LNCT GROUP OF COLLEGES

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Designation: Associate Professor

Department: LNCP

Subject: Medicinal Chemistry

Code: BP-402T Unit: IV(C)

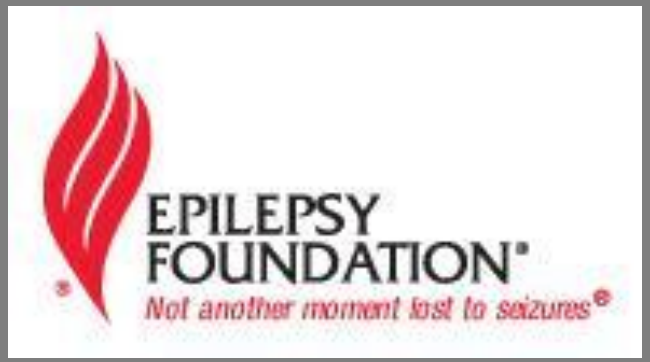
Topic: Anticonvulsants-Mechanism of action

Objectives

- At the end of this lecture, pharmacy students should be able to:
  - describe the overall neurochemistry of seizures (AED targets).
  - list the procedures to induce seizures.
  - contrast by PD and AE the different 1st generation AED.

Epidemiology of Epilepsy

- 200K new cases/year
- Age: 20: 1%; 75: 3%
- Minorities > Caucasians
- Developing (2) : Developed (1)



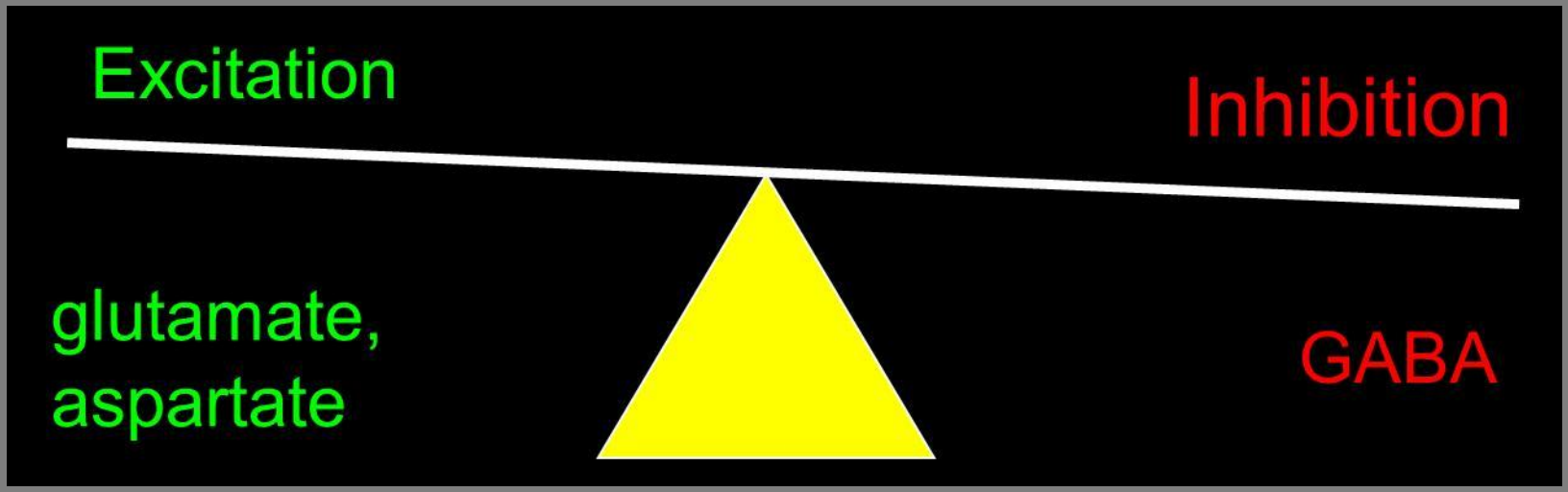
Condition	%
mental retardation	26
stroke	22
Cerebral palsy	13
lzheimer's Disease	10

Seizure Classification

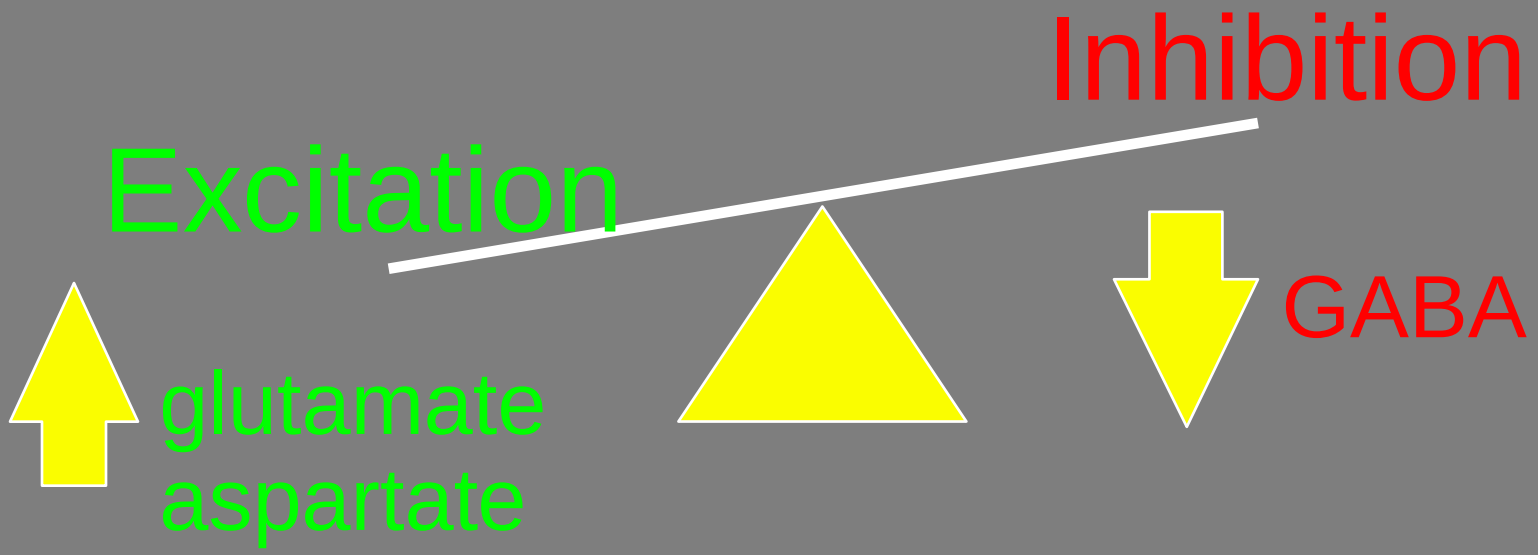
- Partial (focal): origin of seizure is localized
  - simple partial: consciousness maintained
  - complex partial: consciousness lost
- Generalized: origin of seizure is distributed
  - tonic-clonic (grand mal$_g$):
    - tonic: continuous muscle contraction
    - clonic: rapid contraction & relaxation
  - absence (petit mal$_p$): brief loss of consciousness

