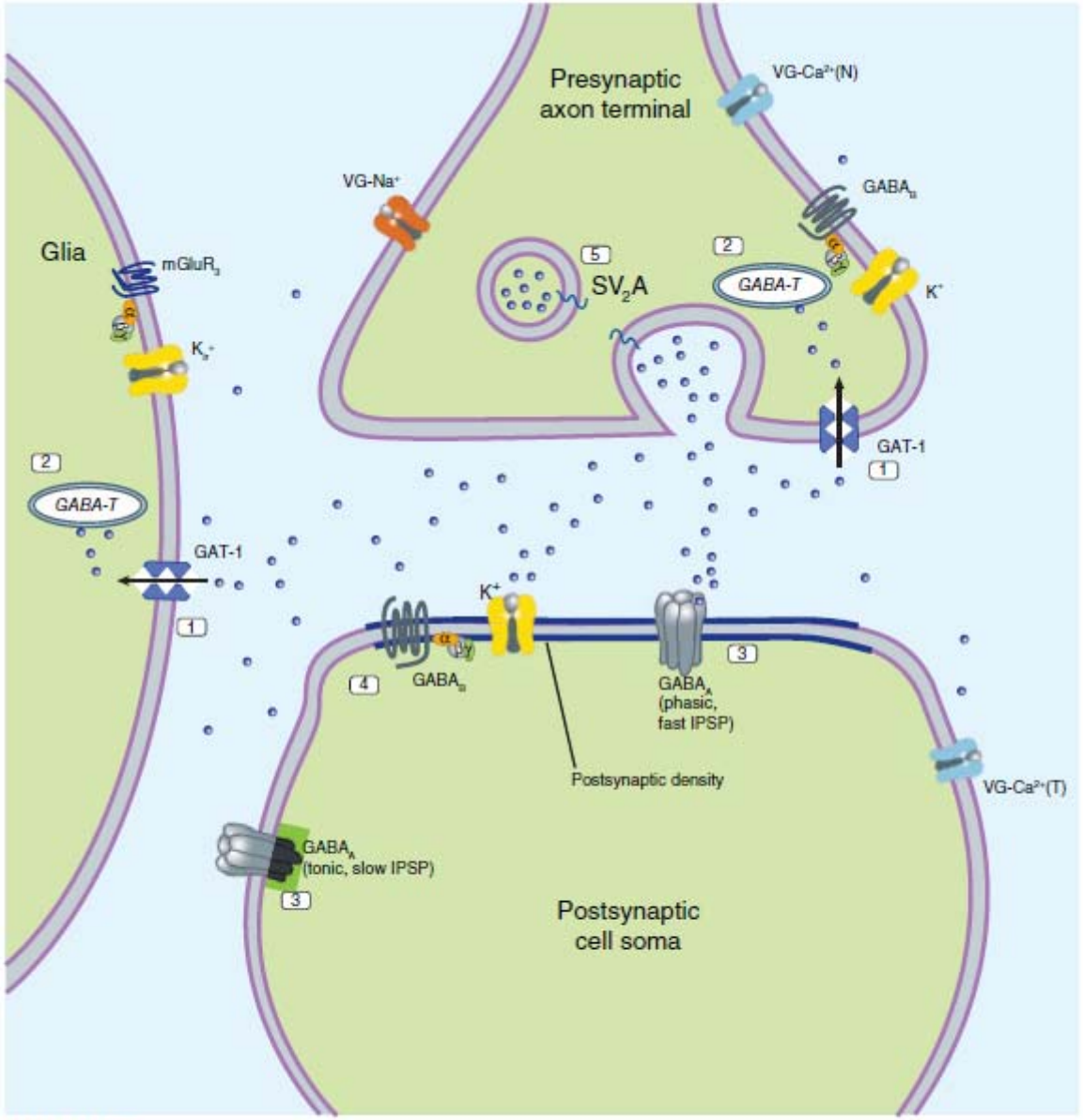
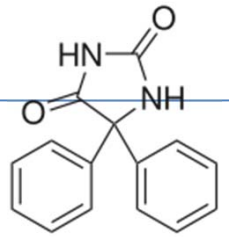


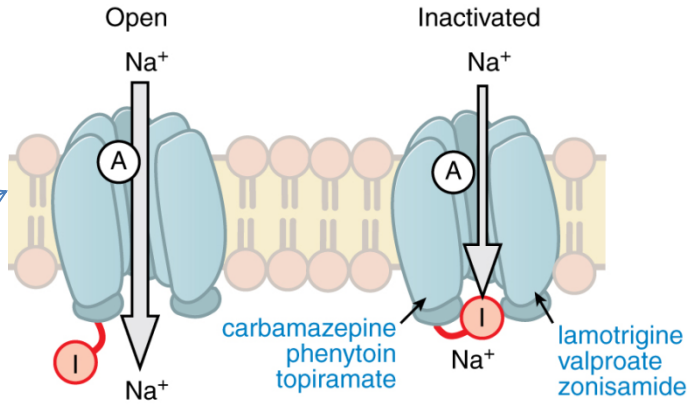
FIGURE 24–2 Molecular targets for antiseizure drugs at the inhibitory, GABAergic synapse. These include "specific" targets: 1, GABA transporters (especially GAT-1, tiagabine); 2, GABA-transaminase (GABA-T, vigabatrin); 3, $GABA_A$ receptors (benzodiazepines); potentially, 4, $GABA_B$ receptors; and 5, synaptic vesicular proteins (SV_2A). Effects may also be mediated by "nonspecific" targets such as by voltage-gated (VG) ion channels and synaptic proteins. IPSP, inhibitory postsynaptic potential. Blue dots represent GABA.

