ACE SERIES

Essentials of Pharmacology
A Concise Textbook

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As per the latest CBME curriculum (NMC 2024 guidelines)

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Q&A Videos

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About Ace Series

For years, Q&A-format books have been synonymous with last-minute exam preparation, designed primarily to help students navigate university examinations with efficiency and precision. Although this approach has served its purpose, the evolving needs of medical education demand a more integrated, concept-driven learning resource, one that supports not just recall, but also enhanced understanding of the core concepts.

This shift marks the launch of Thieme Ace Series, with **academically aligned, institution-relevant learning tools** that complement teaching, curriculum alignment, and structured learning. **Ace** literally means to do very well.

At the core of the Ace Series lies a simple but powerful principle: student-centric learning anchored in conceptual clarity.

What Sets the Ace Series Apart?

- **Concise Learning Resources, Not Just Test Prep**
  These books are not limited to serving as revision guides. They have been carefully structured to function as **concise textbooks**, covering all **essential and high-yield topics required for MBBS curricula**. Each answer is designed not only to help students reproduce information in exams but also to build foundational understanding.
- **Proactive Learning, Not Reactive Studying**
  Q&A-format books are primarily optimized around anticipated exam questions. The approach followed in this series expands this scope, ensuring that students can rely on these books throughout their academic cycle, from first exposure to final revision.
- **Structured Clarity Instead of Fragmented Knowledge**
  Topics are curated and organized to provide logical flow, clinical relevance, and conceptual continuity, enabling students to connect ideas rather than memorize isolated answers.
- **From Concept Building to Exam Readiness**
  These books bridge the crucial gap between building concepts and preparing the students well for not only their university exams but PGME as well. This is achieved by integration of MCQs (clinical, conceptual, and case-based) with these resources.

How Will Ace Series Serve the Readers?

The strengths that make these books indispensable are:

- Exam alignment: All content is mapped to university requirements and frequently tested areas
- Q&A format: To ensure clarity, accessibility, and efficiency in learning
- High-yield focus: Emphasis on what truly matters—clinically and academically

Why This Matters?

Medical education today requires resources that do more than help students pass exams—it requires tools that help them understand various aspects of medicine.

By bridging the gap between concise textbooks and exam-oriented preparation, these books serve multiple stakeholders:

- Students: who gain a reliable, structured, and easy-to-navigate learning companion
- Faculty and institutions: who can integrate these books into teaching frameworks as standardized, curriculum-aligned resources

The Outcome

The result is a resource that is:

- Comprehensive yet concise
- Exam-relevant yet concept-driven
- Student-friendly yet institution-ready

The Ace Series reflects our commitment to evolving with the needs of modern medical education, ensuring that students are not only prepared to clear university examinations, but also equipped to build strong clinical foundations.

In essence, these are not just books to help students pass exams; they are books designed to help students understand, retain, and apply medicine with confidence.

Key Highlights

PH3.1	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of general anesthetics and preanesthetic medications
PH3.2	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of different sedative and hypnotic agents, and explain the pharmacological basis for the selection and use of different sedative and hypnotic agents

All the chapters are carefully aligned with the latest CBME competencies (NMC 2024 curriculum).

The updated CBME-aligned content is structured in concise Q&A format which enhances clarity, boosts engagement and strengthens retention.

1. Define seizure and epilepsy. List different classes of antiepileptic drugs with examples from each class.

Seizure

An abnormal neuronal electrical discharge in the brain is called a seizure. This could be due to trauma, high-grade fever, or infection. *(Remember: Seizure = single episode.)*

Note

Flumazenil is used in benzodiazepine overdose. It is a competitive benzodiazepine receptor antagonist.

Concise, high-impact notes summarize critical information and serve as quick revision checkpoints within the text.

Mnemonics are incorporated in each chapter to help students quickly remember complex drug names, mechanisms, side effects, and interactions, making study easier and improving recall during exams.

- **G**riseofulvin *(Mnemonic: Govt. Medical College, MP, Chhattisgarh).*
- **M**etronidazole.

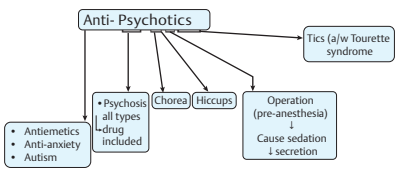


Table 3.3 Differences between barbiturates and benzodiazepines

Barbiturates	Benzodiazepines
▪ Act at alpha-beta subunit *(mnemonic: BArbi = AB)*	Act at alpha-gamma subunit *(mnemonic: Benz car–AG laga degi)*
▪ Increases the duration of chloride channel opening	Increases the frequency of chloride channel opening
▪ Known as a GABA mimetic	Known as a GABA facilitator
▪ Narrow therapeutic index: unsafe	Wide therapeutic index: safe
▪ Less commonly used	More commonly used

The content incorporates numerous flowcharts and tables to simplify complex concepts such as drug classifications, mechanisms of action, pharmacokinetics, adverse effects, and drug–drug interactions.