p

Normal CNS Function



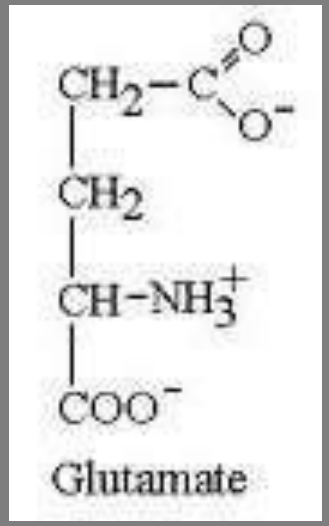
Hyperexcitability reflects both increased excitation and decreased inhibition



Comparison

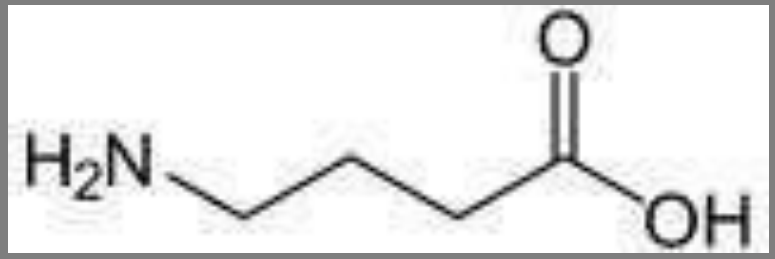
Glutamate

- Ionotropic
  - NMDA
  - AMPA
  - kainate
- Metabotropic
  - mGluR1
  - mGluR2
  - mGluR3
  - mGluR4
  - mGluR5
  - mGluR6
  - mGluR7
  - mGluR8



