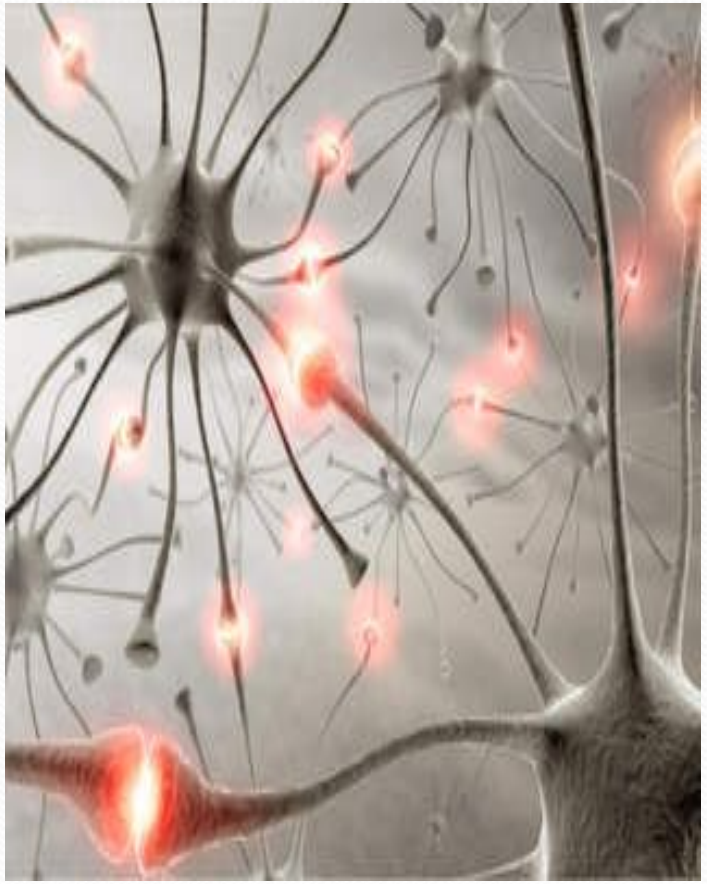
Anti epileptic drugs (AEDs) L2



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:Sodium valproate (carboxylic group) -4