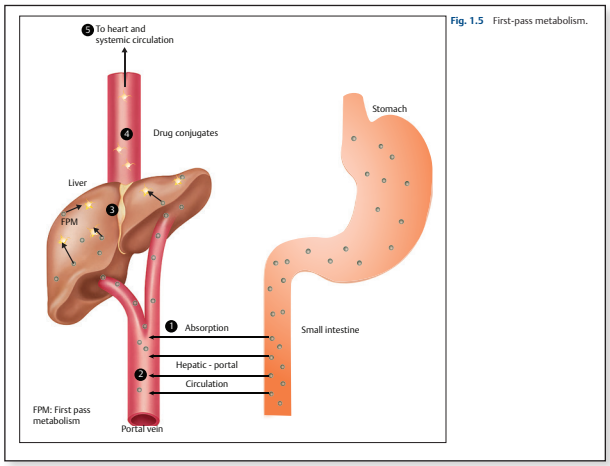
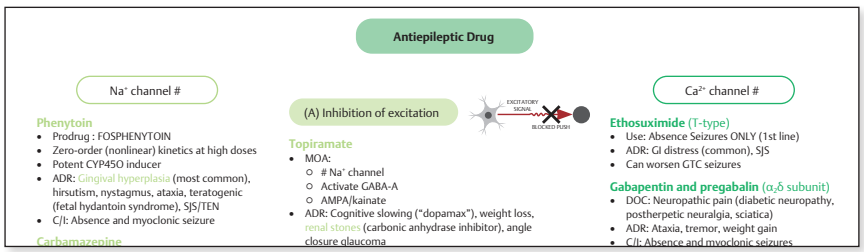


Fig. 1.5 First-pass metabolism.

High-quality illustrations help learning concepts easily.

Each chapter contains mind map at the end that acts as a summarized conceptual tool.



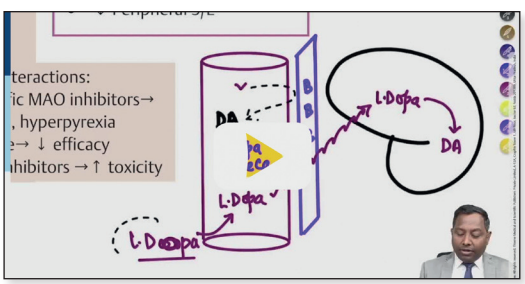
Conditions that can increase digoxin toxicity risk *(mnemonic: "Hy.TRWMP")*	
• **Hy**pokalemia	In hypokalemia, there will be an excessive risk of digoxin binding to the Na^+/K^+ ATPase
• **Hy**pomagnesemia	Mg^{2+} is a cofactor for the Na^+/K^+ ATPase

Critical information has been summarized in boxes to help students learn smarter.

MCQs are provided at the end of the book as well as part of ancillary e-content aligned with the pattern of university and major competitive examinations such as NEET-PG, INI-CET, and FMGE.

2. In a patient with arthritis, Steroid was injected in for relief of joint pain. This route of administration is:
   a. Intravenous
   b. Transdermal
   c. **Intra-articular**
   d. Intra-osseous

Intra-articular administration is a local route of drug administration. It delivers the drug directly into the joint space, providing localized therapeutic effect with minimal systemic exposure.



Videos alongside mind maps are provided as ancillary e-content to make learning an immersive and engaging experience.

3. Central Nervous System

PH3.1	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of general anesthetics and preanesthetic medications
PH3.2	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of different sedative and hypnotic agents, and explain the pharmacological basis for the selection and use of different sedative and hypnotic agents
PH3.3	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of drugs used in epilepsy, and devise a management plan for a case of uncontrolled seizure
PH3.4	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of drugs of opioid analgesics, and explain the special instructions for use of opioids
PH3.5	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of drugs used for depression, and devise a management plan for depressive and psychotic disorders
PH3.6	Describe the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse drug reactions of drugs used in anxiety disorders. Discuss the general goals of pharmacotherapy for the management of the above disorders
PH3.7	Explain the types, salient pharmacokinetics, pharmacodynamics, therapeutic uses, and adverse reactions of drugs used for parkinsonism and other neurodegenerative disorders. Write a prescription to manage a case of drug-induced parkinsonism
PH3.8	Identify and manage methanol poisoning and chronic ethanol intoxication
PH3.9	Describe the drugs that are abused and cause addiction (dependence, addiction, stimulants, depressants, psychedelics, drugs used for criminal offences). Explain the process and steps for the management of drug deaddiction

1. Define seizure and epilepsy. List different classes of antiepileptic drugs with examples from each class.

Seizure

An abnormal neuronal electrical discharge in the brain is called a seizure. This could be due to trauma, high-grade fever, or infection. *(Remember: Seizure = single episode.)*

Epilepsy

Repeated episodes of such seizures due to a similar underlying cause are called epilepsy. *(Remember: Epilepsy = every now and then.)*

Convulsion

Epilepsy with motor involvement is a convulsion. *(Remember: Convulsion = contraction of muscles.)*

The main neurotransmitters in the brain that control neuronal activity are the following:

- **GABA** (gamma-aminobutyric acid): Inhibitory neurotransmitter.
- **Glutamate:** Excitatory neurotransmitter.