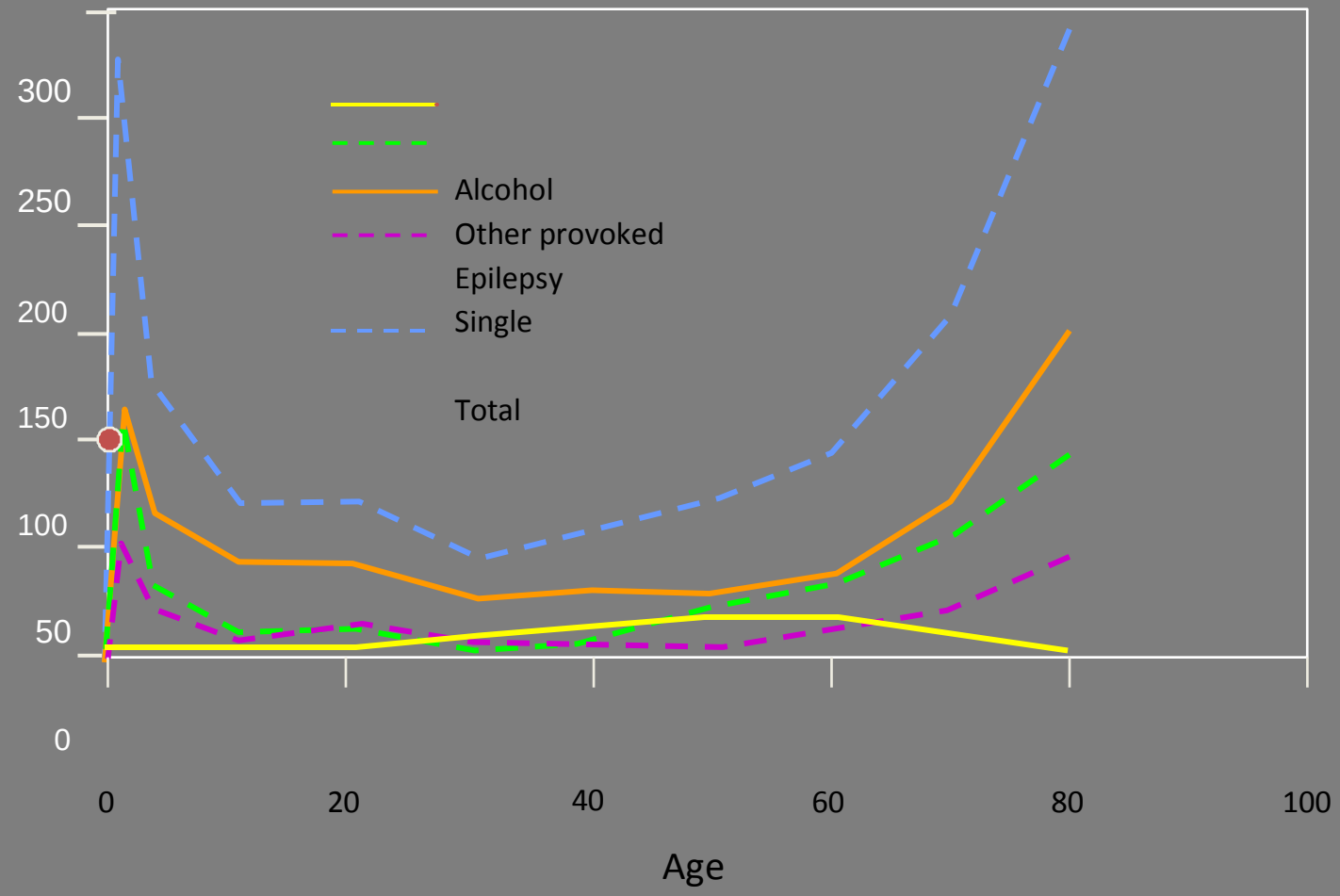
GABA

- *Ionotropic*
  - $GABA_A$
- *Metabotropic*
  - $GABA_B$

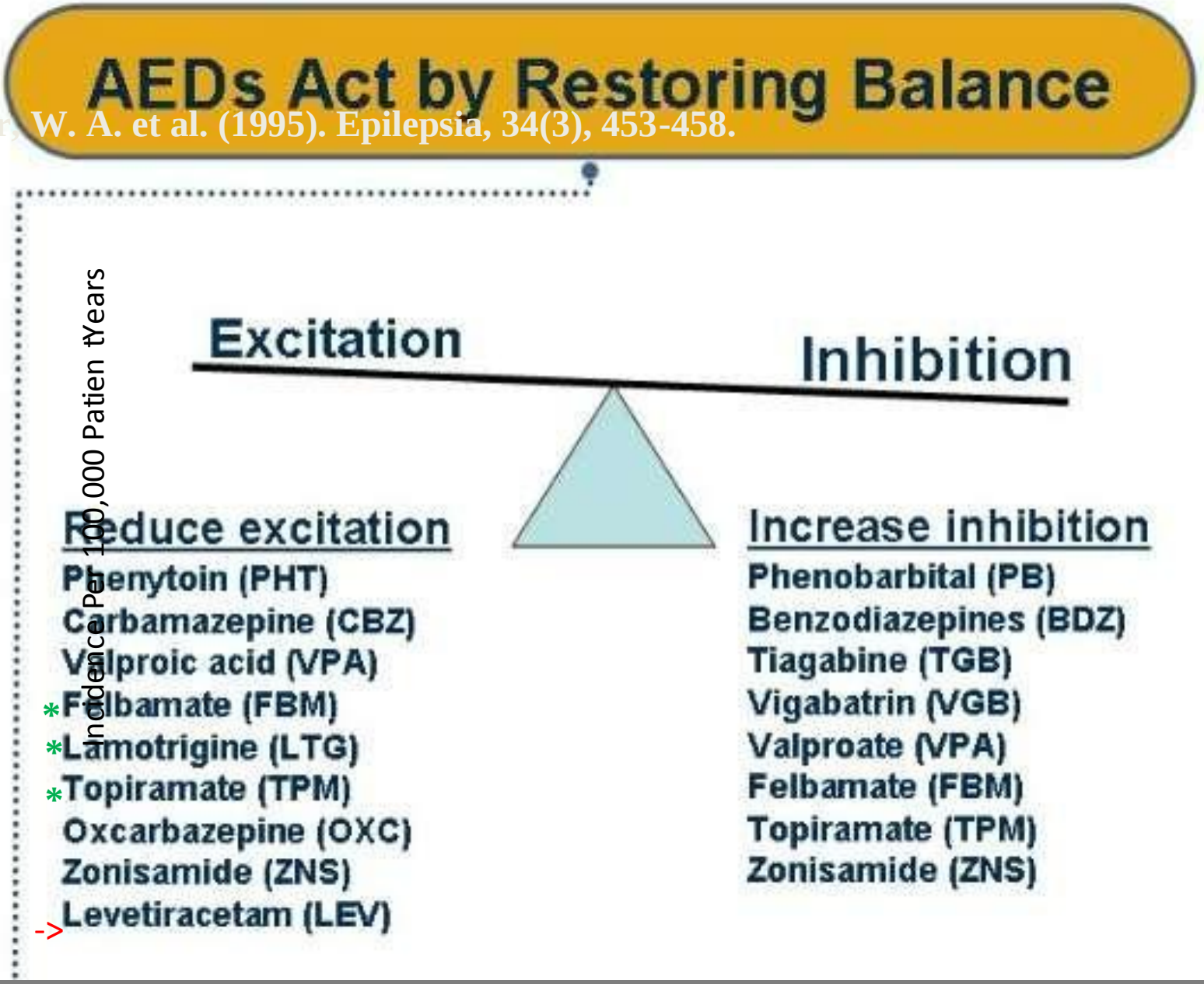


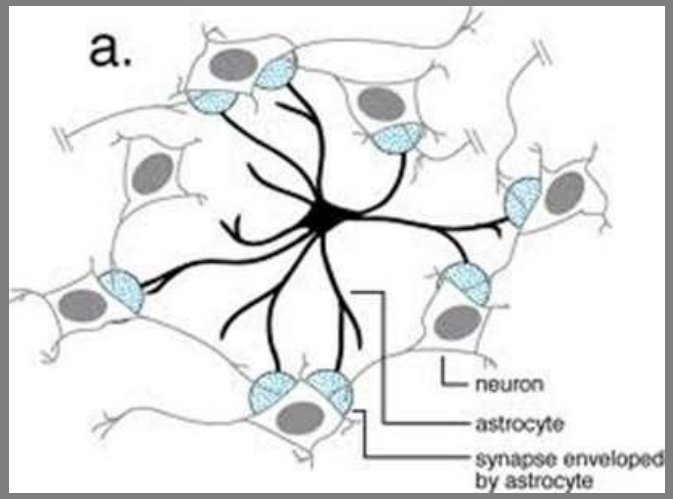
AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Overall Incidence of Convulsive Disorders: Increased frequency at extremes of age (Rochester, MN 1935-84)



Hauser, W. A. et al. (1995). Epilepsia, 34(3), 453-458.