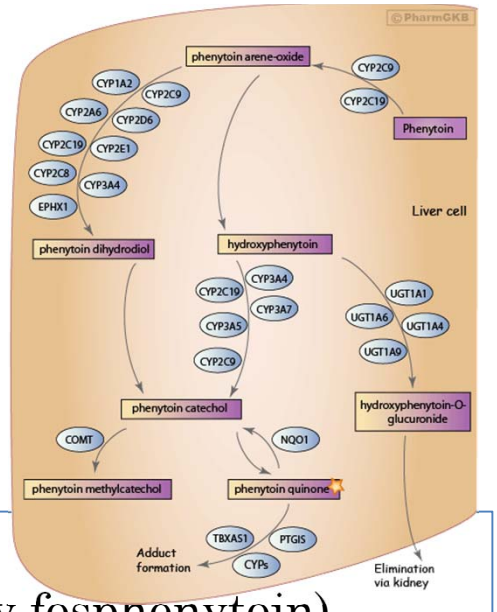
Phenytoin

(DIPHEDAN, EPANUTIN)

Effects:
- Use-dep. Na^+ ch. blocker
- Ca^{++} ch. blocker
- PTP
- 5-HT release↓
- Dopamine uptake ↑
- MAO ↓



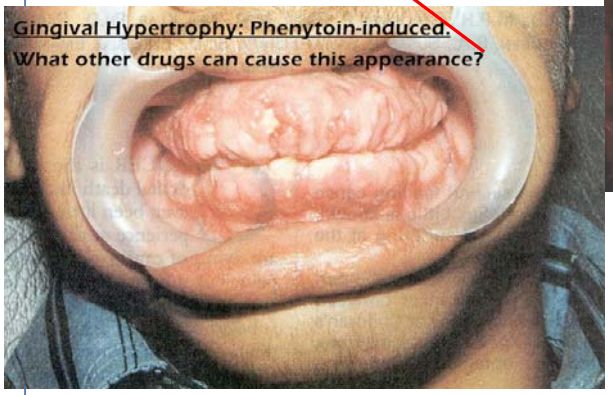


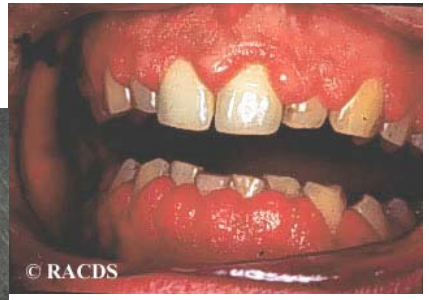


PK:
A: Variable absorption. (i.m. only fosphenytoin)
D: 80-90 % albumin (interaction with salicylates, phenylbutazone, valproate)
M: HMFOS (enzyme induction), 1→0, SATURABLE!
E: glucuronide form (kidney) ($t_{1/2}$= 12-36 h)

Unwanted effects:
Acut: Vertigo, ataxia, headache, nystagmus, morbilliform rashes, arrhythmias
Chr: gingival hyperplasia, hirsutism, megaloblastic anemia, fetal hydantoin sy. idiosyncratically: hepatitis, neoplastic lymphocyte disorders

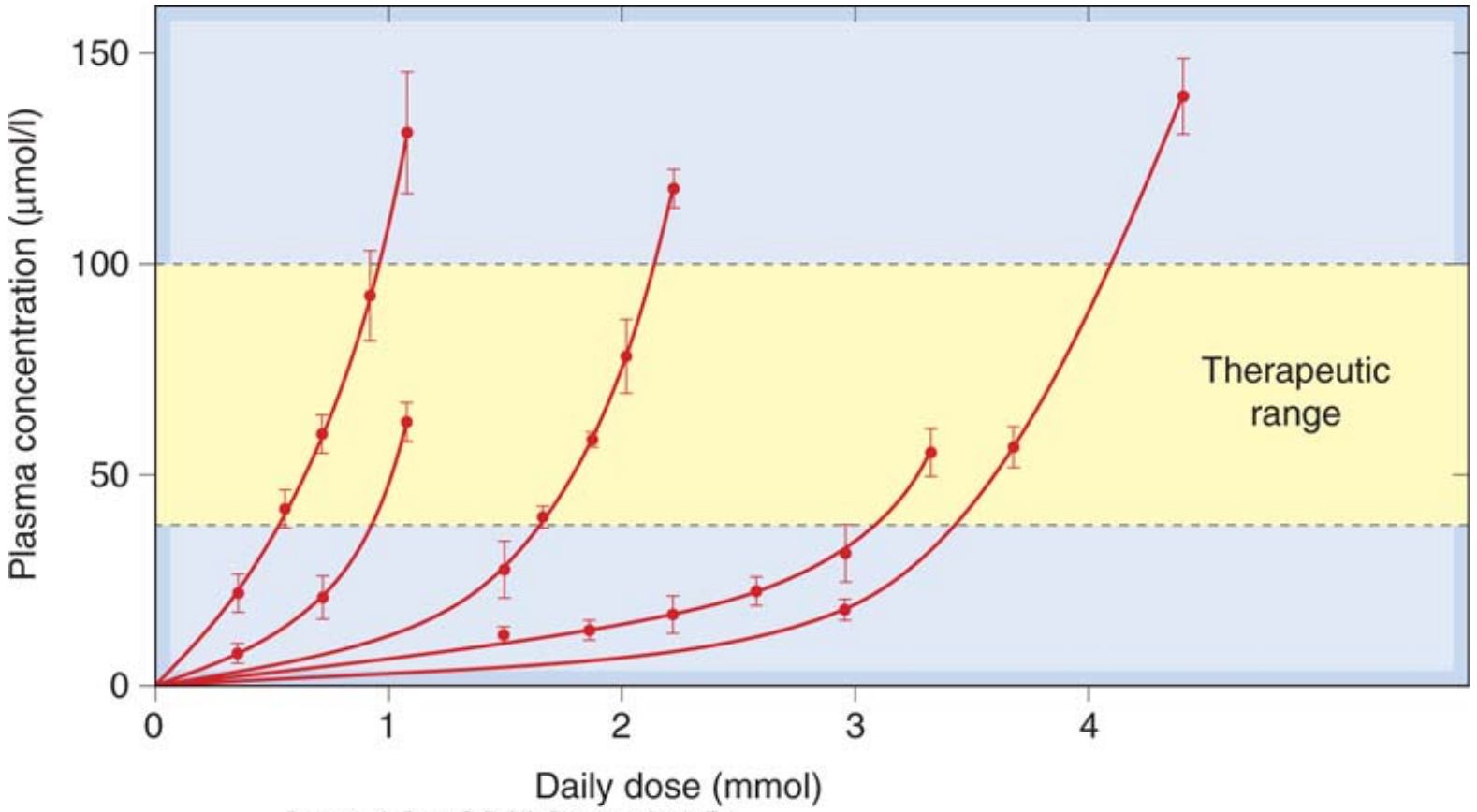
Cyclosporin, amlodipine, nifedipine, phenobarbital, fetal valproate syndrome