The abnormal neuronal discharge in seizure/epilepsy could be due to an imbalance between neurotransmitters GABA (decreased GABA) and glutamate (increased glutamate).

The treatment aims of antiepileptic agents are targeted toward either reducing the level of glutamate

Table 3.1 Classification of antiepileptic drugs

Class	Examples
1. Barbiturate	▪ Phenobarbitone
2. Deoxybarbiturate	▪ Primidone
3. Hydantoin	▪ Phenytoin ▪ Fosphenytoin
4. Iminostilbene	▪ Carbamazepine ▪ Oxcarbazepine ▪ Eslicarbazepine
5. Succinimide	▪ Ethosuximide
6. Aliphatic carboxylic acid	▪ Valproate sodium ▪ Divalproex
7. Benzodiazepines	▪ Clonazepam ▪ Diazepam ▪ Lorazepam ▪ Clobazam
8. Phenyl triazine	▪ Lamotrigine
9. Cyclic GABA analog	▪ Gabapentin ▪ Pregabalin
10. Newer drugs	▪ Topiramate (VG-Na^+ blocker) ▪ Levetiracetam, brivaracetam (SV2A inhibitors) ▪ Zonisamide (VG-Na^+ blocker) ▪ Vigabatrin (GABA transaminase inhibitor) ▪ Tiagabine (GAT-1 inhibitor) ▪ Lacosamide (VG-Na^+ blocker, collapsin resposne mediated protein (CRMP) inhibitor)

or increasing the level of GABA. In some patients, a combination of both is also often used.

Classes of Antiepileptic Drugs

The types of antiepileptic drugs (AEDs) are listed in **Table 3.1**.

2. List the antiepileptic agents acting by reducing glutamate release by causing voltage-gated sodium channel blockade. Write down the different uses of sodium valproate.

- Glutamate is a neuroexcitatory neurotransmitter, the excess of which is responsible for seizure activity in the brain. Glutaminergic neurons are depolarized due to the influx of sodium and calcium through presynaptic VG-Na^+ (voltage-gated sodium) and Ca^{2+} channels, respectively.
- By blocking the VG-Na^+ channels, the depolarization of the neuron is inhibited; hence, there is no release of glutamate. A similar effect can also be achieved by blocking the Ca^{2+} channel at presynaptic neurons (**Fig. 3.1**).
- **Antiepileptic agents acting by blocking VG-Na^+ channels are the following:**
  - Sodium valproate, lamotrigine, phenytoin, carbamazepine, oxcarbazepine, lacosamide, rufinamide, topiramate, and zonisamide.
- **Antiepileptic agents acting by blocking Ca^{2+} channels are the following:**
  - Pregabalin and gabapentin.

Uses of Valproate

Valproate is a VG-Na^+ channel blocker at presynaptic neurons. It has multiple epileptic and nonepileptic uses.

Epileptic Uses

- Generalized tonic–clonic seizure (GTCS).
- Partial/focal seizure.
- Tonic seizure and clonic seizure.
- Absence seizure.
- Dravet's syndrome.

Nonepileptic Uses

- Bipolar disorder.
- Rapid cycler—drug of choice (DOC).
- Migraine prophylaxis.

3. Write a short note on sodium valproate. What will be the outcome if valproate is started in a patient who is on the anticoagulant warfarin?

- Valproate is an AED used in multiple seizure disorders and has several nonepileptic uses too.
- It is a broad-spectrum antiepileptic agent that acts by reducing the level of glutamate and increasing GABAergic activity.

Mechanism of Action of Valproate

- VG-Na^+ channel blocker.
- Calcium channel blocker.

