ANTICONVULSANT DRUGS

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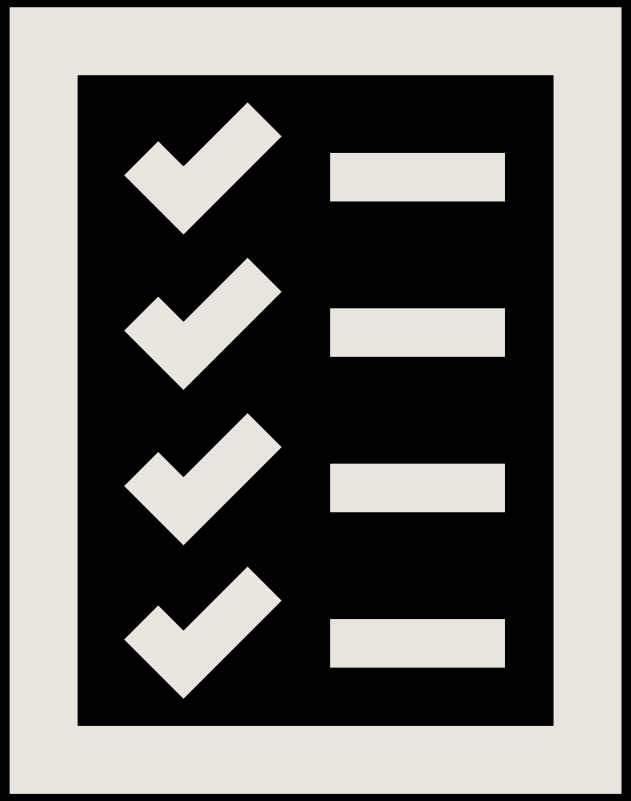
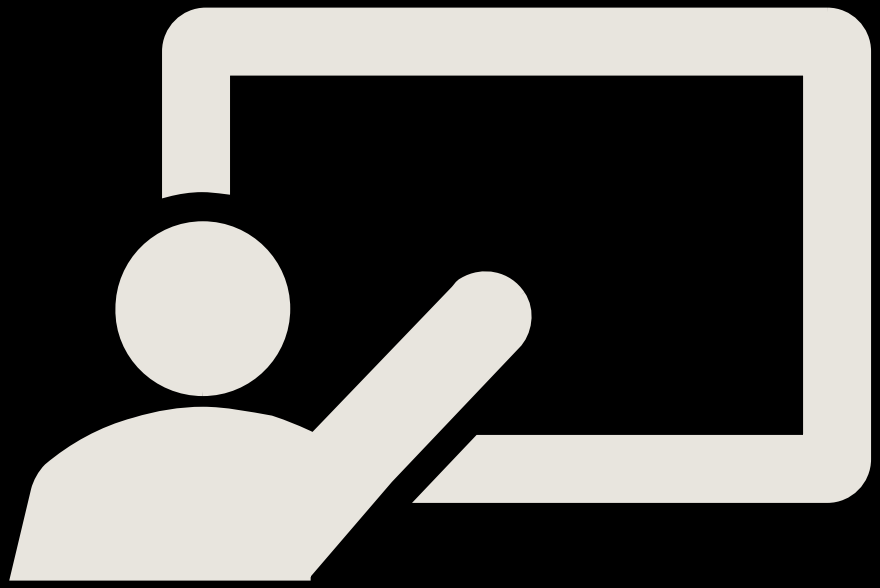


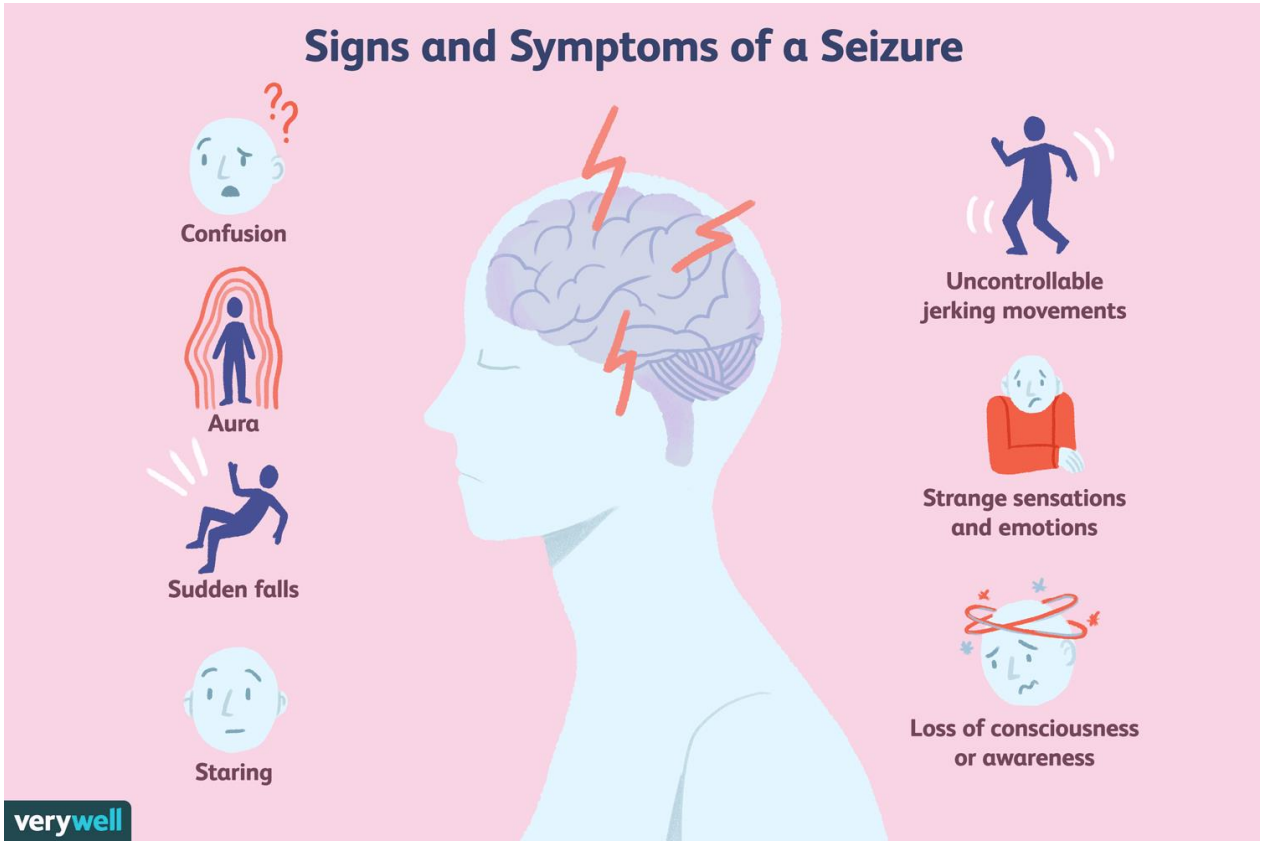
By the end of this lecture, the student will be able to:

LECTURE OUTLINE:



Seizures

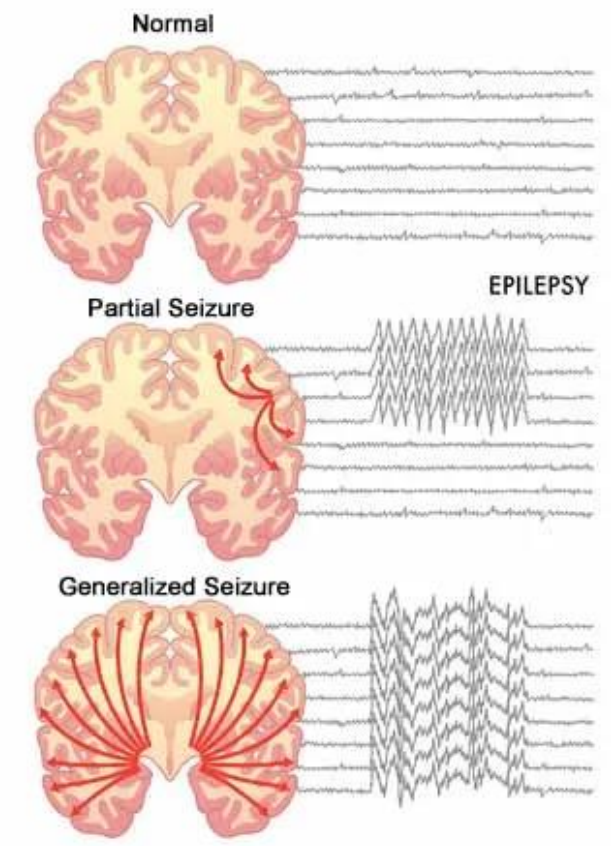
Episodes of **abnormal electrical activity** in the **brain** that may lead to **involuntary** movements and sensations, which are accompanied by characteristic **changes on electroencephalography** (EEG).