Fibroblasts, keratinocytes, collagen, Langerhans cells

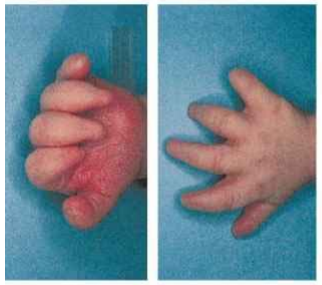
Phenytoin should be administered individually!!!



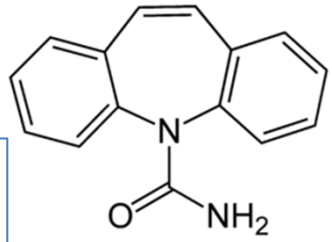
Non-linear relationship between daily dose of phenytoin and steady-state plasma concentration in five individual human subjects. The daily dose required to achieve the therapeutic range of plasma concentrations (40-100 µmol/l) varies greatly between individuals, and for any one individual the dose has to be adjusted rather precisely to keep within the acceptable plasma concentration range.

Fetal hydantoin sy. (FHS)

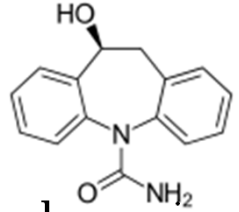
- Cardiac defects
- Malformation of ears and
- Lips, palate, mouth, nasal bridge
- Mental retardation
- Microcephaly
- Underdeveloped nails
- Distal phalanx hypoplasia



Carbamazepine (TEGRETOL, NEUROTOP, STAZEPINE, TIMONIL)



Dibenzazepine (*iminostilbene*) structure related to TCAs
MOA: Slows down the rate of recovery of voltage-activated Na^+ channels
Blocks adenosine receptors → upregulation
Blocks NAT (like TCAs)
Dose: 2-3x400 mg, max: 2000mg/d



Eslicarbazepine

PK
A: Slow and erratical
D: Rapid (V_d~1L/kg), 70-75% protein bound
M: Conversion to 10,11-epoxid (active), CYP3A4, glucuronidation
Induces: CYP2C, 3A4, UDP
E: kidney

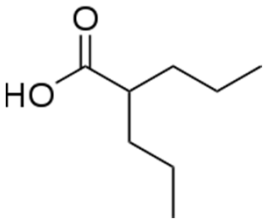
Tox:
Acut: Sedation, ataxia, stupor
resp depression, hyperirritability, convulsions
Chr:Aplastic anemia, agranulocytosis
Nausea, emesis
Diplopia (above 7µg/ml)
Water retention
Enzyme induction
Hepatic transaminases ↑

Clinical indications:
Generalized tonic-clonic
Simple/complex partial
Trigeminal/glossopharyngeal neuralgias
Bipolar affective disorder

Oxcarbazepine (TRILEPTAL) (10,11-dihydro-10-oxocarbamazepine) is a keto analog of carbamazepine. Enzyme iduction is less but not for CYP3A4! (Dose: 600-2400 mg/d)

Valproic acid

(CONVULEX, DEPAKINE, ORFIRIL)



Dose: 20 mg/kg, max: 2400 mg/d

150, 300, 500 mg capsules

MOA

- GABA-transaminase inhibitor
- Voltage-gated Na^+ channel inhibitor
- T-type Ca^{++} channel inhibitor
- Facilitate GAD

Unwanted effects
Anorexia, vomiting later:
Increased apetite/weight gain
Sedation, ataxia, tremor
Rash, alopecia
Thrombocytopenia
Pancreatitis
Hepatic transaminase ↑
Spina bifida