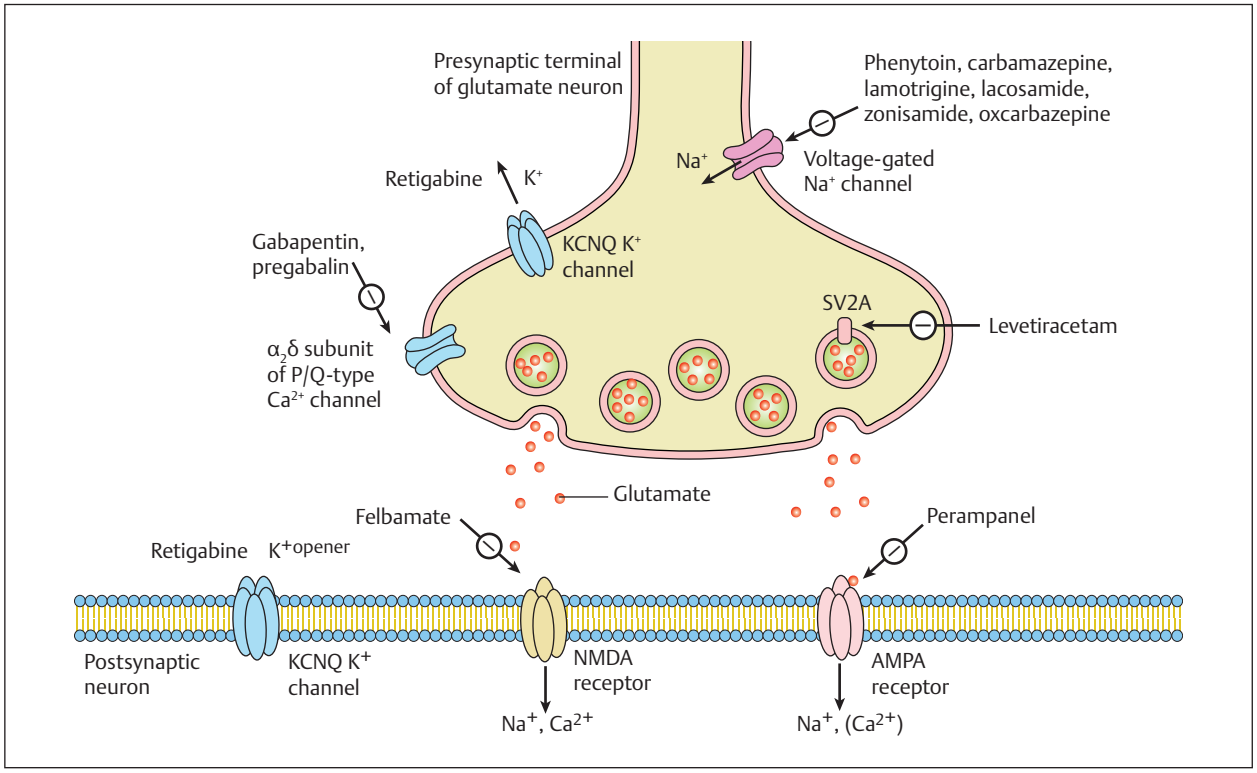


Fig. 3.1 Action of antiepileptic drugs at different sites of glutaminergic neuron nerve ending.

- Increases GABA by:
  - GABA transaminase inhibition.
  - SSA-DeH (succinic semialdehyde dehydrogenase) inhibition.
- Inhibit histone deacetylase.

Pharmacokinetic Property

Absorption: Good oral absorption.

Distribution: Wide distribution. It can cross the blood–brain barrier (BBB) and blood–placental barrier (BPB). Owing to this BPB crossing capacity, it is associated with a teratogenic effect known as **spina bifida** (**Fig. 3.2**).

Metabolism: Undergoes hepatic metabolism and has enzyme inhibitory property. Therefore, it is associated with drug interaction like increasing risk of drug toxicity.

Excretion: Undergoes biliary secretion. Hence, it is contraindicated in hepatic failure patients.

- Therapeutic plasma concentration: 50 to 100 µg/mL.
- It is the most teratogenic drug associated with spina bifida (**Fig. 3.2**).

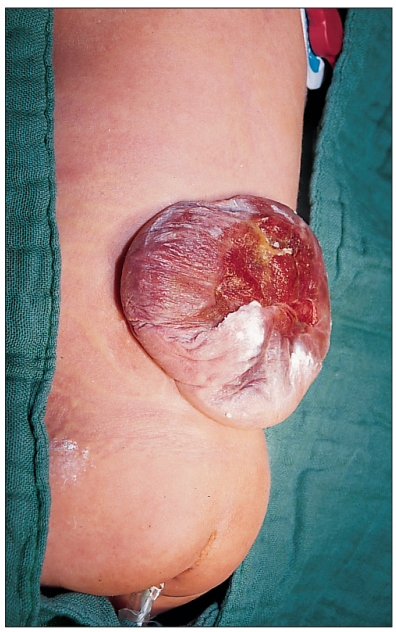


Fig. 3.2 Spina bifida (associated with valproate). (Reproduced from Niethard, Kinderorthopädie, Thieme, 2010)

Uses

Epileptic Uses

- GTCS.
- Partial/focal seizure.
- Tonic seizure and clonic seizure.
- Absence seizure.
- Dravet's syndrome (DOC).
- Atonic seizure; myoclonic seizure (DOC).
- Lennox–Gastaut syndrome (DOC).
- Atypical absence seizure (DOC).

Nonepileptic Uses

- Bipolar disorder—rapid cycler (DOC).
- **Rheumatic chorea (DOC).**
- Migraine prophylaxis.