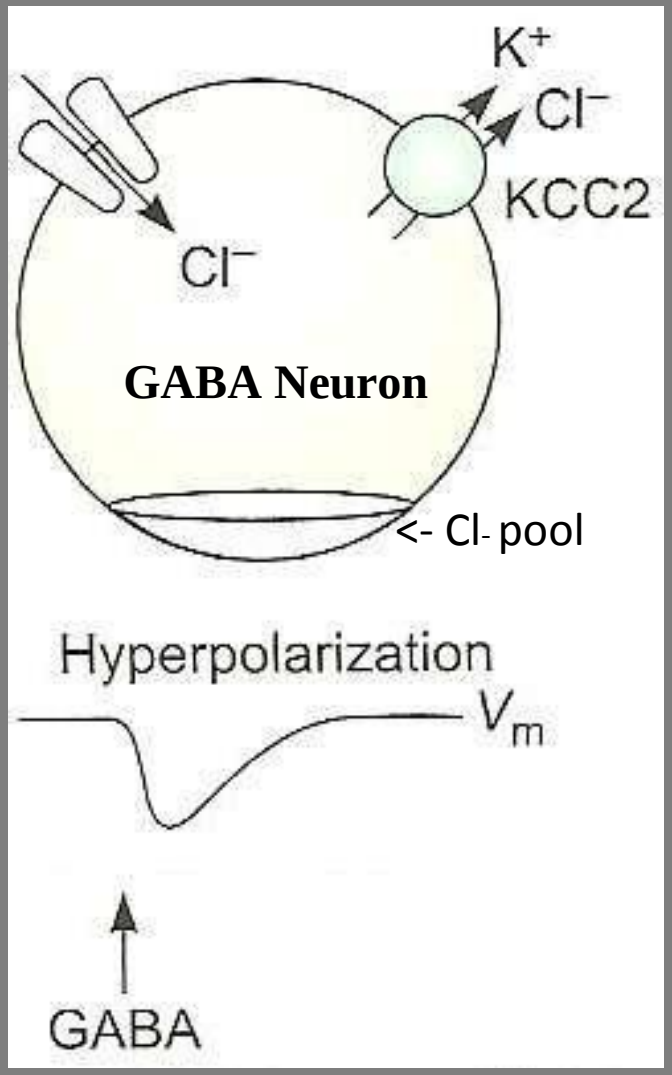


GABA Biosynthesis & Breakdown (so **many** drug targets)

- **GAD**: glutamic acid decarboxylase converts glutamate to GABA

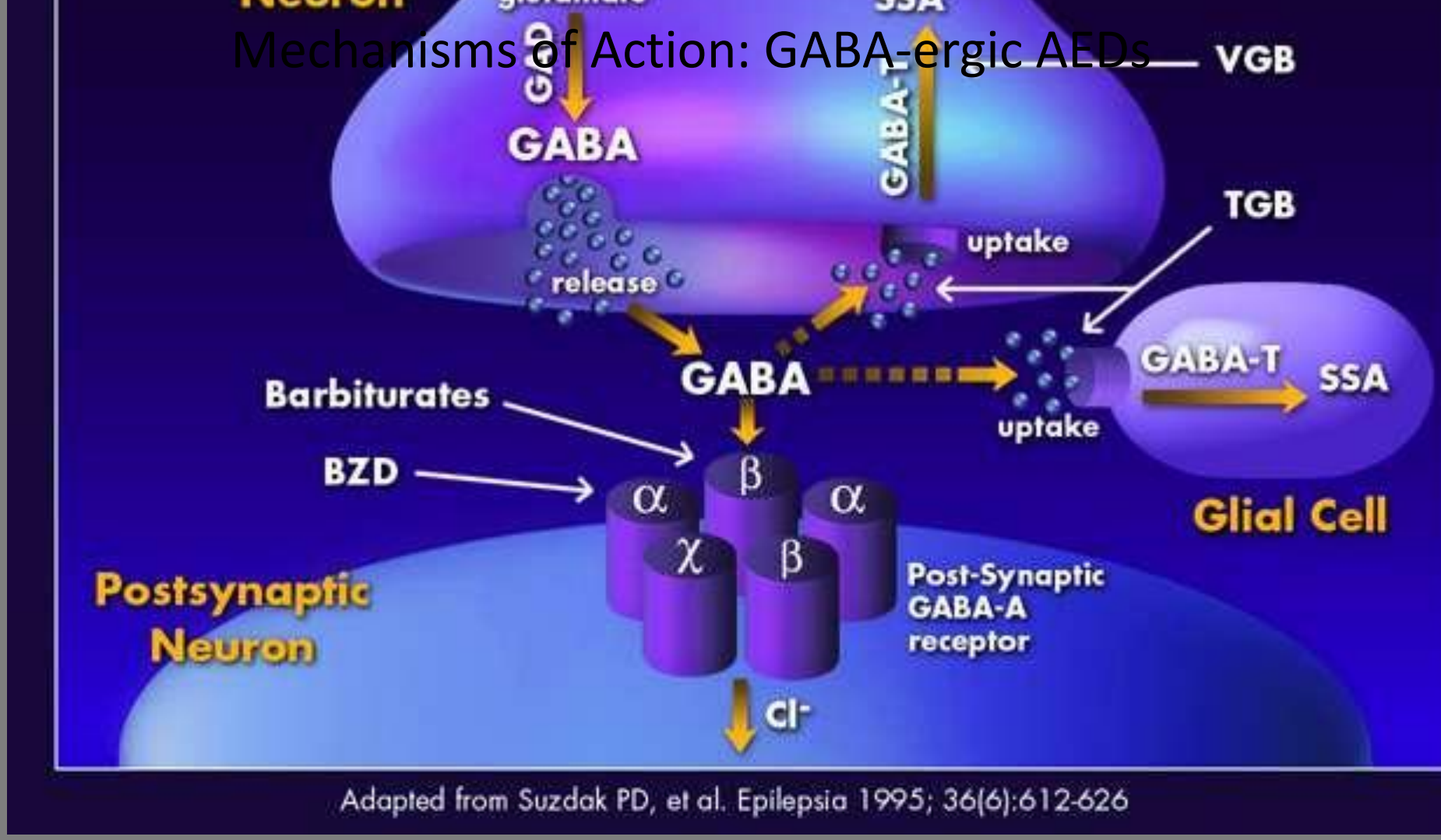
- **VGAT**: vesicular GABA transporter
- **GAT-1**, **GAT-2**: membrane GABA transporter found on neurons & astrocytes
- **GAT-3**: membrane GABA transporter found on astrocytes
- **GABA-T**: GABA Aminotransferase, begins conversion of GABA to succinic semialdehyde (SSA)