Classification of seizures

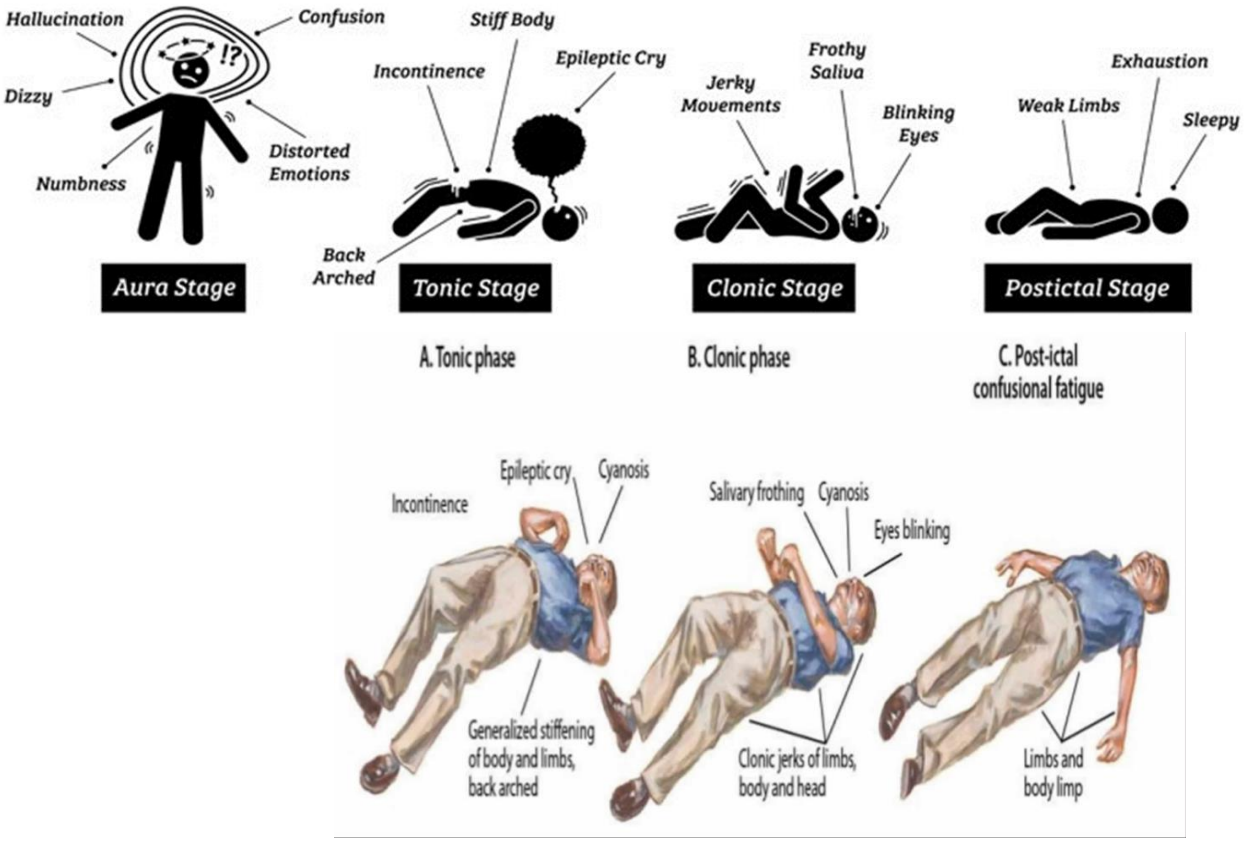
According to the **focus** and **spread** of discharges, seizures may be classified into ways.

- **Partial (focal)**, which originate at **a specific focus** and **do not spread** to involve other cortical areas.
- **Generalized**, which arise in **both cerebral hemispheres**, and accompanied by **loss of consciousness.**



International classification of partial and generalized seizures

Partial (focal)	
Simple partial seizure	No alteration of consciousness
Complex partial seizure	Altered consciousness, automatisms, and behavioral changes
Secondarily generalized seizure	
Focal seizure becoming generalized and accompanied by loss of consciousness	
Generalized seizures	
Tonic-clonic (grand mal) seizure	Increased muscle tone 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 (less than 10s), with minor muscle twitches and eye blinking

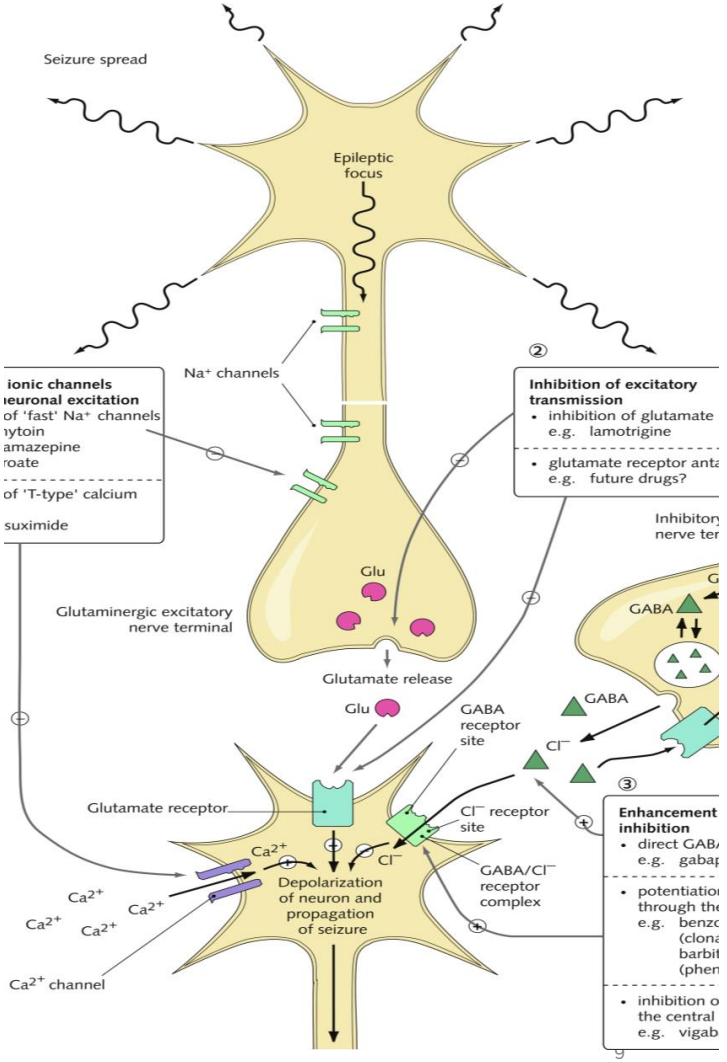


Tonic-clonic Seizures

Treatment of epilepsy

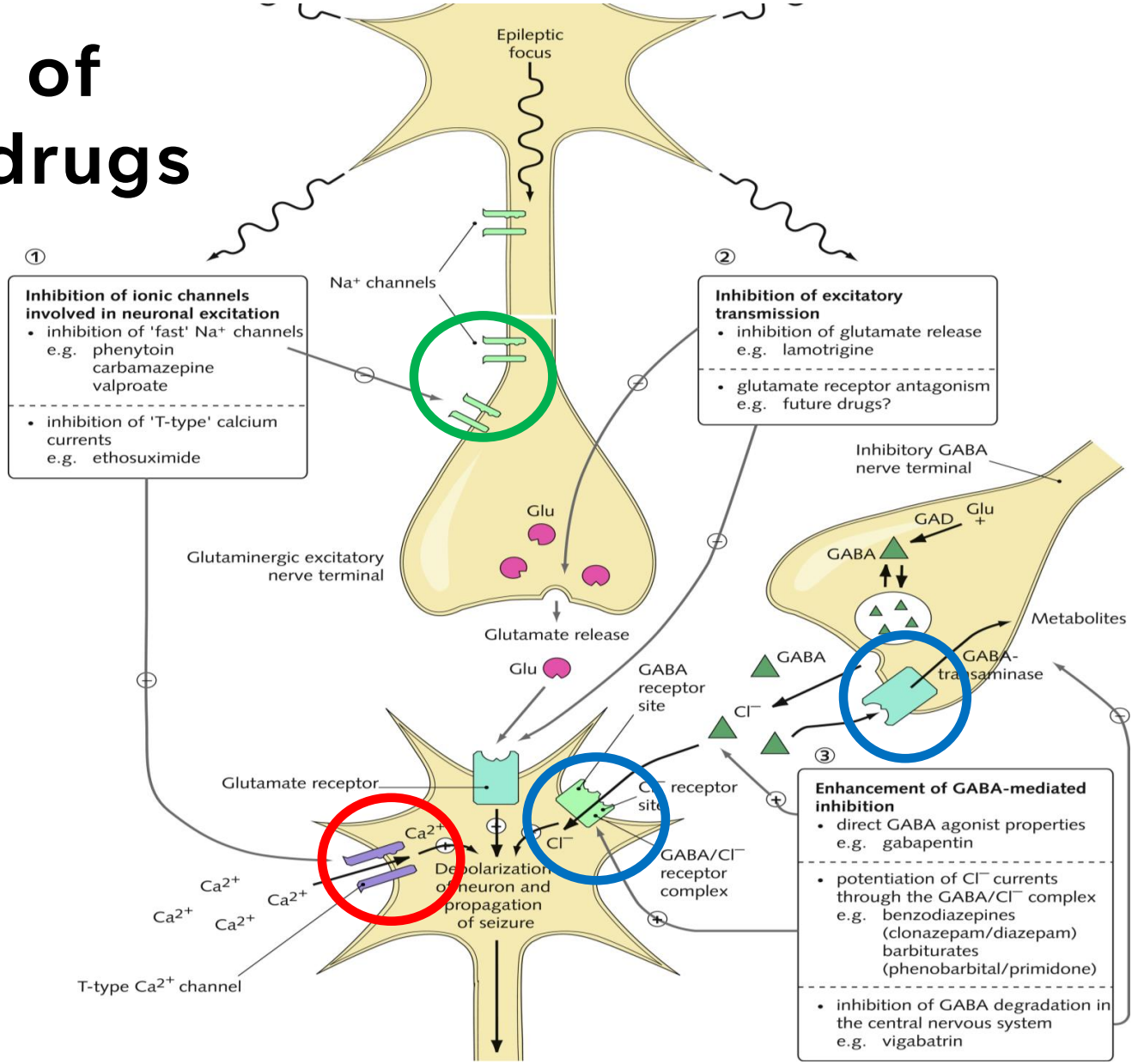
- The etiology of the abnormal neuronal discharges in epilepsy is **unknown** in 60% to 70% of cases, but **a family history** is an important factor.
- **Damage to the brain,** e.g., by tumors, head injury or infections, may subsequently cause epilepsy.
- Antiepileptic drugs **limit the propagation** of this abnormal discharge (inhibit the rapid, repetitive neuronal firing) → so they prevent the development of seizures.