Adverse Drug Reactions (Mn: VALPROATE)

- **V**omiting.
- **A**lopecia.
- **L**iver toxicity (fulminant hepatitis: the most grave side effect).
- **P**ancreatitis/**P**ancytopenia (bone marrow suppression).
- **R**etention of fats (weight gain)—PCOS (Polycystic ovary syndrome).
- **O**edema (peripheral).
- **A**norexia.
- **T**remor, teratogenic (maximal risk with valproate among antiepileptics).
- **E**nzyme inhibitor (increased risk of toxicity of other drugs).

Outcome if Valproate Started in Patient on Warfarin

Since valproate is a potent enzyme inhibitor, if it is added with warfarin, it will slow down the warfarin metabolism due to its enzyme-inhibiting property. This leads to increased risk of warfarin toxicity, which manifests with bleeding.

4. Write a short note on the mechanism of action (MOA), uses, and adverse drug action of phenytoin. Why is phenytoin contraindicated in pregnancy?

Phenytoin

- Phenytoin provides protection against seizures by blocking VA-Na^+ channels, which blocks sustained high-frequency repetitive firing of action potentials. This is achieved by reducing the amplitude of sodium-dependent action potential by enhancing steady-state inactivation.
- Sodium channels exist in three main forms: resting state, open state, and inactivation state. Phenytoin binds to the inactive form.
- The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited.
- It is a potent enzyme inducer and has been shown to follow zero-order kinetics.
- **Therapeutic plasma concentration:** 10 to 20 µg/mL.

Uses of Phenytoin

- Antiepileptic: GTCS, partial seizure.
- Antiarrhythmic property (class IB).
- Wound-healing property.

Contraindication of Phenytoin

It should be avoided in the following cases:

- Pregnancy: If exposed during pregnancy, it is associated with a teratogenic effect, fetal hydantoin syndrome.
- Absence seizure: If exposed in patients with absence seizures, it can precipitate the condition.

Adverse Drug Reactions (Remember: Phenytoin)

- **P** 450 interaction → a potent enzyme inducer.
- **H**irsutism, hyperglycemia.
- **E**nlarged gum/gum hypertrophy (**most common side effect; Fig. 3.3a**).
- **N**ystagmus (early onset adverse drug reaction [ADR]).
- **Y**ellow-brown skin staining, **rash** (exanthemas/pustules).
- **T**eratogenicity (fetal hydantoin syndrome).
- **O**steomalacia.
- **I**nterfere with vitamin B12 and folate absorption → megaloblastic anemia.
- **N**europathies.
- Lymphadenopathy (pseudolymphoma)—due to decreased immunoglobulin A (IgA) level, the patient develops lymphadenopathy, which mimics lymphoma.

Effect of Phenytoin during Pregnancy

- Administration of phenytoin in pregnancy increases the incidence of congenital abnormalities (fetal hydantoin syndrome; **Fig. 3.3b**).