$GABA_A$& Adult Brain



Vm : membrane potential
cotransporter: transports ions against concentration gradient

Mechanisms of Action: GABA-ergic AEDs



Adapted from Suzdak PD, et al. Epilepsia 1995; 36(6):612-626

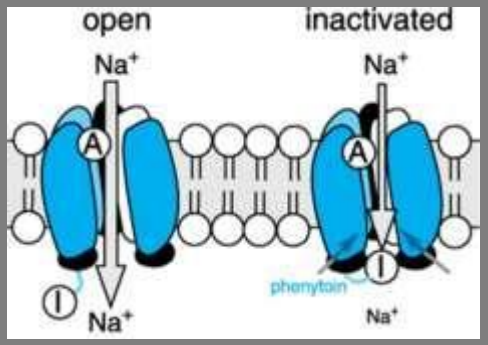
History of AEDs

- **1857**: Sir Charles Locock reports on KBr for hysterical epilepsy
- **1912**: lfred Hauptmann's sleep problems lead to phenobarbital
- **1938**: Maximal electroshock seizure (epilepsy?) model used to identify phenytoin

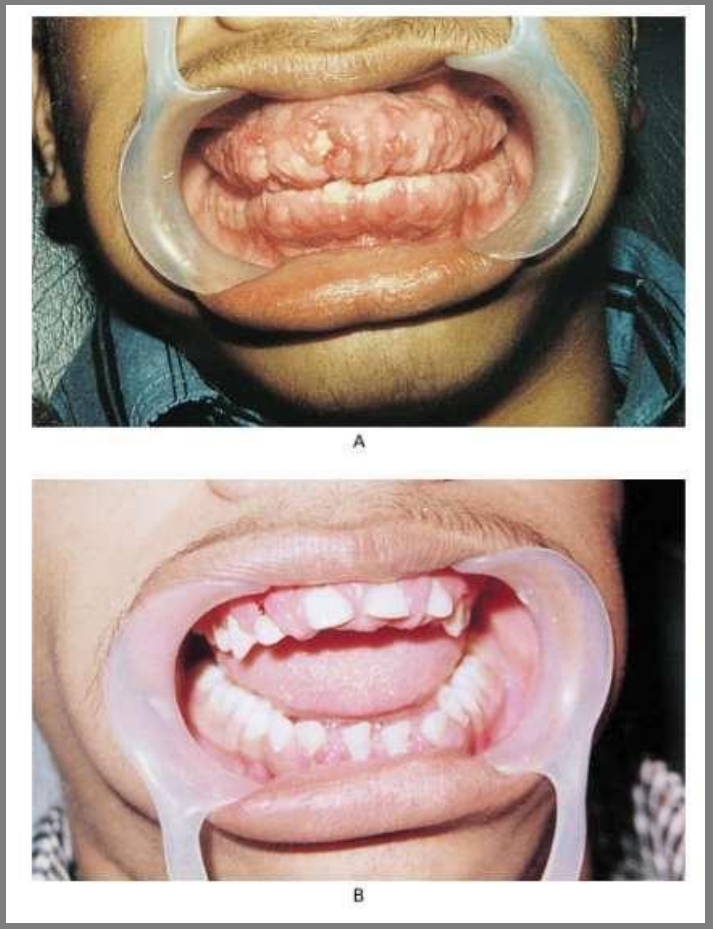
Figure 1. A. Local anesthetic application. **B.** Corneal stimulus application: 50-mA (mice) or 150-mA (rats) fixed current; 50-60–Hz pulse frequency; 0.6-ms pulse width; 0.2-s stimulus duration. **C.** Tonic phase. **D.** Clonic phase.

1) Apply electrode to cornea
2) Apply current
3) Rate tonic-clonic behavior
4) Repeat 1-3 with drug

Phenytoin (1938)



- History: less sedative than phenobarbital
- MOA: decreased recovery of voltage gated Na_+ channels from inactivation
- PK: 3A4 inducer
- Adverse Events: lethargy (transient), gingival hyperplasia