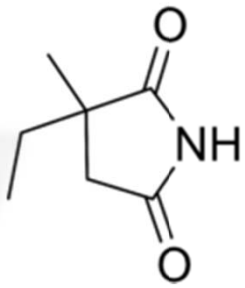
PK
A: good (peak: 1-4 h)
D: Vd~0.15L/kg, binding 90% (sat: 30-50 µg/ml),
Th. plasma level: 30-100 µg/ml
M: t1/2~15h
95% →UGT, ß-oxidation CYP2C9, 2C19,
2-propyl-2-pentenoic acid (active)
2-propyl-4-pentenoic acid (active)
E: 5% unchanged form (kidney)

Clinical use
absence, myoclonic, partial,
and tonic-clonic seizures.
Under invest: HDAC1 inhibition in HIV and cancers (multiple myeloma, melanoma, brain tumors

Fatal hepatic injury in children < 2y
(treated with multiple antiseizure agents)

Ethosuximide

(PETNIDAN)



Dose: 20 mg/kg, max: 1500 mg/d

MOA: T-type Ca^{++} channel blocker

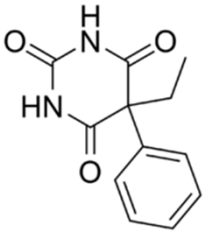
PK
A: good
D: No protein bounding, V_d=0.7 L/kg
M: 75% hepatic microsomal
E: 25% unchanged form (kidney)

Unwanted effects
GI: nausea, vomiting, anorexia (BID to avoid GI upset)
CNS: drowsiness, lethargy, euphoria, dizziness, headache, hiccups
Urticaria, skin reactions, Stevens-Johnson sy., SLE
Bone marrow depression (pancytopenia, aplastic anemia)

Clinical use
Absance

Phenobarbital

(SEVENAL, SEVENALETTA, LUMINAL)



Dose: 50-200 mg, max: 600 mg/d

MOA: $GABA_A$-BZD-Cl^-:

Prolongates the open state of Cl^- channel

PK

A: good

D: 40-60 % protein bound

M: CYP

E: 25% unchanged

10-35 µg/ml plasma cc is required

Unwanted effects

Sedation

Nystagmus, ataxia

Rash (scarlatiform, morbilliform)

Megaloblastic anemia

Osteomalacia

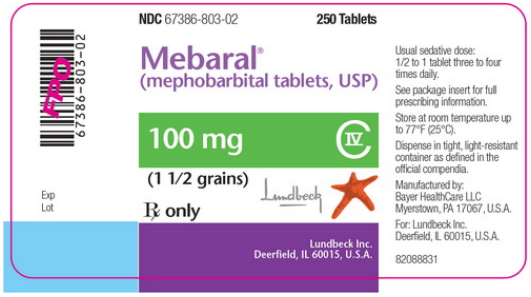
Clinical use

Generalized tonic-clonic seizures

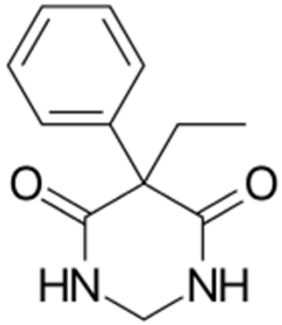
Contraindication

porphyria

Mephobarbital (MEBARAL) is N-methylphenobarbital



Primidon (SERTAN)



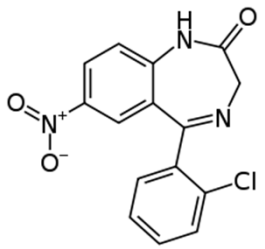
- Barbiturate class
- MOA: inhibits voltage-gated sodium channels
- The active metabolites: phenobarbital, p-hydroxyphenobarbital, and phenylethylmalonamide, are also anticonvulsants.
- Licensed for generalized tonic-clonic and complex partial seizures
- Side effects: drowsiness, listlessness, ataxia, visual disturbances, nystagmus, headache, and dizziness, Dupuytren's contracture, shortening QT

Stiripentol (DIACOMIT)

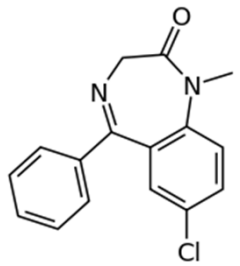
- GABA-related events similar to phenobarbital, enhances GABA release, prolongs GABA action, inhibits LDH
- Only with clobazam and valproate therapy
- Ind: therapy resistant generalized tonic-clonic seizures, myoclonic epilepsy in newborns (SMEI, Dravet sy.)