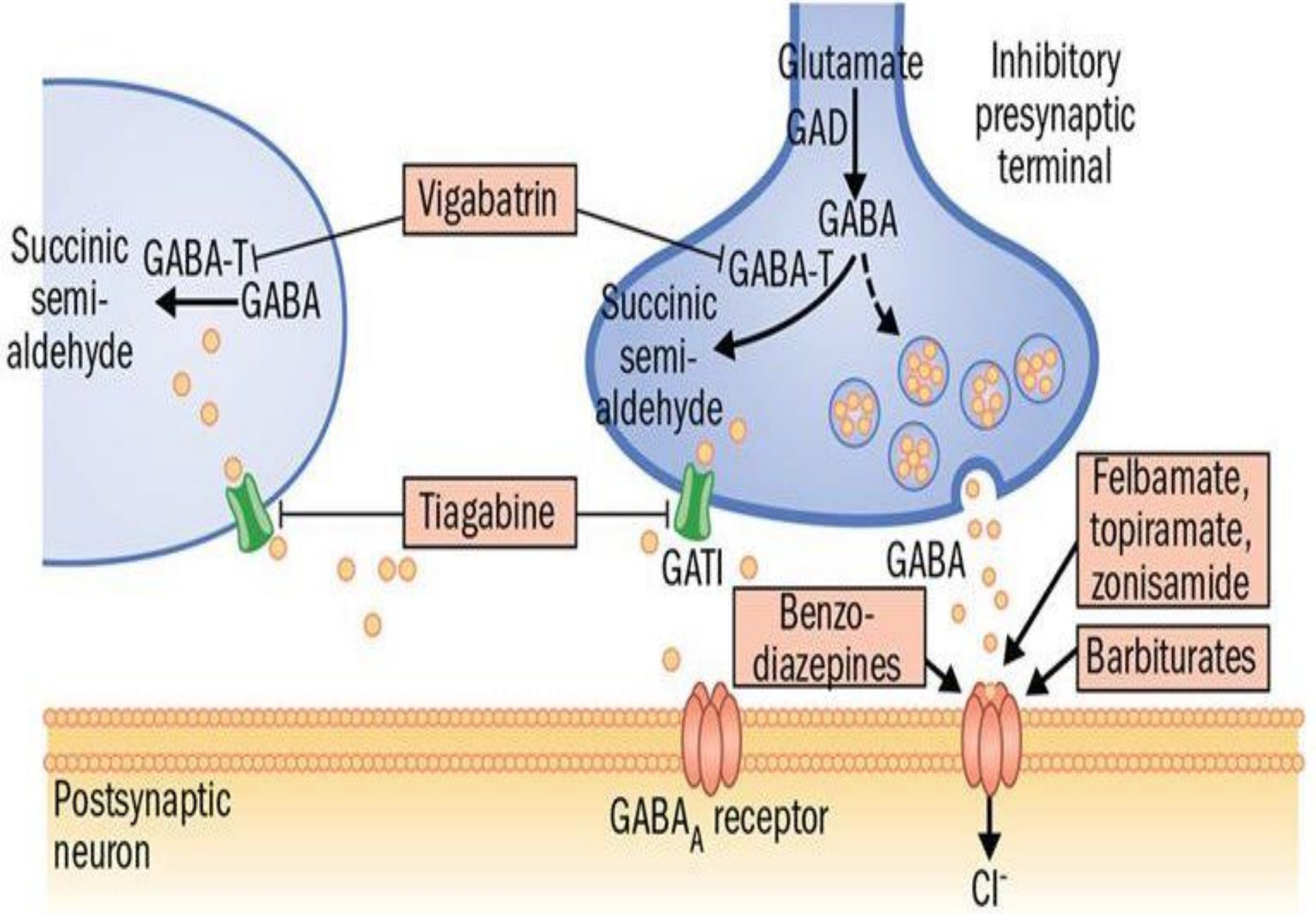
:Mechanism of action

Inhibiting GABA transaminase (the enzyme responsible .1 for break down of GABA) → **increase GABA** → **neuronal firing** .

Increasing the activity of **GAD** (glutamic acid .2 **esis**

block Na+ and Ca++ channel .3

Uses: all types of seizure


Glutamate
GAD
Inhibitory presynaptic terminal
GABA
Vigabatrin
GABA-T
Succinic semi-aldehyde
GABA-T
GABA
Succinic semi-aldehyde
Tiagabine
GAT1
GABA
Felbamate, topiramate, zonisamide
Benzo-diazepines
Barbiturates
Postsynaptic neuron
GABA$_A$ receptor
Cl$^-$

:Kinetics

It is effective **orally** and absorbed **rapidly** .

It is **bound** to plasma **ptn, so It displaces phenytoin** • **from its plasma ptn binding**

.It is **metabolized** by the **liver** •

it is an **enzyme inhibitor** so it inhibits its own •

• metabolism and that of other drugs

:Side effects

,**CNS:** **NDA= nystagmus , diplopia, ataxia.**

.**GIT** : nausea and vomiting •

Hepatic toxicity or liver failure which occurs after .
.maximally **2-12** weeks

- **Pancreatitis** (inflammation of pancrease, may be fatal)

Blood : **Coagulation disorders** due to inhibition of platelets •
. aggregation. **neutropenia**

Increase in awareness and increase **appetite(weight gain)** •
(Bs it initiates pancreatic **insulin secretion** that might increase appetite)

Alopecia: (**Note**: phenytoin causes hirsutism) •
Teratogenic which is higher than other anti-epileptics: .
spina bifida, cleft lip and cleft palate