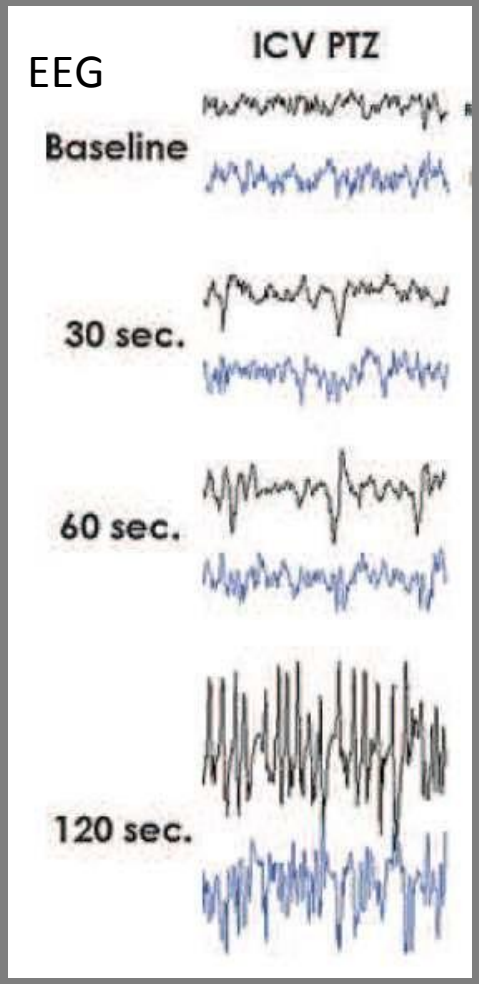


Phenytoin & Category D

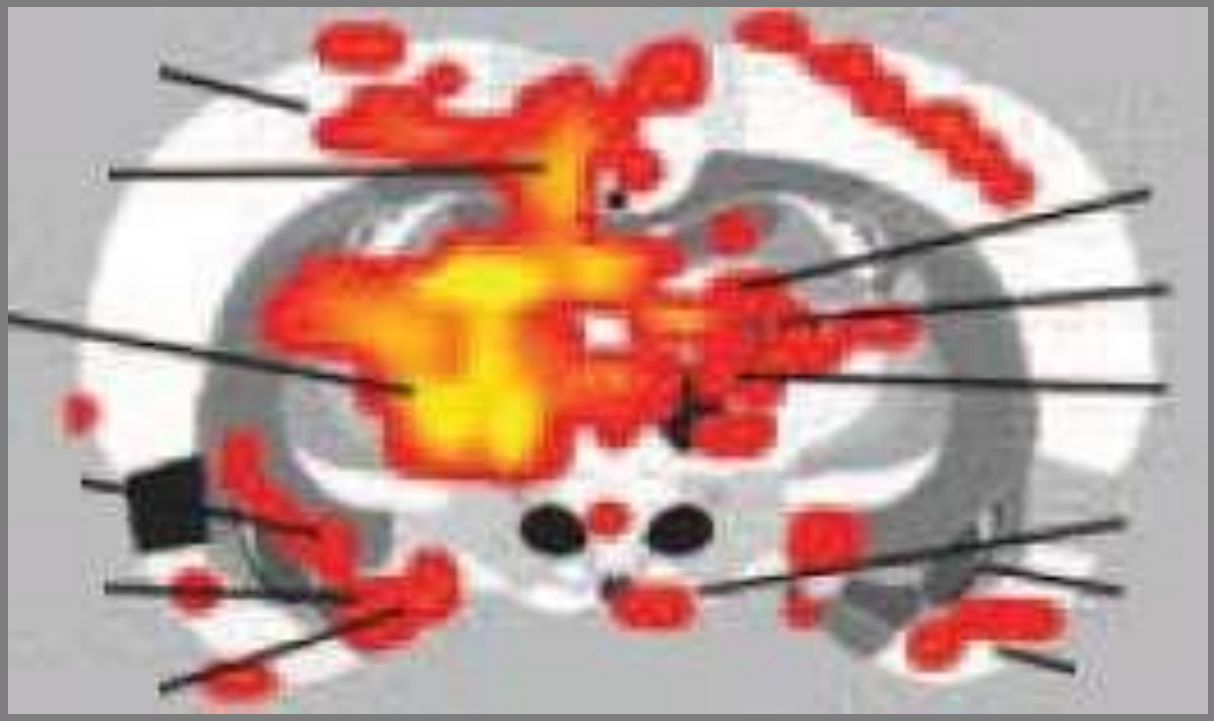
- growth
- Facial Abnormalities
  - nasal hypoplasia
  - maxilla hypoplasia
  - flat philtrum
- IQ (variable)
- K_+

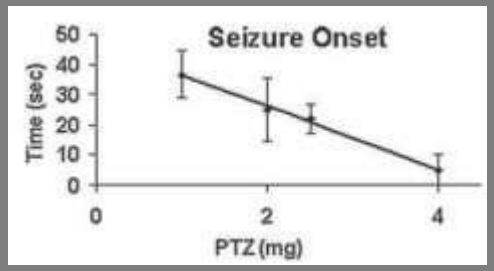
Pentylenetetrazol (1938)

- MOA: GABA antagonist



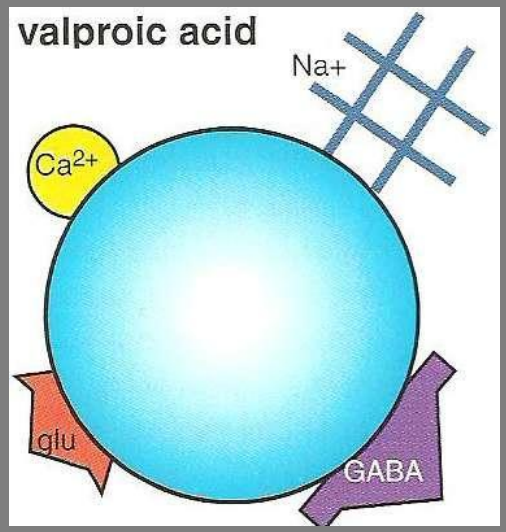
fMRI shows thalamus activation 4 s before PTZ seizure.

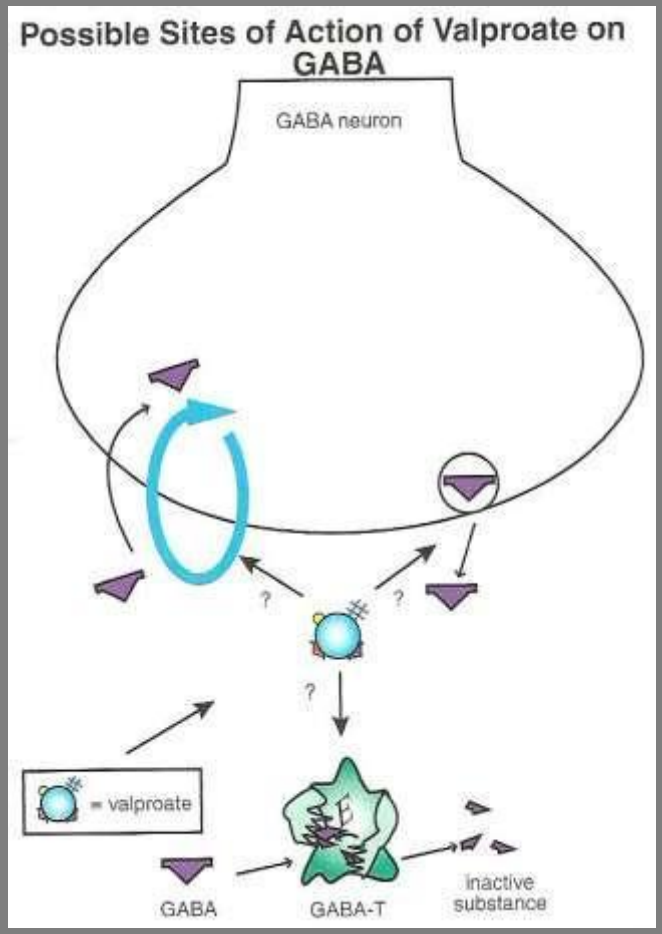




Valproate (1962)