- The **aim of drug treatment of epilepsy** is:
  - **To minimize the seizure frequency, without producing adverse drug effects.**



Classification of anticonvulsant drugs

1. **Drugs that inhibit Voltage-gated Na^+ channels:**
   - Phenytoin & Fosphenytoin
   - Carbamazepine & Oxcarbazepine
   - Valproic acid
   - Lamotrigine
   - Topiramate
   - Zonisamide
2. **Drugs that inhibit T-type Ca^{++} channels**
   - Ethosuximide



Classification of anticonvulsant drugs

3. Drugs that potentiate GABA activity:

a) Stimulate GABA/Cl^- receptor complex

- Phenobarbital & Primidone
- Clonazepam, Diazepam & Lorazepam

b) Block GABA reuptake

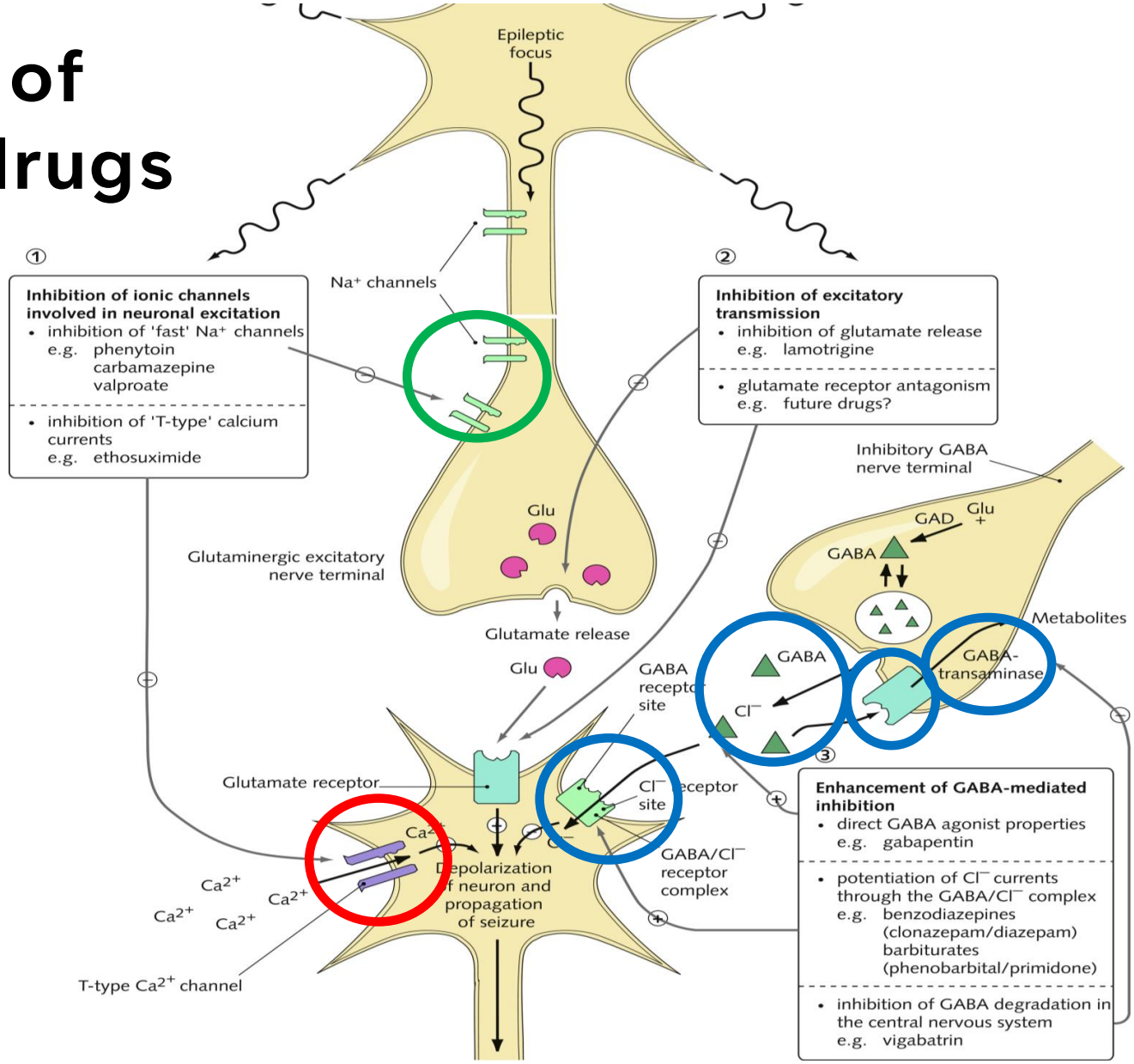
- Tiagabine

c) GABA-mimetics

- Gabapentin
- Pregabalin

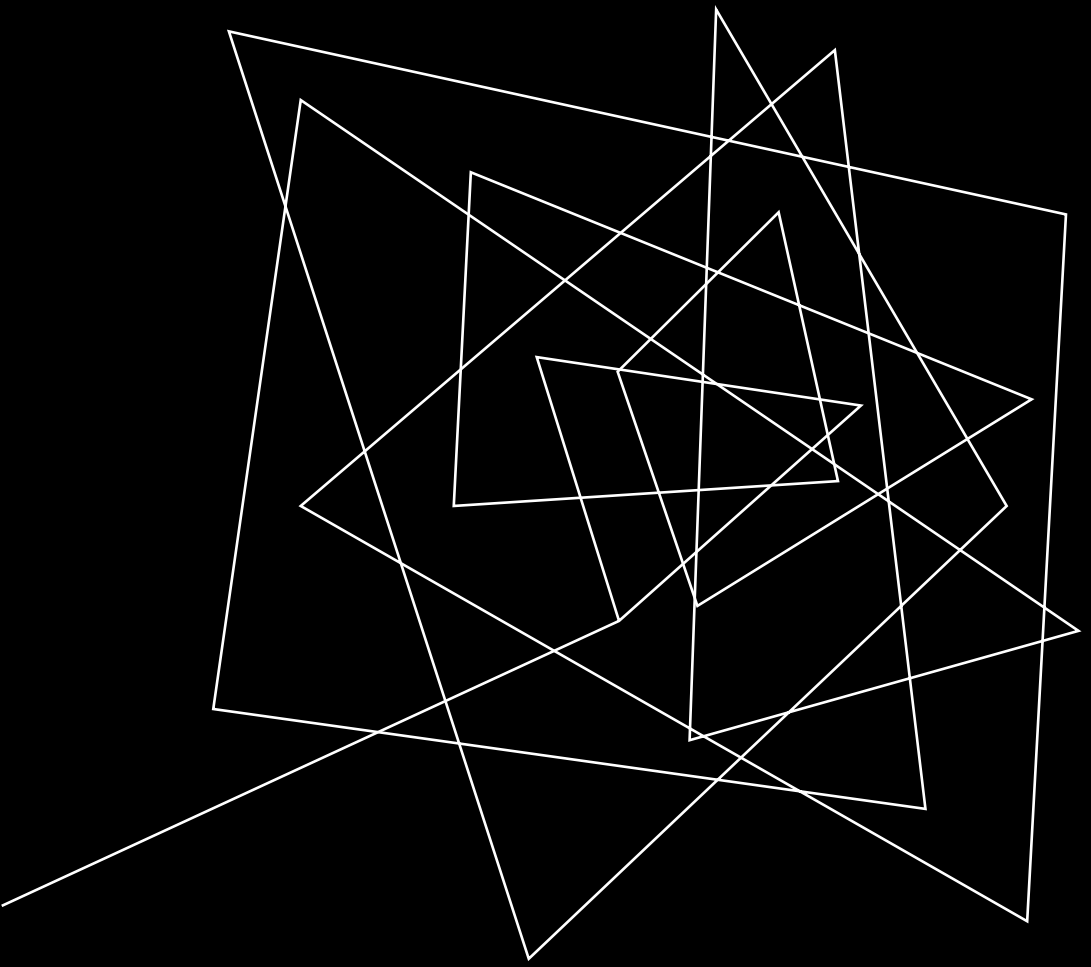
d) Decrease GABA degradation

- Vigabatrin



Clinical uses of anti convulsant drugs

Seizure type	1st choice	2nd choice
Partial and generalized tonic-clonic seizures	• **Carbamazepine** • **Sodium valproate**	▪ Lamotrigine ▪ Phenytoin ▪ Gabapentin ▪ Vigabatrin ▪ Phenobarbital
Absence seizures	▪ **Ethosuximide (children)** ▪ Sodium valproate (adults) ▪ Lamotrigine	
Status epilepticus	▪ **Lorazepam** ▪ Diazepam	▪ Phenytoin or fosphenytoin ▪ Phenobarbital



Drugs that inhibit voltage-gated Na^+ channels

- Phenytoin & Fosphenytoin
- Carbamazepine & Oxcarbazepine
- Valproic acid
- Lamotrigine
- Topiramate
- Zonisamide

Mech. of action

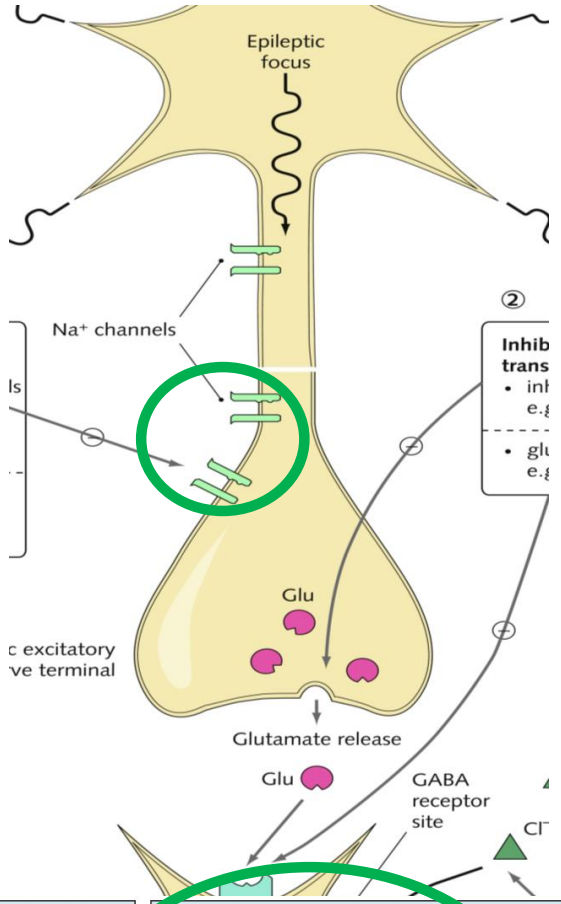
They block the **voltage-gated "fast" Na^+ channels**.

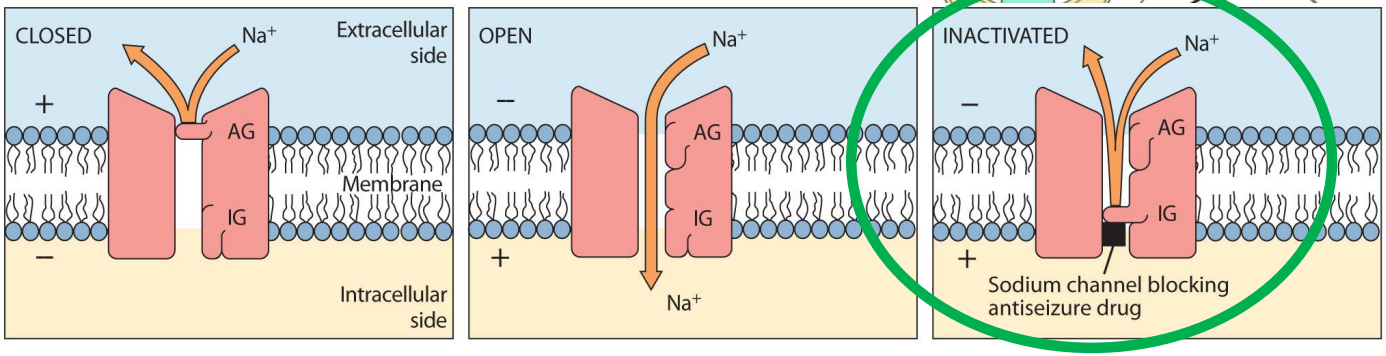
They bind preferentially to **inactivated** Na^+ channels, preventing them from reopening.