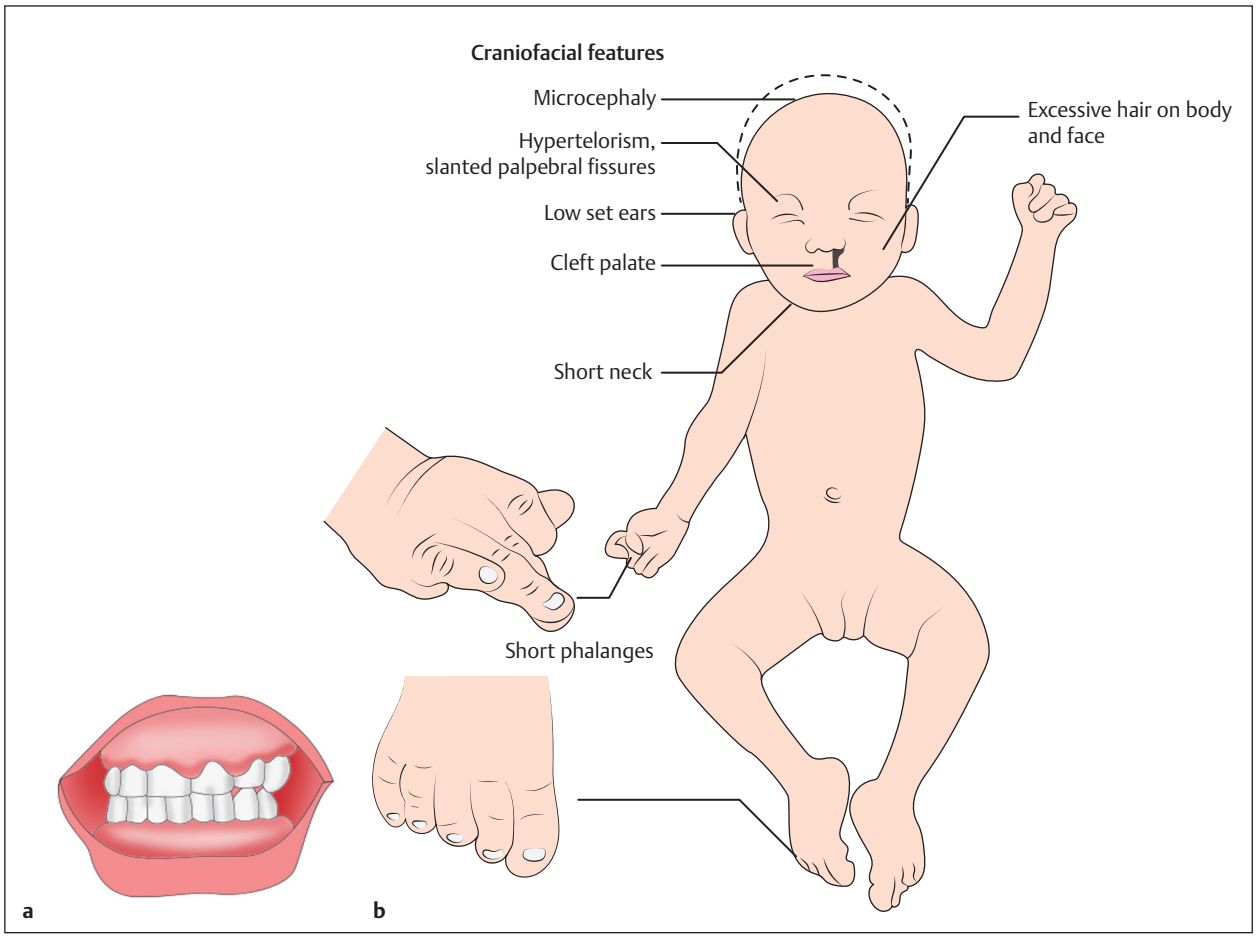


Fig. 3.3 (a) Gum hypertrophy caused by phenytoin. (b) Fetal hydantoin syndrome and gingival hyperplasia by phenytoin.

- This condition is characterized by hypoplastic phalanges, cleft lip and palate, thin upper lip, and microcephaly.
- This teratogenicity most probably caused by its arene-oxide metabolite.

5. Discuss the antiepileptic drug carbamazepine, enumerating its uses and adverse effects. How is carbamazepine effective in central diabetes insipidus (CDI)?

- Carbamazepine is an AED from the iminostilbene class.
- It is the first-line antiepileptic agent used in patients with GTCS and focal seizures.

Mechanism of Action of Carbamazepine

- Carbamazepine is a VG-Na^+ channel blocker.
- It preferentially binds to VG-Na^+ channels in the inactive form to prevent glutamate release and repetitive and constant firing of an action potential.

Uses

- Partial seizure (DOC).
- Trigeminal, glossopharyngeal neuralgia (DOC).
- Benign rolandic epilepsy of childhood (DOC).
- Generalized seizures EXCEPT myoclonic and absence seizures.
- Used as a second line in bipolar disorder.
- Central diabetes insipidus.

Adverse Effects (Remember: CARBAMADES)

- **C**onfusion.
- **A**taxia.
- **R**ashes (Stevens–Johnson syndrome).
- **B**lurring of vision and diplopia.
- **A**granulocytosis (most serious side effect).
- **M**arrow suppression.
- **A**plastic anemia.
- **D**ilutional hyponatremia (elderly; more severe with oxcarbazepine).
- **E**mesis.
- **S**plenomegaly.

Oxcarbazepine and Carbamazepine in Diabetes Insipidus

- Agents like oxcarbazepine and carbamazepine have shown to increase antidiuretic hormone (ADH) secretion from the posterior pituitary. This excess ADH secretion has been associated with conditions like syndrome of inappropriate ADH (SIADH) secretion.
- The risk of SIADH is more commonly associated with oxcarbazepine than with carbamazepine.
- ADH acts at the V_2 receptor of the collecting duct and increases the aquaporin 2 channels (water reabsorption channel).
- This channel increases water reabsorption, leading to excess fluid in the body compared to serum Na^+, causing dilutional hyponatremia.

6. Write a short note on lamotrigine. Discuss its role in grand mal epilepsy (GTCS).

Lamotrigine is a broad-spectrum AED used to treat epileptic disorders and the depressive phase of bipolar disorders.

Mechanism of Action

- VG-Na^+ channel blocker.
- Calcium channel blocker.
- Suppress the release of two dominant neurotransmitters in the central nervous system (CNS): **glutamate and aspartate**.

Uses

- First-line drug in GTCS, juvenile myoclonic epilepsy, partial seizure, and absence seizure.
- Second-line drug in Lennox–Gastaut syndrome and bipolar disorders.

Side Effects (Mn: RAIN-Dance)

- Rash (Stevens–Johnson syndrome).
- Ataxia.
- Insomnia.
- Nausea/vomiting.
- Diplopia.