- History: Pierre Eymard is using pentylenetetrazol to induce convulsions with valproate as solvent/vehicle.
- Uses: different seizure types
- MOA: ?, G B , aspartate

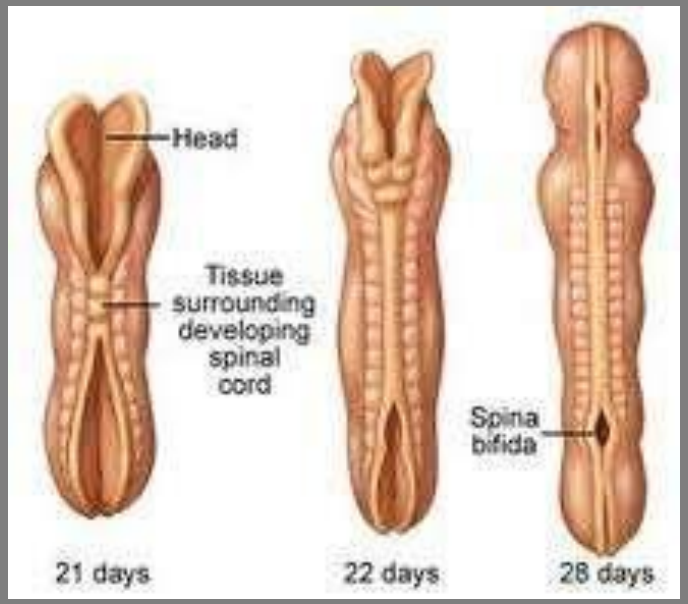




Depakote®
DIVALPROEX SODIUM

Valproate: Category D

- 2% risk of spina bifida
- Cmax
- folic acid supplementation

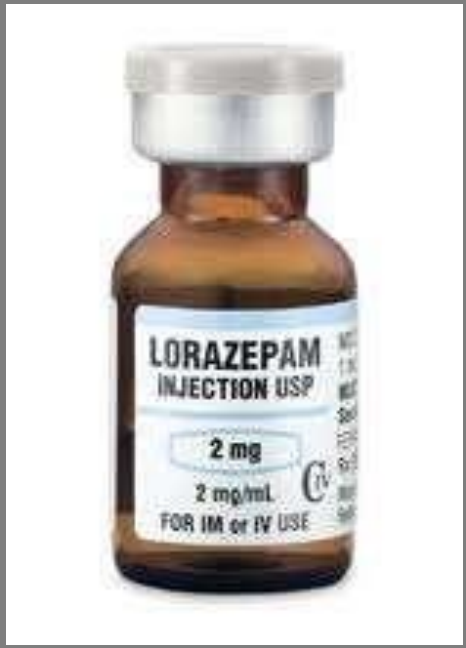


Status Epilecticus (SE)

- continuous, unremitting seizure lasting > 5 min
- convulsive > non-convulsive
- mortality = 20%
- medical emergency

Lorazepam (1977)

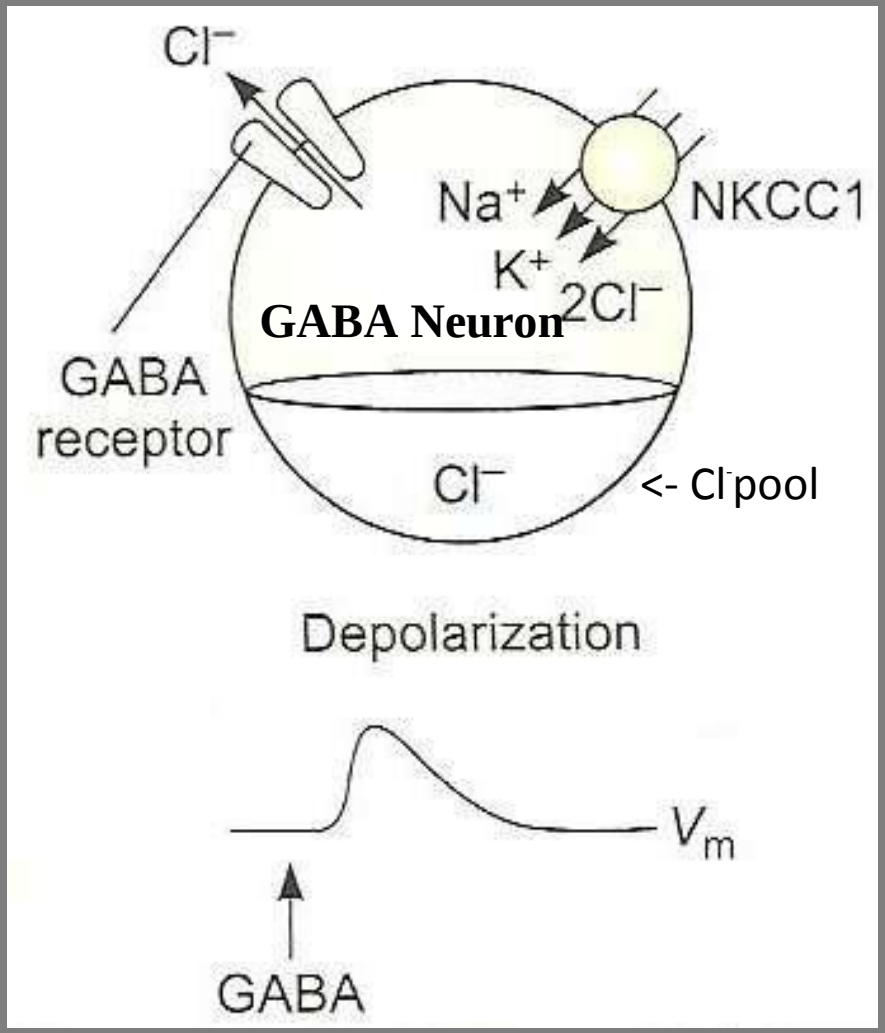
- MOA: $GABA_A\alpha_{1,2,3,5}$
- Dose: 2 mg/ml per min x 2
- Adverse Effects: heavy sedation, especially with alcohol
- $t_{1/2}$: 12 hours