The highly repetitive depolarization of neurons during a seizure increases the number of Na^+ channels in the inactivated state → more channels are susceptible to the blockade by drugs.

Neuronal transmission at normal low frequencies is relatively unaffected because a much smaller number of the Na^+ channels are in the inactivated state.

Use-dependent





Phenytoin

Indications

- Partial and generalized tonic-clonic seizures

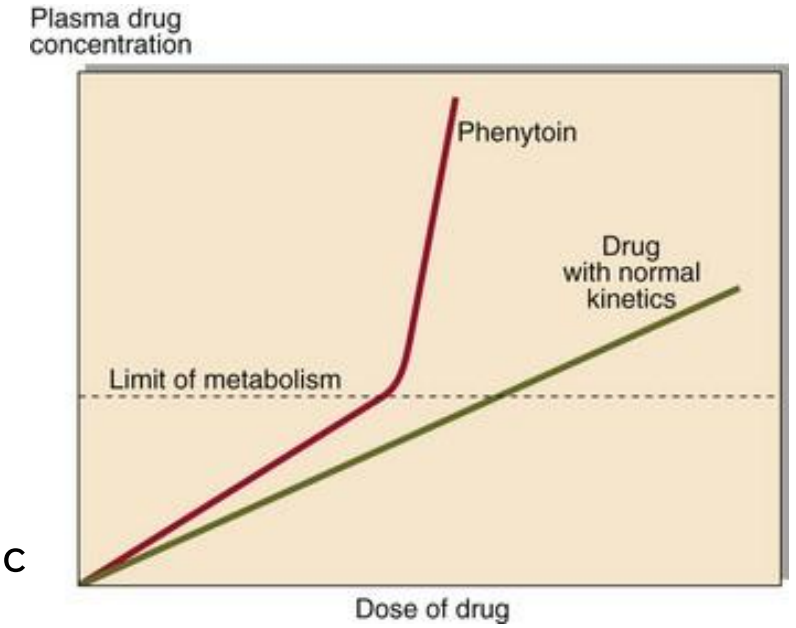
Adverse effects

I. ***Dose-related***: Nystagmus, ataxia, diplopia - sedation and confusion (acute toxicity).

II. ***Non-dose-related:***

- ***Gum hypertrophy*** and ***coarsening of facial features***
- ***Allergic reactions***, e.g., rash, hepatitis and ***lymphadenopathy***
- Hematological effects, e.g., ***megaloblastic anemia*** ***(folic acid deficiency)***
- Endocrine effects, e.g., ***hirsutism*** (hair growth)
- ***Teratogenic*** effects (it may cause congenital malformations).

Phenytoin



Pharmacokinetics

Phenytoin is **no longer a 1st-line** treatment for any of the seizures, **why?**

Phenytoin has **zero-order pharmacokinetics** → it is metabolized by hepatic enzymes saturated at therapeutic levels → the relationship between dose and plasma concentration is nonlinear → Small increase in dosage may produce large rises in plasma concentrations

Phenytoin has **a narrow therapeutic index** → needs continuous monitoring of its plasma concentration (total plasma concentrations **should not exceed 20 µg/mL**)

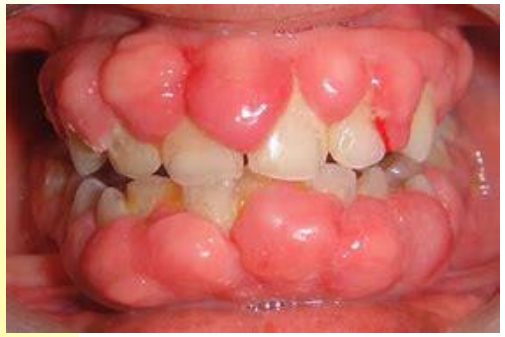
Drug interactions:

- Phenytoin **induces the hepatic CYP450 oxidase system**, increasing the metabolism of **oral contraceptives**, **anticoagulants and dexamethasone.**

Adverse Effect Of Phenytoin

mnemonic : HOT MALIKA

- Hirsutism
  - Hypertrophy of gums
- Osteomalacia
- Teratogenicity
- Megaloblastic anemia
- Ataxia and nystagmus
- Lymphadenopathy
- Inhibits insulin release (hyperglycemia)
- Vitamin K deficiency
- Arrhythmias



medicolearning

https://medicolearning.com/

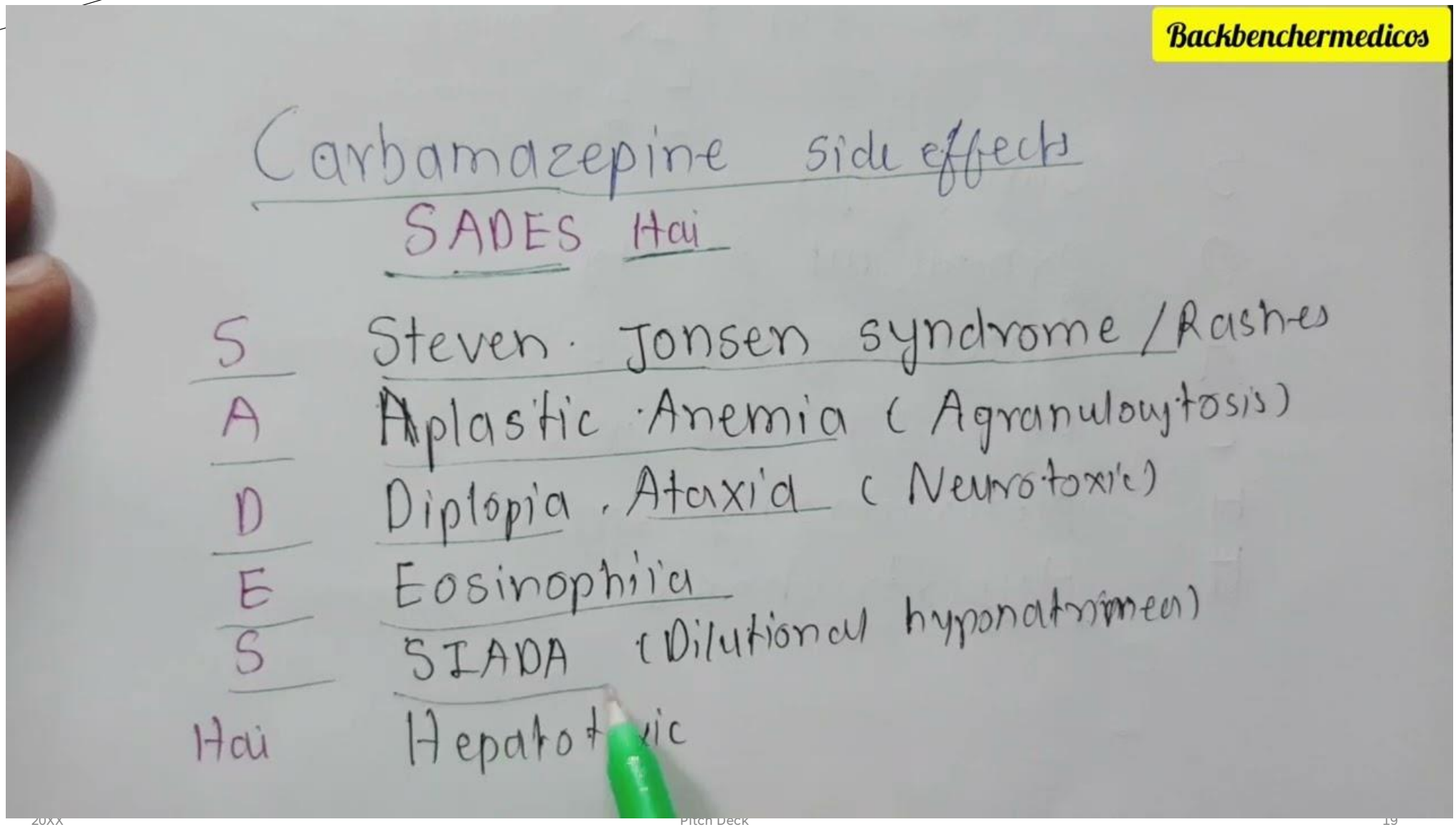
Carbamazepine

Indications

- Partial and generalized tonic-clonic seizures
- Also used in:
  - trigeminal neuralgia & neuropathic pain
  - Bipolar disorder

Adverse effects

- Nystagmus, ataxia, diplopia - sedation and vertigo.
- ***Allergic*** reactions, e.g., ***rash***
- Hematological effects, e.g., ***aplastic anemia***
- Endocrine effects, e.g., ↑ ADH secretion → water retention and ***hyponatremia***
- ***Teratogenic*** effects.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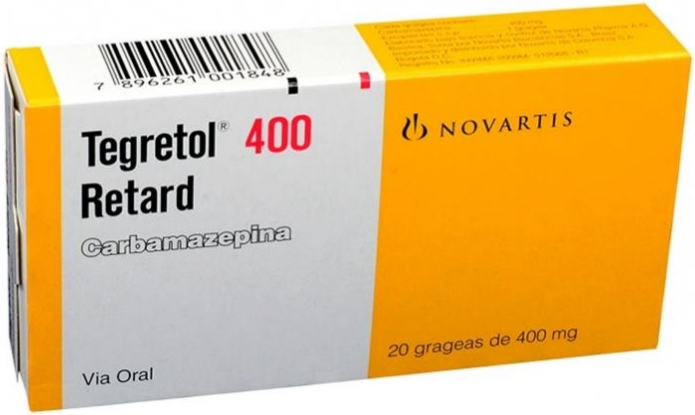
Carbamazepine side effects
SADES Hai
S Steven · Jonsen syndrome / Rashes
A Aplastic · Anemia (Agranulocytosis)
D Diplopia . Ataxia (Neurotoxic)
E Eosinophilia
S SIADA (Dilutional hyponatremia)
Hai Hepatotoxic