Benzodiazepines

- For long-term epilepsy treatment
  - Clonazepam (RIVOTRIL, *KLONOPIN*) Dose: 3x1-2 mg/d
  - Clorazepate *(TRANXENE-SD)*
  - Clobazam (FRISIUM)
  - Nitrazepam (EUNOCTIN)
- For Status Epipelpticus
  - Diazepam (SEDUXEN, *VALIUM, DIASTAT*)
  - Lorazepam *(ATIVAN)*



Clonazepam



Diazepam

MOA

$GABA_A$-BZD-Cl^-: Increase the frequency of open state of Cl^- channel

PK

A: good (clorazepate (+HCl) → nordazepam

D: Clonazepam 85% protein bound

Diazepam 99%

Lipid soluble (redistribution)

M: CYP 3A4, 2C19

N-desmethyl-diazepam, oxazepam

partial agonists

E: glucuronide form (kidney)

Unwanted effects

Drowsiness, lethargy

Ataxia

Hypotony

Dizziness

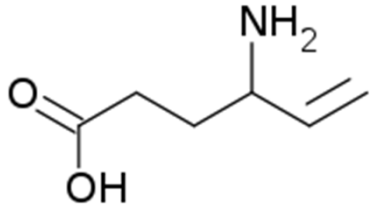
Behavioral disturbances (aggression, hyperactivity, irritability,

Anorexia-hyperphagia

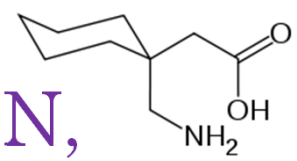
Antidote: Flumazenil (ANEXATE)

Vigabatrin (SABRIL) γ-vinyl-GABA

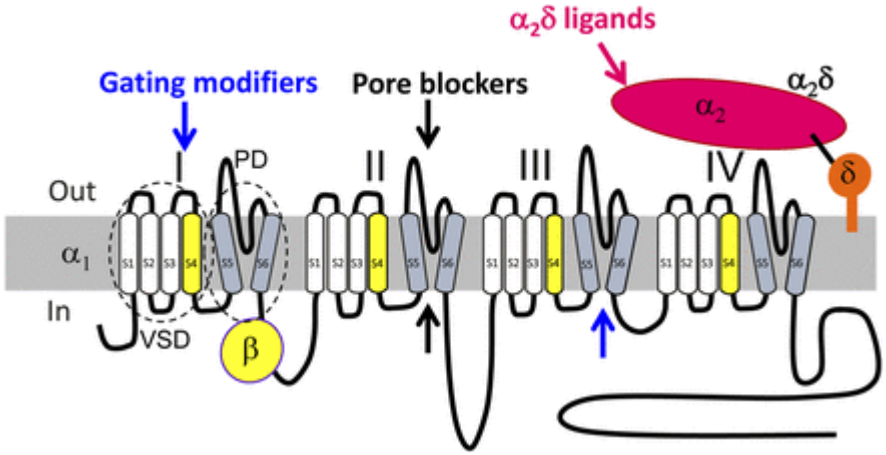
- MOA: irreversibly inhibits GABA transaminase
- Vigabatrin is a racemic compound, and its [S]-enantiomer is pharmacologically active
- Unwanted eff: somnolence, headache, dizziness, diplopia,peripheral visual field defect (in every half year kinetic perimetry determination is necessary) (Taurin depletion → irreversible diffuse atrophy of the retinal nerve fibre.)
- Adjunctive treatment (with other drugs) in treatment resistant epilepsy, complex partial seizures, secondary generalized seizures, and for monotherapy use in infantile spasms in West syndrome
- Eliminated by the kidney! Dose reduction if creatinine clearance < 60ml/min!



Gabapentine (GABAGAMMA, NEURONTIN, NEUROBA, GRIMODIN, GORDIUS)



- MOA: Inhibits α2δ subunit of the cortical L-type voltage-sensitive Ca^{2+} channel
- GABA releaser
- PK: Absorbs with L-amino acid carrier system (saturable!), $t_{1/2}$ = 4-6 h, excreted unchanged, kidney failure: dose should be reduced (creatinine clearance describes the excretion), can be removed by dialization
- Th use: partial seizures, neuropathic pain, hot flashes, and restless legs syndrome. Adm. 2-3 times/day.



Pregabalin (LYRICA)

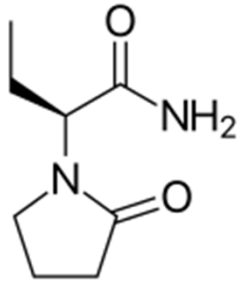
MOA: Like gabapentin, pregabalin binds to the α2δ subunit of the VDCC in the central nervous system.
PK: good absorption, $t_{1/2}$ 6-12 h

Levetiracetam (KEPPRA, LEVIL, KAPIDOKOR)

- MOA: blocks N-type Ca^{2+} channels, reduces Ca^{2+} release from ic. stores, binds to synaptic vesicular protein 2A
- PK: A. good, (F=1), D: No protein bounding, time C_{max}= 1.3 h, Vd= 0.5 l/kg, M: acetamide group hydrolysis (CYP independent), ucb L057 active metabolite, E: kidney (60% unchanged form), $t_{1/2}$=7.5 h, clearance 1 ml/min/kg
- Th use: Recommended in adjuvant therapy, partial and secondarily generalized tonic-clonic seizures.

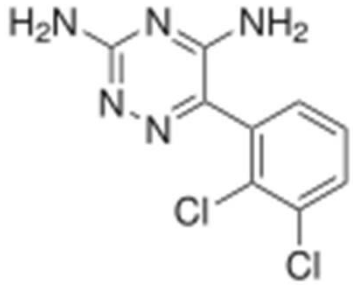
Brivaracetam

4-n-propyl analog of levetiracetam
MOA: synaptic vesicle protein 2A (SV2A) ligand



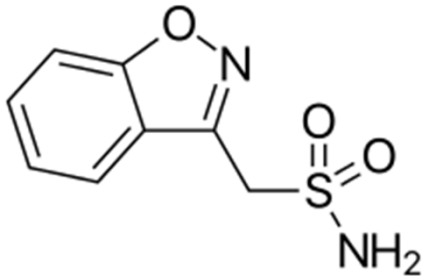
Lamotrigine (LAMICTAL, GEROLAMIC, LAMITRIN, LAMOLEP, LATRIGIL)