Summary

	MOA	Concern
phenobarbital 	$GABA_A$ Cl^- channel duration	sedation
phenytoin	voltage gated Na+ channels	Category D 
lorazepam	$GABA_A\alpha_{1,2,3,5}$ Cl^- channel frequency	addiction (Schedule IV)
valproate 	G B (?)	Category D 

$GABA_A$ & Neonatal Brain



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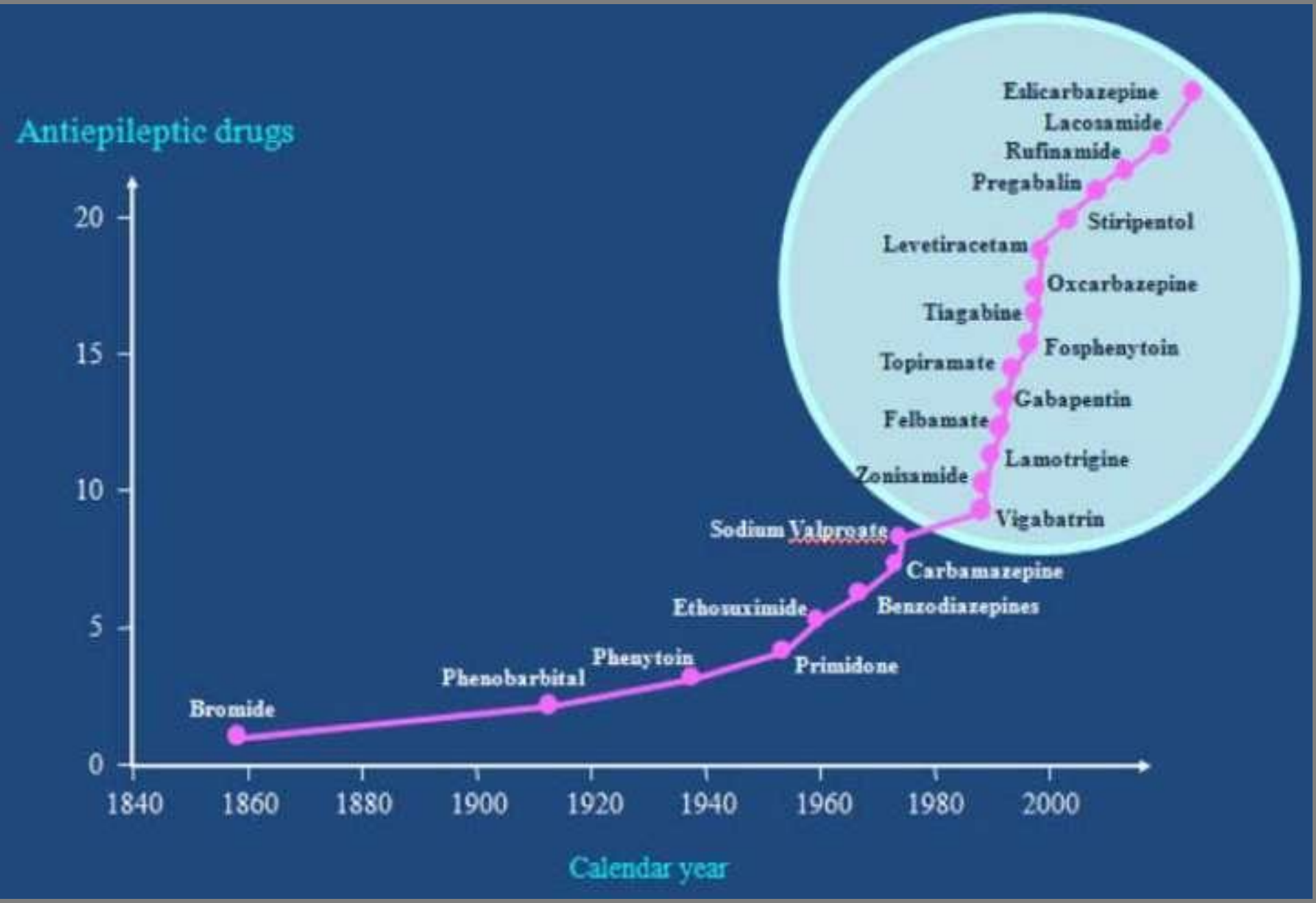
Antiepileptic drugs
20
15
10
5
0
1840
1860
1880
1900
1920
1940
1960
1980
2000
Calendar year
Bromide
Phenobarbital
Phenytoin
Primidone
Ethosuximide
Benzodiazepines
Carbamazepine
Sodium Valproate
Vigabatrin
Zonisamide
Felbamate
Gabapentin
Topiramate
Fosphenytoin
Tiagabine
Oxcarbazepine
Levetiracetam
Stiripentol
Pregabalin
Rufinamide
Lacosamide
Eslicarbazepine

Summary

- MES and PTZ have been used to identify many AED.
- Pharmacotherapy for epilepsy is complex and polypharmacy is common.

Self-Test

- Match the AED on the left with the potential adverse effect.
  - valproic acid
  - phenytoin
  - phenobarbital