Carbamazepine



Drug interactions:

- Phenytoin **induces the hepatic CYP450 oxidase system**

  It accelerates its own metabolism and the metabolism of other drugs

Oxcarbazepine

is a derivative of carbamazepine and **has the same mechanism of action**

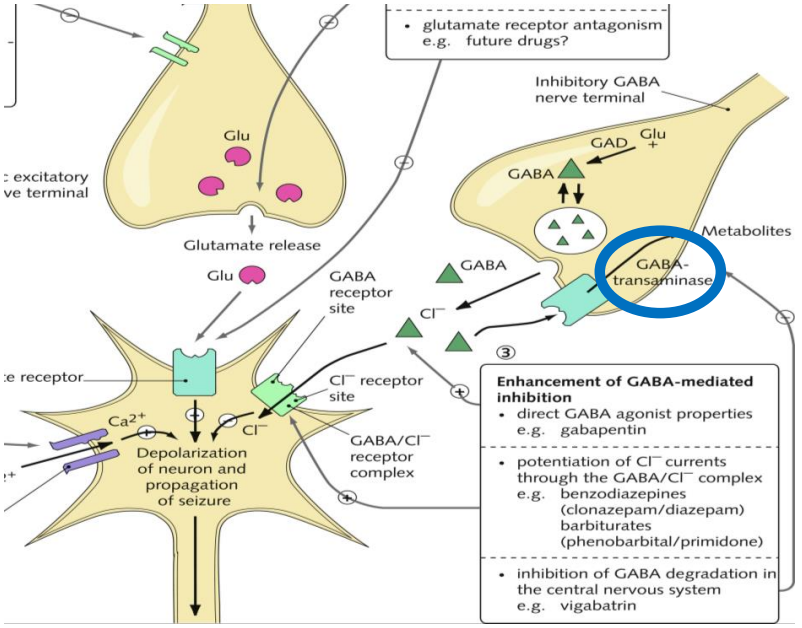
it differs from carbamazepine in:

1. **Less hepatic CYP450 enzyme induction.**
2. **Lower incidence of aplastic anemia.**
3. **Higher incidence of hyponatremia.**

Sodium valproate

Mech. Of action

- Blocks voltage-gated Na+ channels +
- Potentiates GABA action via inhibition of GABA transaminase → decrease GABA metabolism.



Indications

- Partial and generalized tonic-clonic seizures
- Absence seizures
- Also used in migraine prophylaxis.

Sodium valproate

Adverse effects

Sodium valproate has fewer side effects

I. Gastrointestinal upset

II. Importantly, **liver failure,** especially if used in combination with other antiepileptics.

III. Teratogenic effects (neural tube defects & autism)

Contraindications

- should not be given to people with **liver disease.**

Drug interactions:

- Valproic acid **inhibits the hepatic CYP450 oxidase system**

MNEMONIC

Valproate Side Effects (VALPROATE)

V omiting
A lopecia
L iver toxicity
P ancreatitis/pantcytopenia
R etention of fat (weight gain)
O edema (edema)
A ppetite increase
T remor/thrombocytopenia
E nzyme **inhibitor** (liver)

@MEMORYPHARMSTUDY

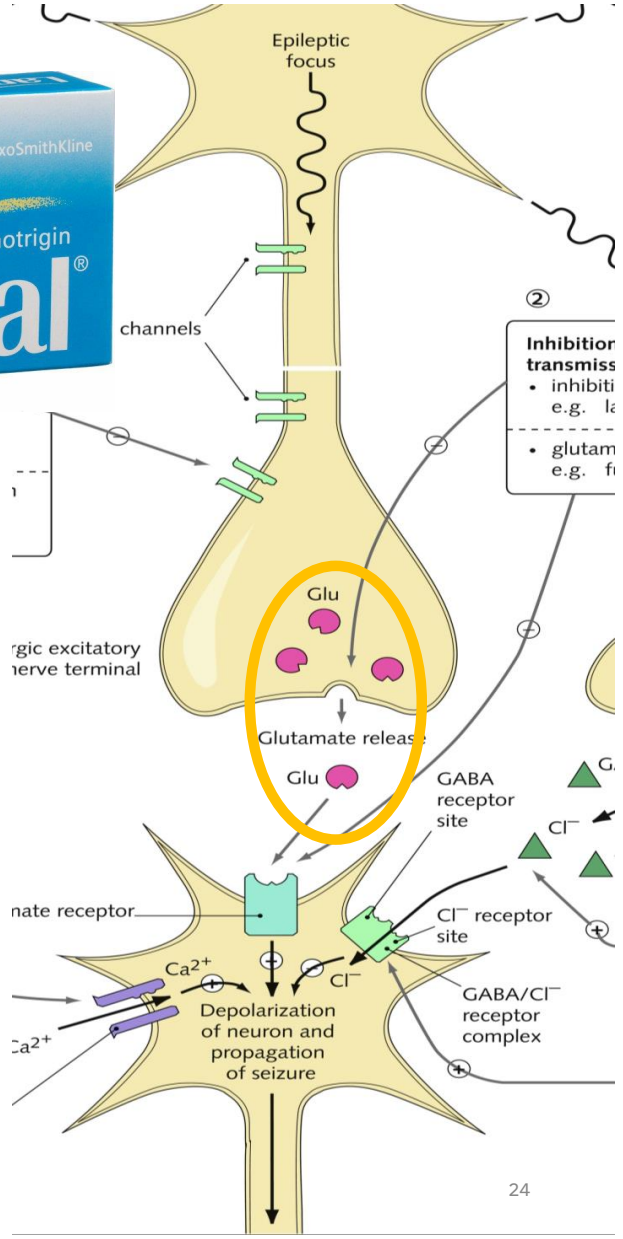
Lamotrigine

Mech. Of action

- Blocks voltage-gated Na+ channels +
- Inhibits the release of excitatory glutamate.

Indications

- Partial and generalized tonic-clonic seizures
- Absence seizures, although it is not as effective as ethosuximide or valproate
- Also used in bipolar disorder.



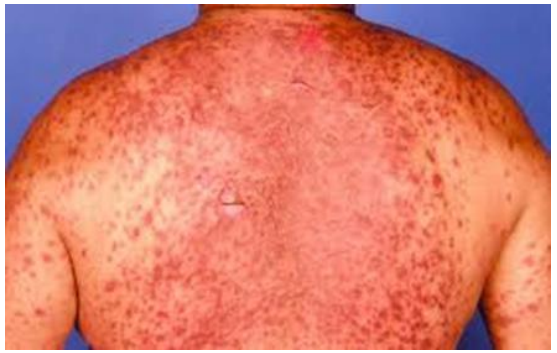
Lamotrigine

Adverse effects

I. CNS depression: dizziness, diplopia and sleepiness.

II. **Rash** → may progress to Stevens-Johnson syndrome, toxic epidermal necrolysis, or angioedema, which can be life-threatening.

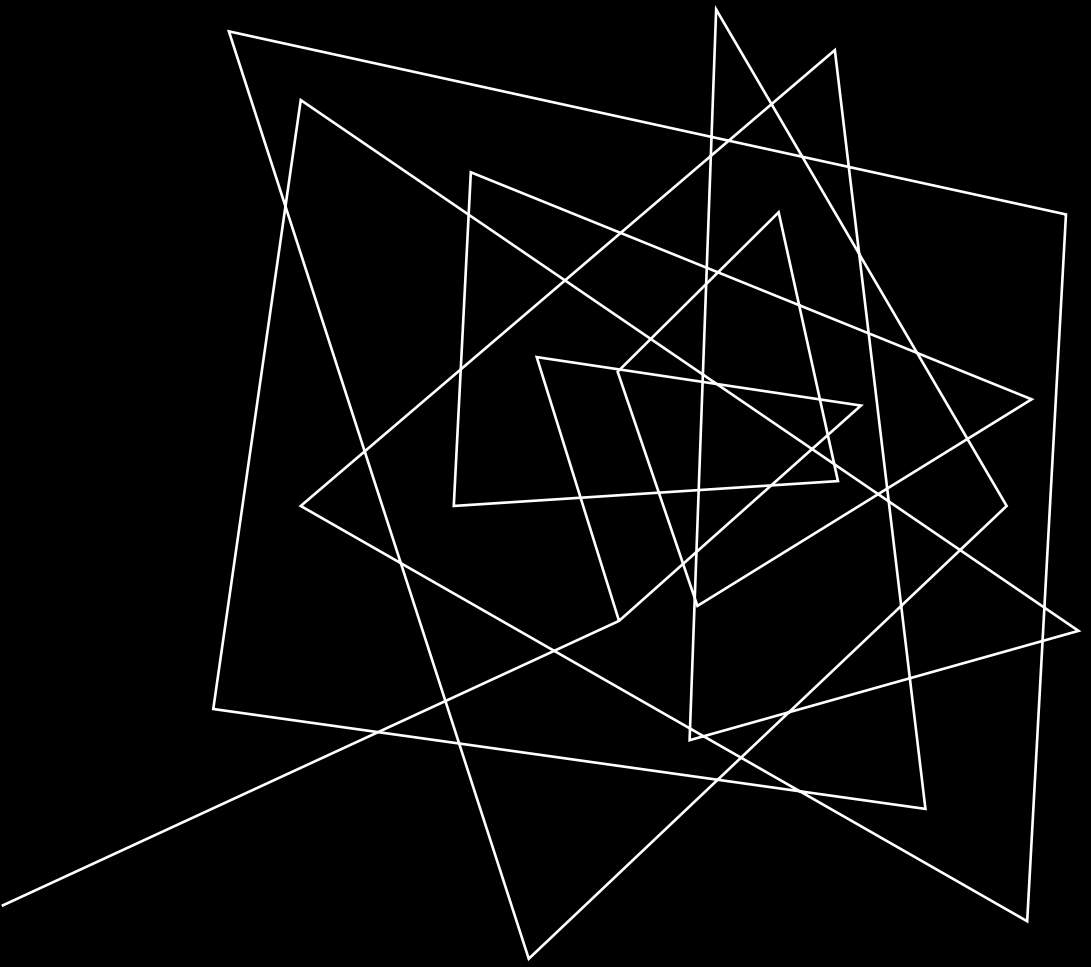
Slow dose titration is essential to reduce the risk of developing a rash.