- MOA: Use-dep. Na^+ ch. blocker
- PK: A: good, D: 55% binds to plasma proteins, Vd: 1 l/kg, M: (UDP-glucuronyl-transferase) glucuronidation (valproic acid inhibits it significantly), E: 10% without metabolization, 98% by the kidney
- Th use: Partial and secondarily generalized tonic-clonic seizures in adults and Lennox-Gastaut syndrome in both children and adults. Bipolar disease



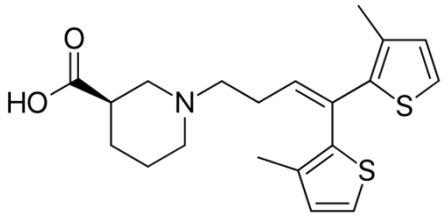
Zonisamide (ZONEGRAN)

- MOA: Use-dep. Na^+ ch. blocker, T-type Ca^{2+} channel blocker
- PK: A: good, D: 40% protein bound, M: CYP3A4 (sulfamoylacetyl phenol), E: 85 % unchanged in urine, $t_{1/2}$: 60-80 h
- Th use: refractory partial seizures (partial-onset seizures; infantile spasm, mixed seizure types of Lennox–Gastaut syndrome, myoclonic and generalized tonic clonic seizure.) + adjunctive therapy in Parkinson's disease
- Unwanted effects:
  - sulfonamide (allergic) reaction
  - Acute myopy and closed-angle glaucoma
  - Suicide behavior
  - Nephrolithiasis
  - Metabolic acidosis
  - Pancreatitis
  - Rhabdomyolisis
  - Heat stroke
  - Appetite suppression
  - Weight loss



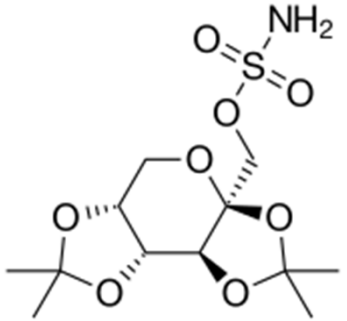
Tiagabine (GABITRIL)

- MOA: GABA reuptake (GAT-1) inhibitor (GRI)
- PK: A: OK, D: Protein bound, M: CYP3A, $t_{1/2}$= 8 h.
- Unwanted e: dizziness, somnolence, and tremor
- Th use: Tiagabine is effective as add-on therapy of refractory partial seizures, with or without secondary generalization.



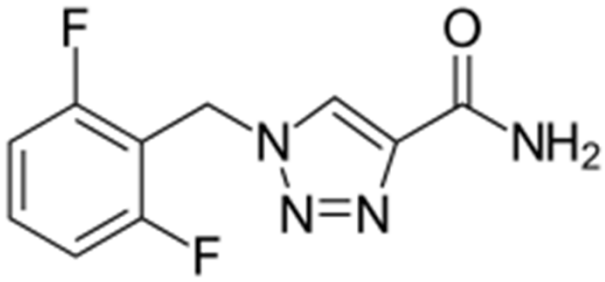
Topiramate (TOPAMAX, TOPEPSIL, TOPILEX, TALOPRAM, ETOPRO)

- MOA: Use-dep. Na^+ ch. blocker, activates a hyperpolarizing K^+ current, limits activation of the AMPA-kainate-subtype(s) of glutamate receptor, weak CA inhibitor (do a little of everything)
- PK: A: OK, D: 10-20 % prot bound, indices CYP3A4, E: unchanged (kidney), reduces estradiol level (!)
- Unwanted effects: somnolence, fatigue, weight loss, renal calculi, visual field defects
- Th use: partial and primary generalized epilepsy, migrain prevention



Rufinamide (INOVELON)

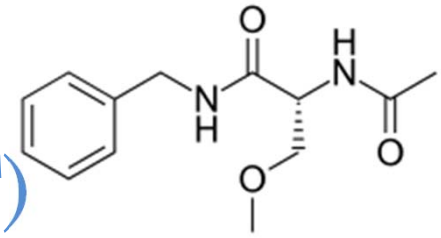
- MOA: enhancing sodium channel inactivation and may also inhibit GABA reuptake, Inhibits voltage-gated sodium channels
- PK: Low protein binding, not betabolized by CYP.
- Ind: Lennox-Gastaut sy, partial seizures.



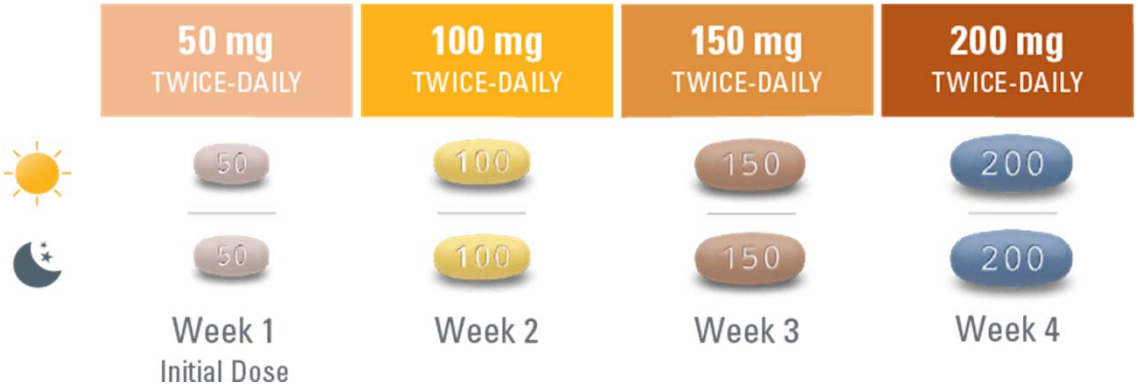
Retigabine, Ezogabine (POTIGA)