:Ethosuxamide (succinimide group) .5

It is the drug of **choice** in **absence** seizures

.It acts by **blocking t-type Ca+2 channel** in thalamo-cortical neurons -

Absorbed **orally**-

.**not** bound to plasma **ptn**-

excreted unchanged 25%-

.metabolized in the liver 75%-

***

GIT: **Irritating to the stomach** -

.**CNS**: drowsiness, lethargy, sedation-

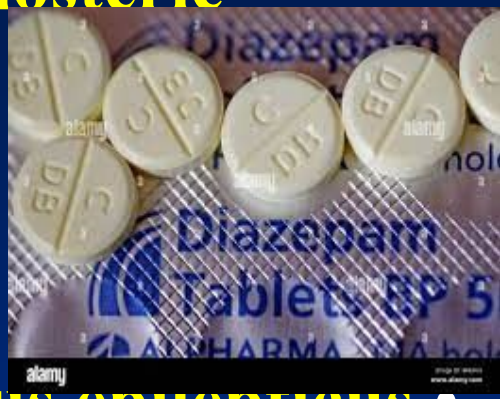
.**bone marrow suppression-** -

Skin: it produce skin **allergic reaction** called **(Steven Johnson-**

.Syndrome)

:Benzodiazepines .6

Act by **enhancing the action of GABA (by allosteric modulation of GABA A receptor)** they are among the **safest** and the most **well tolerated**



:Including

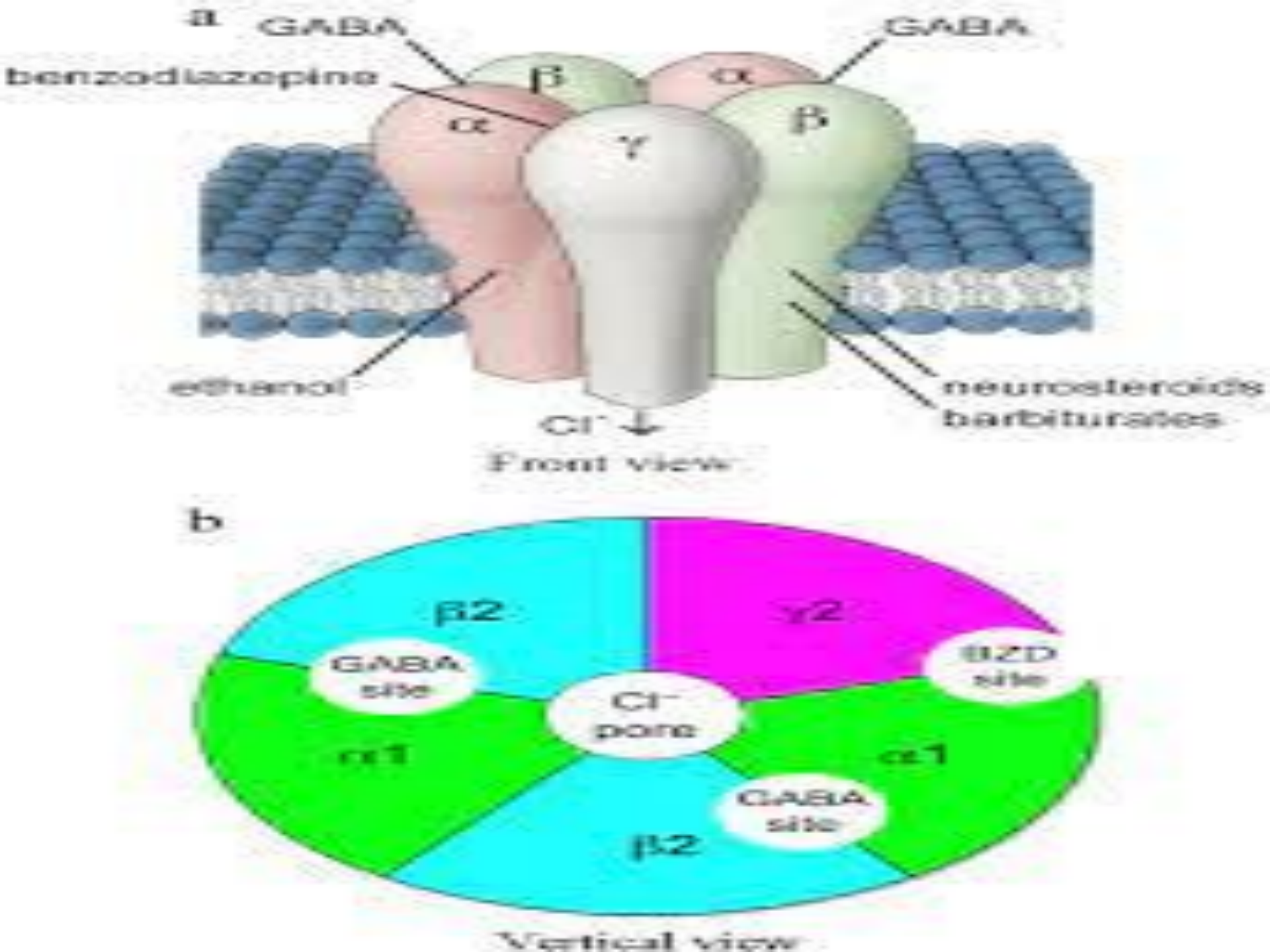
Diazepam: it is the drug of first **choice** in **status epilepticus** • **and febrile convulsion**