III. Rarely, hepatotoxicity

Contraindications

- should not be given to people with **liver failure.**



Drugs that inhibit T-type Ca^{++} channels

Ethosuximide

Ethosuximide

Mech. Of action

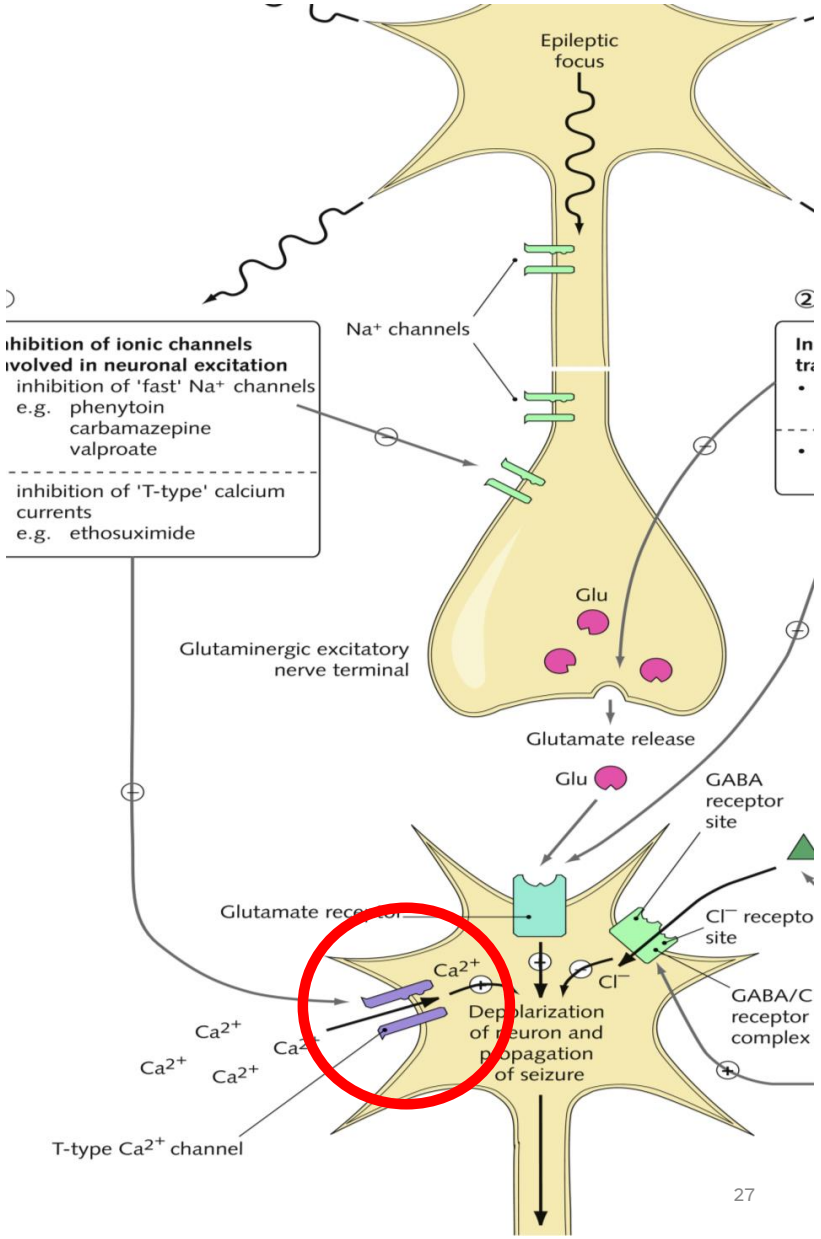
- Blocks the **low-threshold T-Type Ca^{++} channels** in the thalamus

Indications

- The drug of choice in simple absence seizures and is particularly well tolerated in children.

Contraindications

- **CI in tonic-clonic generalized seizures** → make them worse.



Ethosuximide

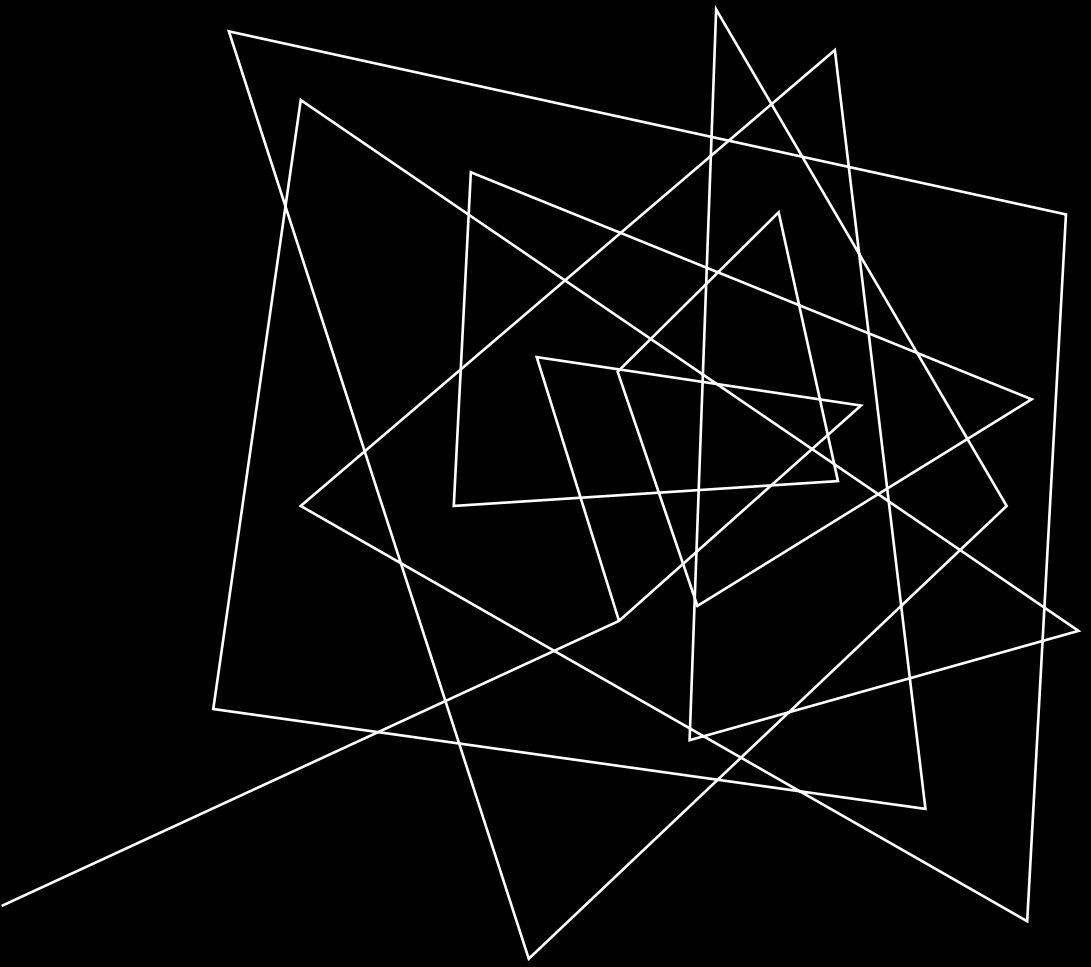
Adverse effects

- Gastrointestinal upset,
- Drowsiness and mood swings
- Rarely, it causes serious bone marrow depression.

Q

A 6-year-old girl and her mother come to see you because the girl's teacher observed episodes of staring and inability to communicate. These episodes last 3–5 seconds and occur 10–20 times during the school day. An EEG shows synchronized three-per-second spike-wave discharges generalized over the entire cortex. Which antiepileptic medication would you try first in this young girl?

A. Phenytoin
B. Clonazepam
C. Primidone
D. Carbamazepine
E. Ethosuximide



Drugs that potentiate GABA activity:

a. **Stimulate GABA/Cl^- receptor complex**
- Phenobarbital & Primidone
- Clonazepam, Diazepam & Lorazepam

b. **Block GABA reuptake**
- Tiagabine

c. **GABA-mimetics**
- Gabapentin
- Pregabalin

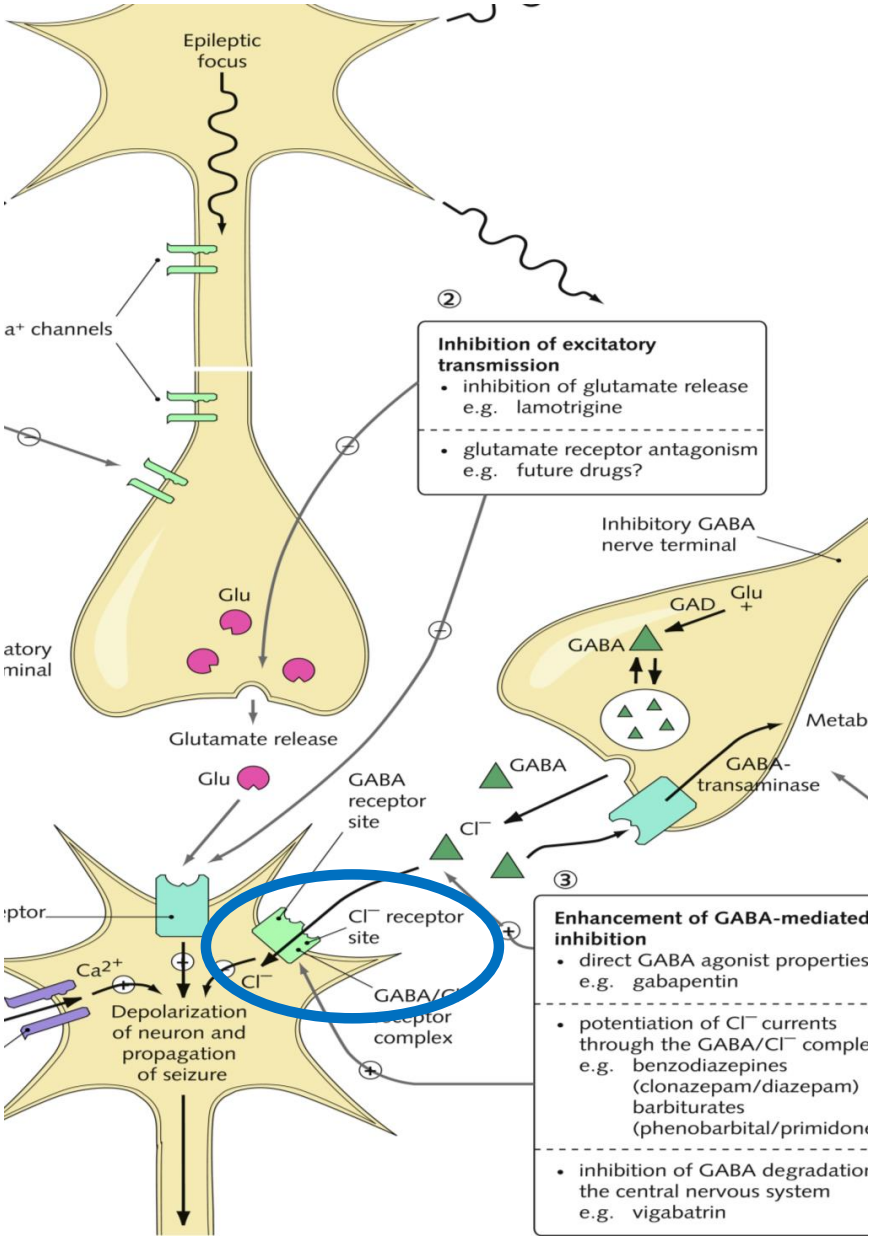
d. **Decrease GABA degradation**
- Vigabatrin

Mech. of action

- **Barbiturates,** e.g., phenobarbital and primidone
- **Benzodiazepines,** e.g., lorazepam, diazepam and clonazepam.