- MOA: KCNQ/Kv7 potassium channel opener that underlie the M current which controls membrane excitability
- Quickly absorbes, Oral bioavailability 50–60%, a high volume of distribution (6.2 L/kg), and a terminal half-life of 8 to 11 hours. Retigabine requires 3 daily dosing due to its short half-life.
- Ophthalmologic control is necessary in every half a year (retineal pigmentation), Side effects: drowsiness, dizziness, tinnitus and vertigo, confusion, and slurred speech. Less common side effects included tremor, memory loss, gait disturbances, and double vision.

Lacosamide (VIMPAT)



- MOA: act through voltage-gated sodium channels.
- A: oral bioavailability of nearly 100%. D: Less than 15% albumine binding. M: CYP2C9, CY2C19, and CYP3A4-mediated demethylation. E: 98% kidney
- Adjunctive treatment of partial-onset seizures and diabetic neuropathic pain.



Newer compounds 1.

- Ganaxolone
  - MOA: structurally resembling endogenous neurosteroids
- Tonabersat
  - MOA: neuronal gap junction inhibitor
- Perampanel (FYCOMPA)
  - MOA: selective non-competitive antagonist of AMPA receptor
  - PK:
    - half-life of approximately 70-110 hours
    - 95% bound to plasma proteins
    - metabolism CYP3A4. No induction or inhibition of P450 enzymes.
    - 70% of the dose is excreted in the feces and 30% in the urine; less than 2% of the dose is excreted unchanged into the urine.

Newer compounds 2.

- Brivaracetam
  - 4-n-propyl analog of levetiracetam
  - MOA: synaptic vesicle protein 2A (SV2A) ligand
- Nefiracetam
- Seletracetam
- Imepitoin (PEXION)
  - MOA: $GABA_A$ receptor agonist, Ca^{++} ch blocker
  - ONLY FOR VETERINARY MEDICINE (DOGS)!
- ICA-105665
  - MOA: highly selective opener of neuronal Kv7 (KCNQ) potassium channels
- NAX 810-2
  - MOA: Galanin based analogue
- VX-765
  - MOA: potent and selective inhibitor of interleukin-converting enzyme/caspase-1 with K_i of 0.8 nM
- YKP3089

<u>Other directions of investigation:</u>

Use of pharmacophores

Adenosine Kinase (ADK) and RNAi

N-Hydroxymethyl-p-isoproxyphenylsuccinimide (HMIPPS)

4 P-glycoprotein

Aromatase Inhibitors (AIs)

Antiepileptic drugs in the clinical practice

Antiepileptic drugs of choice depending on the type of seizure (after Donati, in Hess). Drugs of second and third choice are listed in alphabetical order

	Partial seizures with or without generalization	**Absences**	**Primary generalized tonic–clonic seizures**	**Myoclonic seizures**	**West syndrome (salaam seizures)**	**Lennox–Gastaut syndrome** (myoclonic–astatic seizures)	**Rolandic epilepsy** (benign epilepsy of childhood and adolescence, with central spikes on EEG)
1st choice	carbamazepine valproate	valproate ethosuximide	valproate	valproate	valproate vigabatrin	valproate	carbamazepine sulthiame (not available in USA)
2nd choice	gabapentin lamotrigine oxcarbazepine phenytoin tiagabine topiramate levetiracetam	lamotrigine	lamotrigine	clonazepam ethosuximide lamotrigine	ACTH	ACTH clobazam felbamate	valproate
3rd choice	vigabatrin clonazepam phenobarbital primidone	clonazepam	phenobarbital primidone	primidone	clonazepam	carbamazepine phenytoin	phenytoin

ANTISEIZURE DRUGS

TONIC-CLONIC & PARTIAL SEIZURES	ABSENCE SEIZURES	MYOCLONIC SEIZURES	BACK-UP ADJUNCTIVE DRUGS
CARBAMAZEPINE	ETHOSUXIMIDE	VALPROIC ACID	FELBAMATE
PHENYTOIN	VALPROIC ACID	CLONAZEPAM	GABAPENTIN
VALPROIC ACID	CLONAZEPAM		LAMOTRIGINE
			LEVETIRACETAM
			TIAGABINE
			TOPIRAMATE
			VIGABATRIN
			ZONISAMIDE