Clonazepam: is effective in **absence seizure** •

Clobazam: used for **focal seizure**. But in the **United States**, . it **only** approved use is for treatment of seizures associated with **Lennox-Gastaut syndrome** in patients **2** .**years** of age or older

Lorazepam has a **shorter pharmacokinetic half-life** but . **stays** in the **brain longer** than diazepam

…….**S.E:** tolerance, physical dependence, memory disturbance


a
GABA
GABA
benzodiazepine
β
α
α
γ
β
ethanol
neurosteroids
barbiturates
Cl⁻
Front view
b
β2
γ2
GABA site
BZD site
Cl⁻ pore
α1
α1
GABA site
β2
Vertical view

:2nd generation antiepileptic drugs

.**Lamotrigine**: used for all types of seizure.**1**

MOA: act by

Blockage Na channels -1

Decrease release of glutamate (**excitatory a.a.) -2**

:S.E

Skin: maculopapular rash (most common),

.rash(Steven-Jonson syndrome)

.**GIT:** nausea and vomiting

.**CNS:** headache, diplopia

.**Pregnancy** : preferred bs of **lower teratogenicity****

Vigabatrin: (Vi = vision) **-2**

MOA: It **irreversibly** inhibit GABA **Transaminase** → **increase GABA**

.it is not metabolized and not induce liver enz**

:Uses

Focal seizure -1

infantile spasm (west syndrome=EEG abn.+ mental -2 retardation)

.seizure refractory for other antiepileptics -3

S.E: irreversible **visual loss** in 40% of patients (visual acuity_ .should be **checked** every **6 month**)

3. Topiramate — 1995

Mechanism	Therapeutic uses	Adverse effects	Important points
1. Block Na+ channels 2. ↑ GABA 3. Blocks AMPA/kinate receptors	1. ALL types (Focal and generalized) seizures 2. Migrain prophylaxis	1. ↑↑ IOP (glaucoma) 2. Renal stones 3. Teratogenic → Cleft palate 4. Weight loss →↓ body fat mass	

4. Levetiracetam — 2000

Mechanism	Therapeutic uses	Adverse effects	Important points
Binds to SV2A, a synaptic vesicle protein, →↓ glutamate release	ALL types (Focal and generalized) seizures	Very low	— Broad spectrum — Low toxicity — Favorable pharmacokinetic profile — No drug interactions