GABA is the major inhibitory neurotransmitter in the brain → it causes fast inhibition through its action on **$GABA_A$ receptors**.

- **Barbiturates** → act as allosteric activators of $GABA_A$ receptors → **prolong the duration** of Cl^- channel openings after activation by GABA → neuronal hyperpolarization.
- **Benzodiazepines** → are also allosteric activators of $GABA_A$ receptors, acting at a different site than that of the barbiturates → **increase the frequency of Cl- channel openings** after activation by GABA → neuronal hyperpolarization.



Phenobarbital

Indications

- Partial and generalized tonic-clonic seizures
- Status epilepticus

Adverse effects

I. Sedation is the main side effect → limits its use clinically,

II. Potentially fatal CNS and **respiratory depression** in overdose.

III. Phenobarbital is **an inducer of CYP450** → interacts with many medications.

Contraindications

- should not be used in **children**, **elderly**, and people with **respiratory depression.**

Benzodiazepines

Indications

- Clonazepam → Partial and generalized tonic-clonic seizures
- Lorazepam (IV) and diazepam (rectal or iv) → Status epilepticus

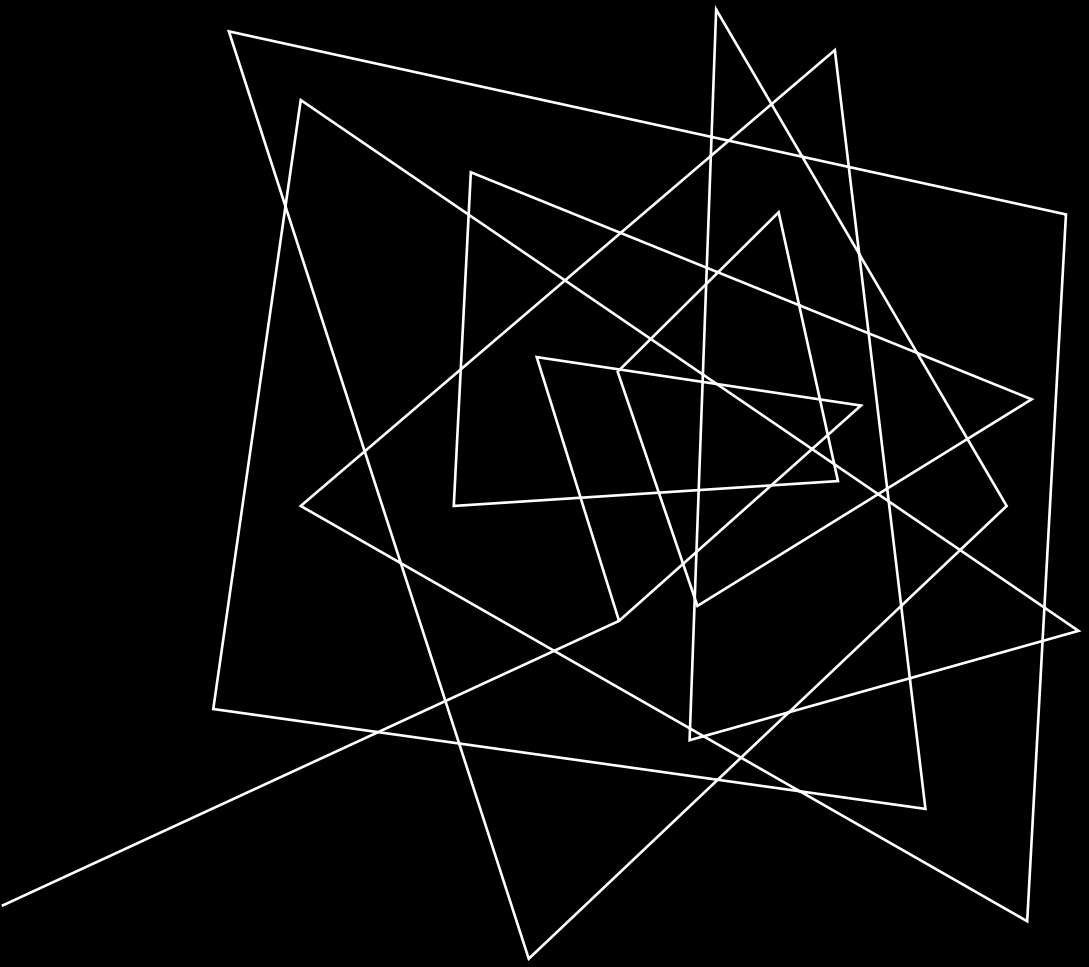
Adverse effects

I. Sedation is the main side effect

II. **Respiratory depression**

Contraindications

- should not be used in people with **respiratory depression.**



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b. **Block GABA reuptake**

- Tiagabine

c. **GABA-mimetics**

- Gabapentin
- Pregabalin

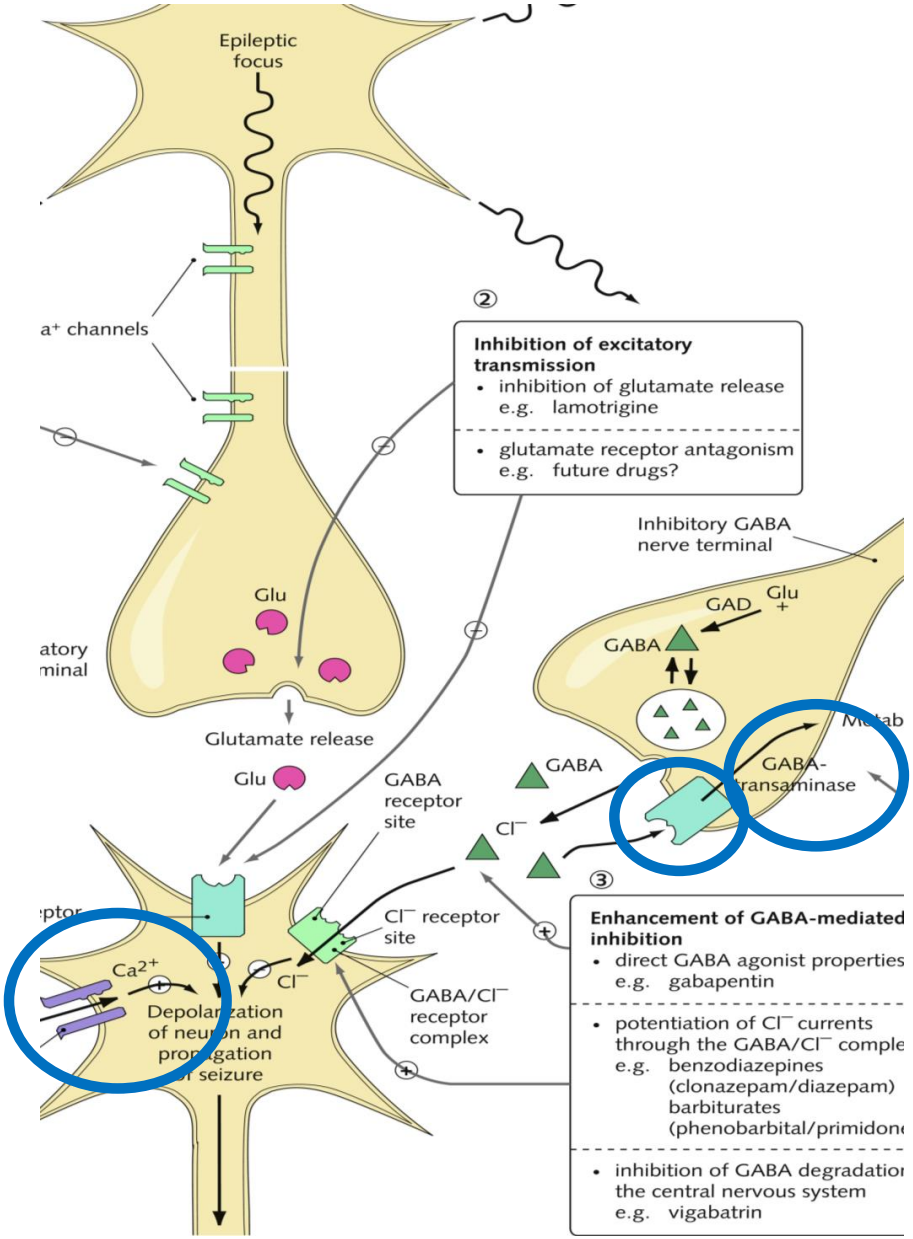
d. **Decrease GABA degradation**

- Vigabatrin

Mech. of action

- **Tiagabine** blocks GABA reuptake into presynaptic neurons by **inhibiting the GABA transporter (GAT-1)**
- **Vigabatrin** → an **irreversible inhibitor of GABA transaminase**, the enzyme that inactivates GABA
- **GABA-mimetics,** e.g., **gabapentin and pregabalin**

  They are structurally similar to GABA but **do not affect GABA receptors**. Rather, they exert their antiseizure activity by **inhibiting the voltage-gated Ca^{++} channels.**