Clinical indications of antiepileptic drugs

- **Drugs for Partial Seizures and Generalized Tonic-Clonic Seizures**
  - Carbamazepine (TEGRETOL)
  - Oxcarbazepine (TRILEPTAL)
  - Phenytoin (DILANTIN)
  - Phenobarbital (LUMINAL)
  - Primidone (MYSOLINE)
  - Valproic acid (DEPAKENE)
- **Adjunct Drugs for Partial Seizures**
  - Clorazepate (TRANXENE)
  - Felbamate (FELBATOL)
  - Gabapentin (NEURONTIN)
  - Lamotrigine (LAMICTAL)
  - Topiramate (TOPAMAX)[a]
- **Drugs for Generalized Absence, Myoclonic, or Atonic Seizures**
  - Clonazepam (KLONOPIN)
  - Ethosuximide (ZARONTIN)
  - Lamotrigine (LAMICTAL)
  - Valproate (Valproic acid, DEPAKENE)
- **Drugs for Status Epilepticus**
  - Diazepam (VALIUM)
  - Lorazepam (ATIVAN)
  - Phenobarbital (LUMINAL)
  - Fosphenytoin (CEREBYX)

Contraindocations

- Absolute contraindocations
  - Allergy
  - Idiosyncratic effect
- Realtive contraindications
  - Pregnancy
  - Breast feeding
  - Other (drug specific)

Marketed antiepileptics in Hungary

- acetazolamid
- ACTH
- diazepam
- eslicarbazepin (ESL)
- ethosuximid (ESM)
- felbamat (FBM)
- phenitoin (PHT)
- phenobarbital (PB)
- gabapentin (GBP)
- carbamazepin (CBZ)
- clobazam (CLB)
- clonazepam (CLO)
- lacozamid (LAC)
- lamotrigin (LTG)
- levetiracetam (LEV)
- nitrazepane (NTZ)
- oxcarbazepin (OXC)
- pregabalin
- primidon (PRM)
- retigabin (RG)
- rufinamid (RUF)
- steroid
- sulthiam, (SUL)
- tiagabin (TGB)
- topiramát (TPM)
- valproát (VPA)
- vigabatrin (VGB)
- zonisamid (ZNS)

Drug-drug interactions

- 1. Plasma protein binding
  - High: VPA, BDZ, CBZ, PHT, PHB, PRM
  - Medium: LTG, ESC, FBM, OXC
  - No interaction: LEV, TPM, GBP,PGB, VGB, ZNS
- 2. Liver enzymes (CYP450)
  - 3A4 inducer: CBZ, OXC, PHT,PHB, PRM
  - 1A2 inducer: CBZ
  - 2C9, 2C19 inducer: CBZ, PHT, PHB, OXB
  - 2C9, 2C19 inhibitor: VPA (!)
  - No effect at all: GBP, LTG, LEV, GVG, ZON

Interactions of Anti-Seizure Drugs with Hepatic Microsomal Enzymes

	INDUCES		INHIBITS		METABOLIZED BY	
DRUG	CYP	UGT	CYP	UGT	CYP	UGT
Carbamazepine	2C9/3A	Yes			1A2/2C8 2C9/3A4	No
Ethosuximide	No	No	No	No	?	?
Gabapentin	No	No	No	No	No	No
Lacosamide	No	No	No	No	2C19	?
Lamotrigine	No	Yes	No	No	No	Yes
Levetiracetam	No	No	No	No	No	No
Oxcarbazepine	3A4/5	Yes	2C19	Weak	No	Yes
Phenobarbital	2C/3A	Yes	Yes	No	2C9/19	No
Phenytoin	2C/3A	Yes	Yes	No	2C9/19	No
Pregabalin	No	No	No	No	No	No
Primidone	2C/3A	Yes	Yes	No	2C9/19	No
Rufinamide	3A4	2C9/19	No	?	No	Yes
Tiagabine	No	No	No	No	3A4	No
Topiramate	No	No	2C19	No		
Valproate	No	No	2C9	Yes	2C9/19	Yes
Vigabatrin	No	No	No	No	No	No
Zonisamide	No	No	No	No	3A4	Yes

CYP, cytochrome P450; UGT, uridine diphosphate-glucuronosyltransferase.

International League Against Epilepsy (ILAE) guideline

- First line drugs: CBZ, PHT, LEV, ZON
  - But PHT has serious side effects and ZON is very expensive.
- Other possible first line drugs: LAM (focal), VAL (gen), SUC (absance)
- Monotherapy first with a selected drug, then change to another drug (bridging), then combinational therapy
- Original-generic or generic-generic change is the only competence of the neurologist, not the physician, nor the pharmacist have any competence in it.

Therapeutic considarations

- Monotherapy first with a selected drug, then change to another drug (bridging), then combinational therapy
- Original-generic or generic-generic change is the only competence of the neurologist, not the physician, nor the pharmacist have any competence in it.
- Vitamine-D plasma control and supplementation!

KEY DRUGS		
SUBCLASS	**PROTOTYPE**	**OTHER SIGNIFICANT AGENTS**
BARBITURATE	Phenobarbital	Primidone
BENZODIAZEPINE	Diazepam	Clonazepam, clorazepate, lorazepam, nitrazepam
CARBOXYLIC ACIDS	Valproic acid	Sodium valproate
HYDANTOINS	Phenytoin	Fosphenytoin
SUCCINIMIDES	Ethosuximide	Phenosuximide
TRICYCLICS	Carbamazepine	Oxcarbazepine
NEWER AGENTS	Felbamate, gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, vigabatrin, zonisamide	

KEY DRUGS	
SUBCLASS	**Adverse effects**
BARBITURATE	Sedation tolerance and dependence
BENZODIAZEPINE	Sedation tolerance and dependence
CARBAMAZEPINE	Diplopia, ataxia, teratogenic
PHENYTOIN	Diplopia, ginvgival hyperplasia, ataxia, anemia
VALPROIC ACID	GI symptoms, hepatotoxic