Role of Lamotrigine in Grand Mal/GTCS

- Lamotrigine is approved by the Food and Drug Administration (FDA) as an adjuvant treatment of grand mal seizures.
- Initially, it was useful in refractory cases of GTCS as an add-on drug; now it has also been found to be effective as monotherapy.
- Now used as a first-line drug for grand mal seizures.

7. Write a short note on glutamate receptor antagonists as antiepileptic drugs.

Glutamate causes excitotoxicity of neurons by its action on receptors, namely NMDA **(N-methyl-D-aspartate)**, AMPA **(alpha-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid)**, and mGLUR5.

Types of Glutamate Receptor Antagonists

Glutamate receptor antagonists help in reducing neuronal excitability. These are:

- **NMDA receptor blocker:**
  - **Drug:** FELBAMATE.
  - **Uses:** GTCS, partial seizure. Mainly used in resistant cases due to their side effects.
  - **Side effects:** Bone marrow suppression, hepatotoxicity, nausea, and vomiting.
- **AMPA receptor antagonist:**
  - **Drugs:** PERAMPANEL, TALAMPANEL.
  - **Uses:** Partial seizures.
  - **Side effects:** Somnolence, mood abnormality.

8. List the GABAergic drugs utilized as antiepileptic agents.

GABA is a neuroinhibitory neurotransmitter. It reduces neuronal excitability. Hence, GABA agonists are used in the management of epileptic disorders.

Types of GABAergic Drugs

These can have a direct or indirect antiepileptic effect:

- **Direct antiepileptic effect:** This is achieved by $GABA_A$ receptor agonists located in the brain (**Fig. 3.4**).
- **Drugs:** BENZODIAZEPINES, BARBITURATES, GANAXOLONE, and STIRIPENTOL.
- **Indirect antiepileptic effect:** This is achieved by increasing GABA in the synapse by three mechanisms (**Fig. 3.5**).
  - Stimulate presynaptic release of GABA.
    Drugs: PREGABALIN, GABAPENTIN.
  - Inhibit reuptake of GABA by inhibiting GAT-1.
    Drugs: TIAGABINE.
  - Inhibit metabolism of GABA by inhibiting GABA transaminase.
    Drugs: VIGABATRIN, VALPROATE.

9. Write a short note on the pharmacotherapy of absence seizures.

- Absence seizure is a subtype of generalized seizure, which mainly affects pediatric patients in the age group of 5 to 15 years.

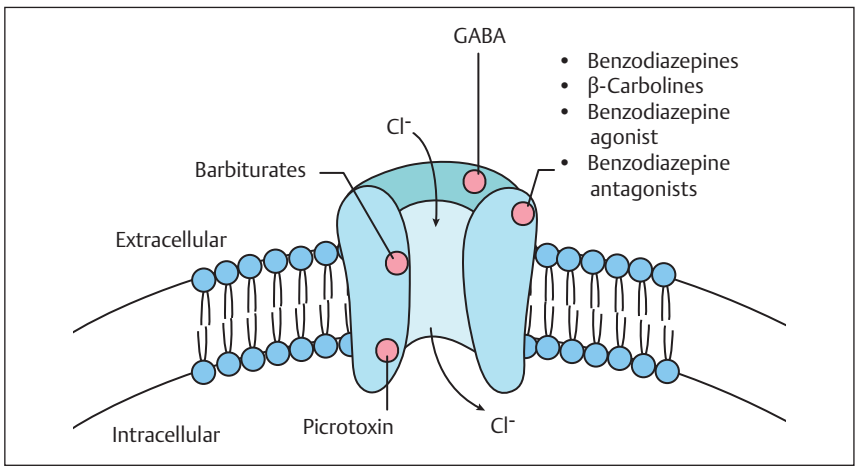


Fig. 3.4 Action of $GABA_A$ agonist.