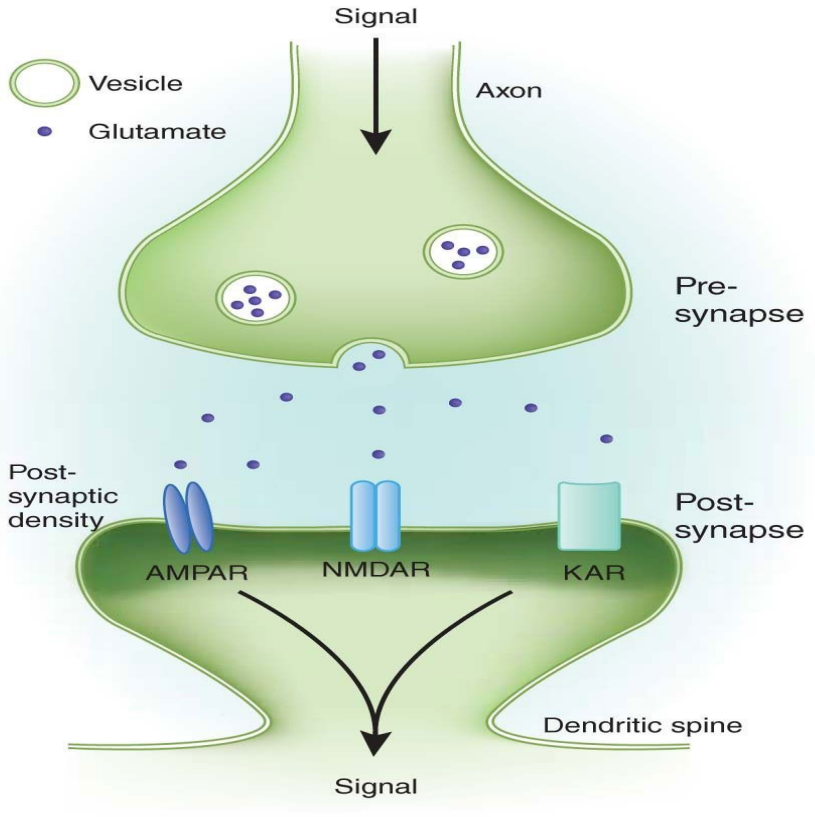
:Notes

AMPA receptor, NMDA and kinate are ion channel glutamate* receptor

*topiramate causes wt. loss bs of **decrease appetite** and **increase metabolism**

*Renal stone formed by **topiramate** is markedly bs lower urinary citrate excretion, and increased urinary pH. These changes increase stones formation.

*Vigabatrin cause damage to photosensitive receptor and to retinal ganglia and tissue



:Gabapentin and pregablin-5

- It inhibits presynaptic P/Q type **Ca++ channel** leading to **decrease Ca influx** and this **decrease glutamate** release.
- it is an **analogue** to **GABA**.

Not: P/Q type **Ca++ channel is high voltage channel contributing**
****to vesicle release at synaptic terminals**

:Uses-

.**Adjuvant** with other antiepileptic in **focal** seizure -1

Neuropathic **pain** (Has **serotogenic** and **nor adrenergic** -2
.activity so used in treatment of pain)