Gabapentin & pregabalin

Indications

- Partial seizures
- **Neuropathic pain**
- Post-herpetic neuralgia

Adverse effects

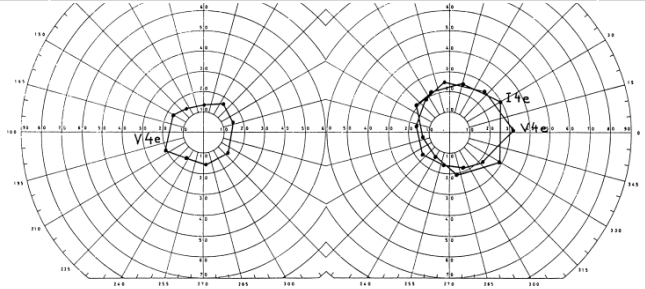
- Dizziness, ataxia, fatigue
- Weight gain

Contraindications

- **Avoid sudden withdrawal**
- Avoid use in **elderly** patients and in those with **renal impairment.**

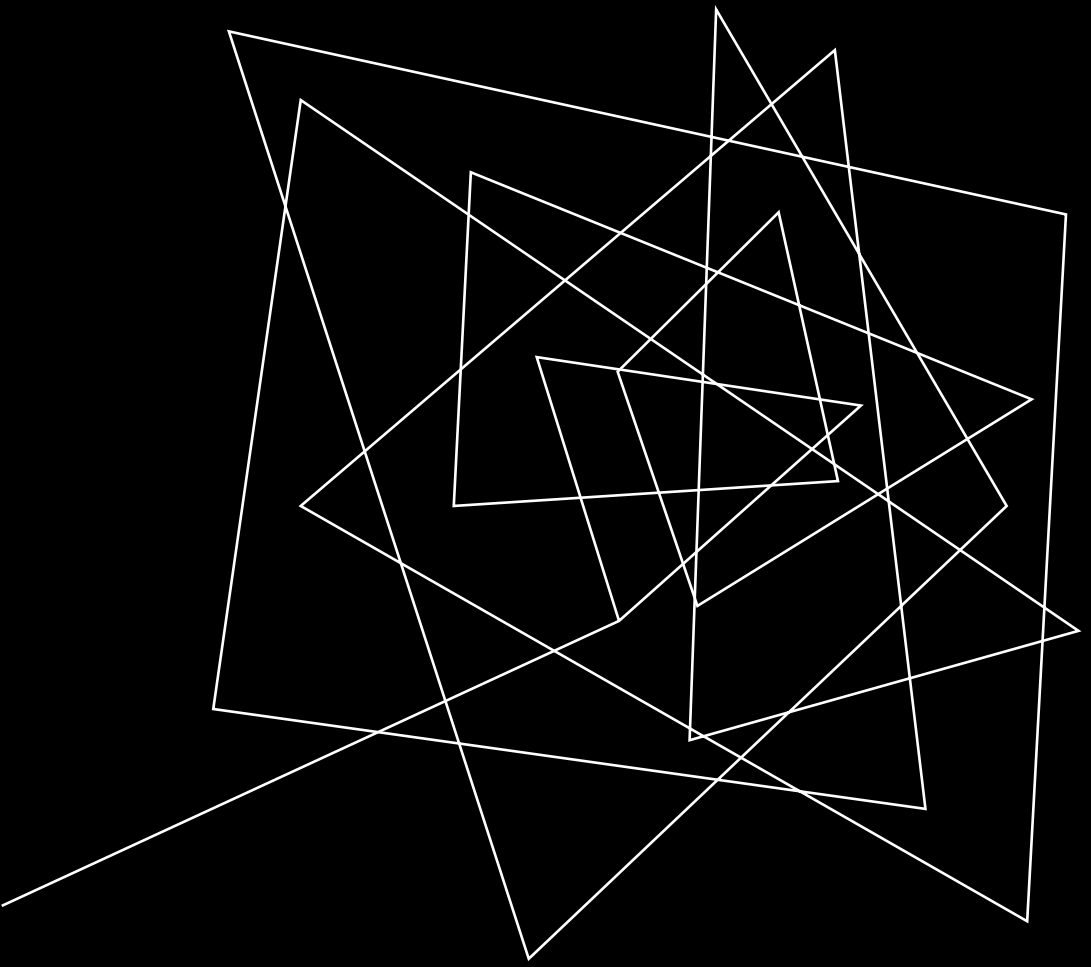
Vigabatrin vs Tiagabine

	Vigabatrin	Tiagabine
Indications	**Partial seizures**	
Adverse effects	Drowsiness, dizziness, **visual hallucinations** and **visual field defects.**	Dizziness, tremor and difficulty concentrating
Contraindications	Should not be used in people with a history of hallucinations.	



When to start/stop treatment

- It is recommended to start treatment when the patient has suffered **two or more seizures within a 2-year period.**
- Choice of anticonvulsant drug depends on **the type of epileptic seizure**
- **One drug should be used**, whenever possible → monotherapy carries **the lowest risk of adverse effects**
- For most anticonvulsant drugs, the correct dose is **the lowest effective dose** that **does not cause side effects.**
- Only for refractory cases, more than one drug may be required.
- The anticonvulsant drug can be withdrawn **after 2 years of being seizure-free**
- **Is there is a risk of recurrence?**
- Yes, around 25–40% risk of recurrence. No one can tell exactly, and seizure recurrence is always less if patients continue with treatment indefinitely → **the decision to stop treatment is largely a personal one**.



Status epilepticus

STATUS EPILEPTICUS

Abnormally **prolonged** (>30 minutes of continuous seizure activity) or **repetitive** seizures (two or more sequential seizures without full recovery of consciousness between seizures)

Status epilepticus is **a life-threatening medical emergency** that requires immediate treatment, because persistent seizure activity causes permanent neuronal injury.

Treatment should start when the seizure duration reaches **5 minutes for generalized** tonic-clonic seizures and **10 minutes for partial** seizures.

Status epilepticus

I. Benzodiazepines

Treatment of choice

The most commonly used → **Lorazepam or diazepam (IV).**

Recently, **midazolam (IM)** is tried with equal effectiveness

II. IV fosphenytoin or phenytoin

A 2nd therapy if seizures continue

III. IV Phenobarbital

An acceptable 2nd therapy if seizures continue, but it causes **persistent sedation** and may induce serious respiratory depression and hypotension.

N.B. Refractory status epilepticus → seizures continue following treatment with 1st and 2nd therapy drugs.

Refractory status epilepticus is treated with **a combination of IV anesthetic drugs**.

Antiepileptic drugs during pregnancy

- Seizures during pregnancy present risks to the mother and fetus → most women with epilepsy who become pregnant require anticonvulsant drug therapy.
- If possible, valproate, phenobarbital, and topiramate should be avoided, most importantly at the time of conception and early in the pregnancy.
- Lamotrigine and levetiracetam present the lowest level of risk to the fetus → considered for use in pregnancy.
- It is recommended to use the lowest possible doses of anticonvulsant drugs during pregnancy.
- Newborns of mothers who have received enzyme-inducing anticonvulsant drugs during pregnancy may develop a deficiency of vitamin K–dependent clotting factors, resulting in serious hemorrhage during the first 24h of life → prevented by administering IM vitamin K to the newborn shortly after birth.

Q

Of the list below, which is the safest antiepileptic drug to take during pregnancy?

A. Sodium valproate.

B. Carbamazepine.

C. Lamotrigine.

D. Phenytoin.

E. Midazolam.

References

- https://www.clinicalkey.com/student/content/toc/3-s2.0-C20150057550?origin=share&title=Brody's%20Human%20Pharmacology&meta=2019%2C%20Wecker%2C%20Lynn%2C%20PhD&img=https%3A%2F%2Fcdn.clinicalkey.com%2Fck-thumbnails%2FC20150057550%2Fcov200h.gif
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- https://www.clinicalkey.com/student/content/book/3-s2.0-B9780702073441000089#hl0001493
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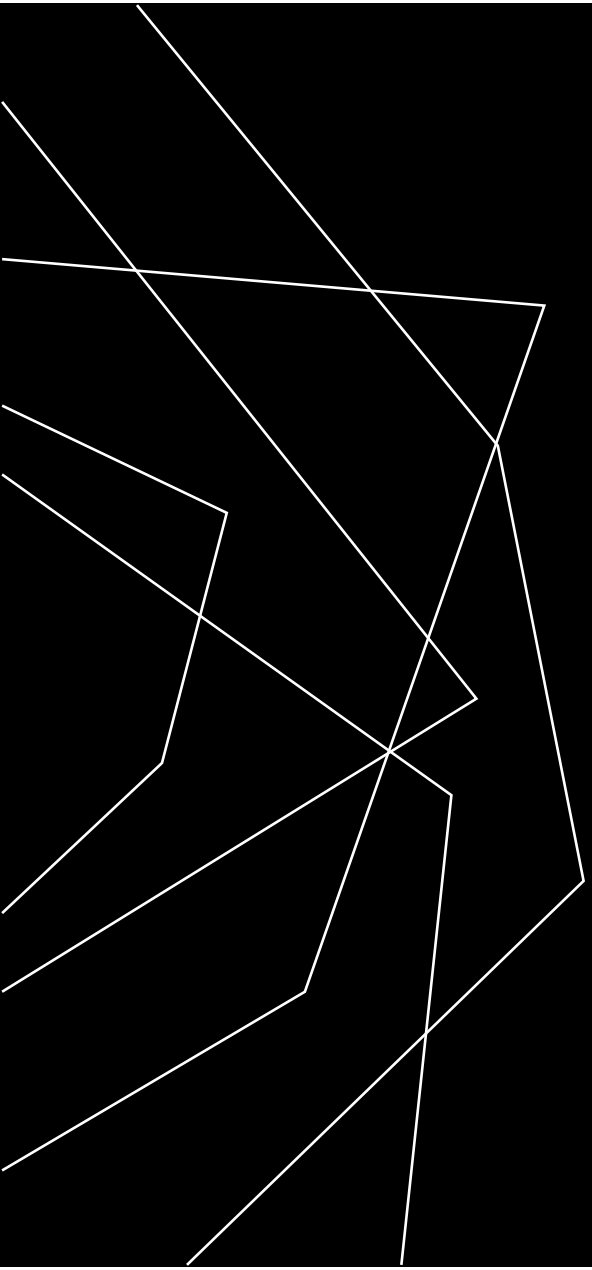

THANK YOU