Reduced dosing is required in **renal disease**-

well **tolerated** by the **elderly**-

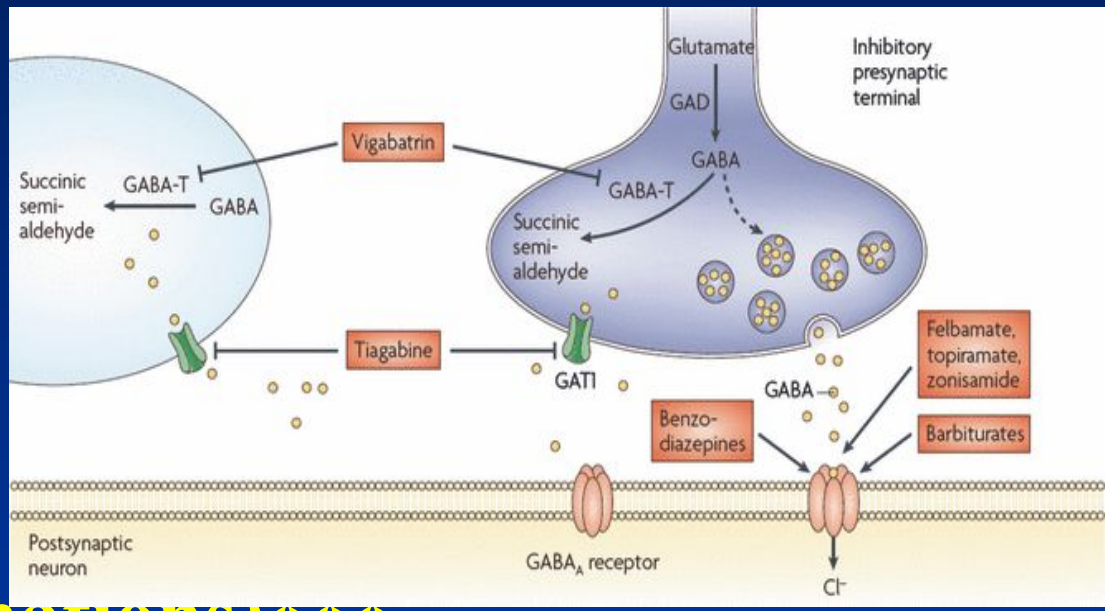
.Has **no** effect on **liver**-

.....S.E: sedation and physical dependence, wt.

Tiagabine: **block GABA uptake into pre synaptic-6**
. .neuron **increase GABA conc**

S.E: GIT upset, sedation, wt. gain and fatigue

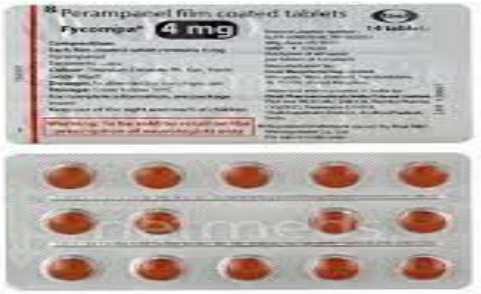
Uses: adjuvant drug in **focal** seizure



Note (for your informations)****

SV2A protein : is a synaptic vesicle memb. Protein, **:** express in **neuron and endocrine** cells, and involve .in **regulation of neurotransmitter release**

Perampanel : is a **potent noncompetitive antagonist** of -7 the **AMPA receptor** (a subtype of ionotropic **glutamate** receptor that is the main mediator of synaptic **excitation** in .CNS by modulation Ca and Na channel)



Uses : 1- **Focal** seizure

.primary generalized **tonic – clonic** seizure -2

Retigabine (**US** Adopted Name: **ezogabine**), **a -8 potassium channel opener**, is a **third-line** treatment for **focal** seizures **Because** retigabine causes **pigment discoloration** of the retina and skin

Felbamate : it has **dual actions on-9**
excitatory (NMDA) and via ion channel -1
.inhibitory (GABA) **-2**

used in RX of
focal seizures 2- Lennox-Gastaut syndrome -1

However, because the drug can **cause** both **aplastic** anemia and **severe hepatitis, Thus** felbamate is **used only** for **refractory seizures** who **respond poorly** to other medication

: **Lacosamide -10**
act by **modulation** of voltage-gated **Na channels**-
used as **monotherapy** or **adjunctive** therapy in **focal** seizures-
. May produce **dependence**-

Table 2. Guideline-Recommended Treatments for Focal Seizures

First-Line Options	Second-Line Options	Other Options
Carbamazepine	Oxcarbazepine	Gabapentin
Phenytoin	Valproate	Lacosamide
Lamotrigine	Levetiracetam	Phenobarbital
Levetiracetam		Topiramate
Zonisamide		Vigabatrin
Valproate		Eslicarbazepine
		Brivaracetam
		Perampanel
		Ezogabine

Source: References 8, 9, 12.

Antiepileptics: Contraindications #2

- Succinimides are contraindicated in patients with bone marrow depression or hepatic or renal impairment
- Carbamazepine is contraindicated in patients with bone marrow depression or hepatic or renal impairment and during pregnancy
- Valproic acid (Depakote) is not administered to patients with renal impairment or during pregnancy
- Oxcarbazepine may exacerbate dementia

Antiepileptics: Interactions #2

Interacting drug	Effect of interaction
Antiseizure medications	May increase seizure activit
Protease inhibitors	Increased carbamazepine levels resulting in toxicity
Oral contraceptives	Decreased effectiveness of birth control, resulting in breakthrough bleeding or pregnancy
Analgesics or alcohol	Increased depressant effect
Antidiabetic medications	Increased blood glucose levels

:Important notes

1- **Start** AEDs following **2nd attack** of seizure.

2- **Start** with **single** AED,

if no benefit: **change** to other drug,

If no benefit :use more than one drug(**combination**)

3-Avoid combination of **valproic** acid and **lamotregin bs** it leads to **stevens-Johnsons syndrome**

4- you **can stop** AED if there is **no attack** of epileptic seizure for **2 years,** stop AED **withen 2 - 3 months.**

AEDS IN PREGNANCY AND BREAST FEEDING

- Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.
- The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus, so her drug should be continued.
- Pregnant should be advised to take folic acid 5 mg/day well before pregnancy to minimize the risk of neural tube defects.
- Best drugs in pregnancy: lamotrigine - levetiracetam
- Breast feeding is acceptable with nearly ALL anti-epileptic drugs

Managment of status epilepticus (stage and drug only)

Premonitoring stage

Diazepam 10mg iv (given over 2-5 min) or rectally, repeated
later if status continues to threaten
Or lorazepam 4mg iv bolus

↓

If seizures continue or status develops

Stage of early status

Lorazepam 4mg iv bolus (if not given earlier)

↓

If status continues after 30 min

Stage of established status

Phenobarbital iv infusion of 10mg/kg at a rate of 100mg/
(i.e, about 700mg in an average adult over 7 min)
or
Phenytoin iv infusion of 15mg/kg at a rate of 50mg/mi
(i.e, about 1000mg in an average adult over 20 min)
or
Fosphenytoin iv infusion of 15mg PE/kg at a rate of 100mg
(i.e, about 1000mg PE in an average adult over 10 min

↓

If status continues after 30-60 min

Stage of refractory status

General anaesthesia with either:
Propofol 2mg/kg iv bolus, repeated if necessary, and then fo
continuous infusion of 5-10mg/kg/h initially, reducing to a
When seizures have been controlled for 12h, the drug dosages
slowly tapered over 12h
or
Thiopental: 100-250mg iv bolus given over 20s, with furthe
boluses every 2-3 min until seizures are controlled, follo
continous iv infusion to maintain a burst supression patt
the EEG (usually 3-5mg/kg/h).
Thiopental should be slowly withdrawn 12h after the last

:Status epilepticus in pregnancy

management based on **IV benzodiazepines**, .**phenytoin**, or **phenobarbital**

Good fetal **outcome** is dependent on **rapid** seizure .**control**

Management of eclampsia is controversial. There is little evidence that **magnesium sulfate** has anticonvulsant properties, and its use as such will probably **decline** steadily in the future. **At present**, it is managed (eclamptic seizures) in the **same way** that .status epilepticus is managed

Thank you

FOR YOUR INFORMATION

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has as been associated with Stevens-Johnson Syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, weight gain, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects such have been observed. Broad spectrum of antiseizure activity.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may causes seizures.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia; hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One-hundred percent renal elimination.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life-threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Fosphenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life-threatening. Not recommended for chronic use. Primary treatment for status epilepticus.
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, weight gain, diplopia, and ataxia. One hundred percent renal elimination.
Primidone	GABA receptor	Sedation, lethargy, behavioral changes, ataxia, hyperactivity, and nausea. Not recommended for chronic use.
Tiagabine	GABA receptor	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia and oligohidrosis. Broad spectrum of antiseizure activity.