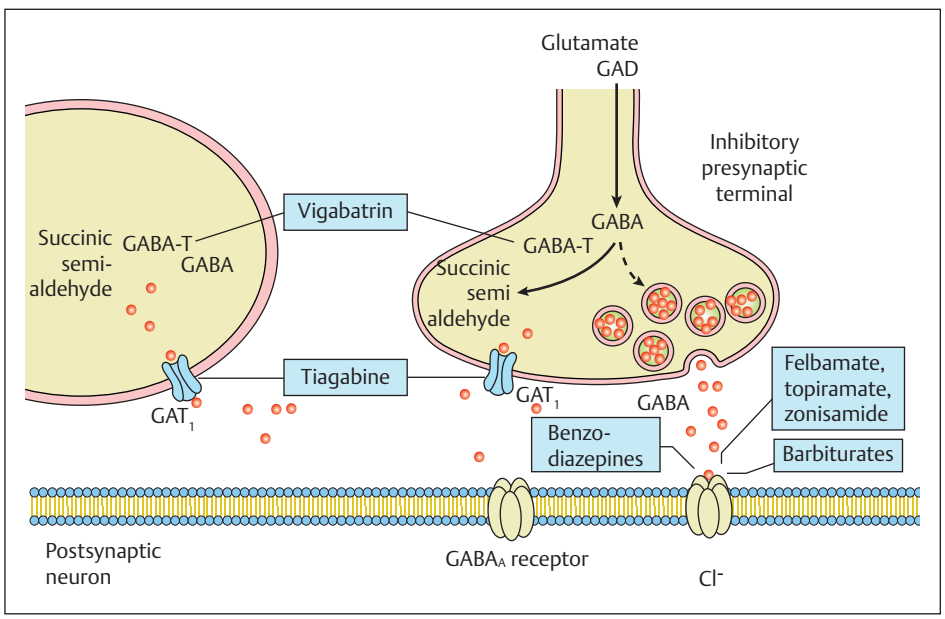


Fig. 3.5 Action of GABAergic drugs at different sites of the GABA nerve ending.

- In absence seizure, transient T-type calcium channels in the thalamus are mainly involved. This abnormality could be due to genes encoding the T-type Ca^{2+} channel. Although the pathophysiology of absence seizure is not fully understood, it is thought to be due to the abnormality of the cortico-thalamic-cortical circuit.
- In thalamocortical pathways, irregular oscillatory rhythms develop, involving GABA-B-mediated inhibition alternating with glutamate-mediated excitation. This leads to generalized spike wave activity.
- This seizure activity persists for 10 to 20 seconds, and the **electroencephalogram (EEG) reveals a 3 Hz/s spike and wave pattern**.
- Absence seizure is characterized by symptoms like blank staring spells, unresponsiveness, and poor scholastic performance.

Drugs Prescribed for Absence Seizure

- **DOC: Ethosuximide** (T-type Ca^{2+} channel blocker).
- **Valproate** is also one of the first-line drugs. It is preferred in atypical absence seizures. It also has a T- Ca^{2+} channel blocking property.
- Start any one of them with a low dose and gradually increase the dose to the maximum tolerable dose. If the required effect is not achieved, then change the drug gradually.
- Increase the dose of the new drug and decrease the dose of the older one till the desired effect is reached.
- **Lamotrigine**, **topiramate**, **clobazam**, or **clonazepam** can be given as alternatives or add-on drugs if valproate and ethosuximide fail to achieve the desired effect.

Drugs that have a tendency to increase $GABA_B$ activity can always precipitate absence seizures. Therefore, these drugs are **contraindicated** in absence seizures. There are the following: carbamazepine, oxcarbazepine, phenytoin, tiagabine, and vigabatrin.

10. Write a short note on the therapy for status epilepticus.

- Status epilepticus is an emergency condition in which seizure activity occurs for more than 30 minutes, or two or more seizures occur without full recovery of consciousness.
- It must be controlled as early as possible so as to prevent death and permanent brain damage.
- **DOC: Intravenous (IV) lorazepam** (has low lipid solubility and slower redistribution).
- **Steps taken are as follows:**
  1. Airway has to be maintained, followed by 20 to 50 mL of 50% dextrose IV to correct hypoglycemia if the seizure is due to hypoglycemia. Apart from this, oxygenation, fluid and electrolyte balance, blood pressure (BP), normal cardiac rhythm, and consciousness must be taken care of.
  2. **Lorazepam** is the first choice of drug now, effective in 75 to 90% cases, and produces a more sustained anticonvulsant effect than diazepam because of lower lipid solubility and slower redistribution.
  3. **Diazepam** was the standard therapy until recently. Its anticonvulsant effect starts fading after 20 minutes and many supplement doses may be required.
  4. **Fosphenytoin** suppresses seizures that have not responded to lorazepam. Phenytoin should be used only when fosphenytoin is not available.
  5. **Phenobarbitone** is used as an alternative to fosphenytoin or when it is ineffective.
  6. All the cases that fail to respond to the above drugs within 40 minutes of the onset of seizure can be managed with IV **midazolam/propofol and/or thiopentone anesthesia** with full intensive care.

Given below is the flowchart for the management of status epilepticus (**Fig 3.6**).

11. Discuss the safer antiepileptic drugs in pregnancy.

- Remember that none of the AEDs are completely safe during pregnancy. They all have some degree of teratogenic potential. Example of teratogenic effects by antiepileptics:
  - **Valproate:** Causes neural tube defect (NTD; i.e., spina bifida).
  - **Phenytoin:** Causes fetal hydantoin syndrome (cleft lip and palate, microcephaly, thin upper lip, short chin).
- **Among the AEDs, the most preferred drugs due to the least teratogenic potential are the following:**
  - **Levetiracetam, brivaracetam:** It is an SV2A inhibitor → promotes GABA release and inhibits

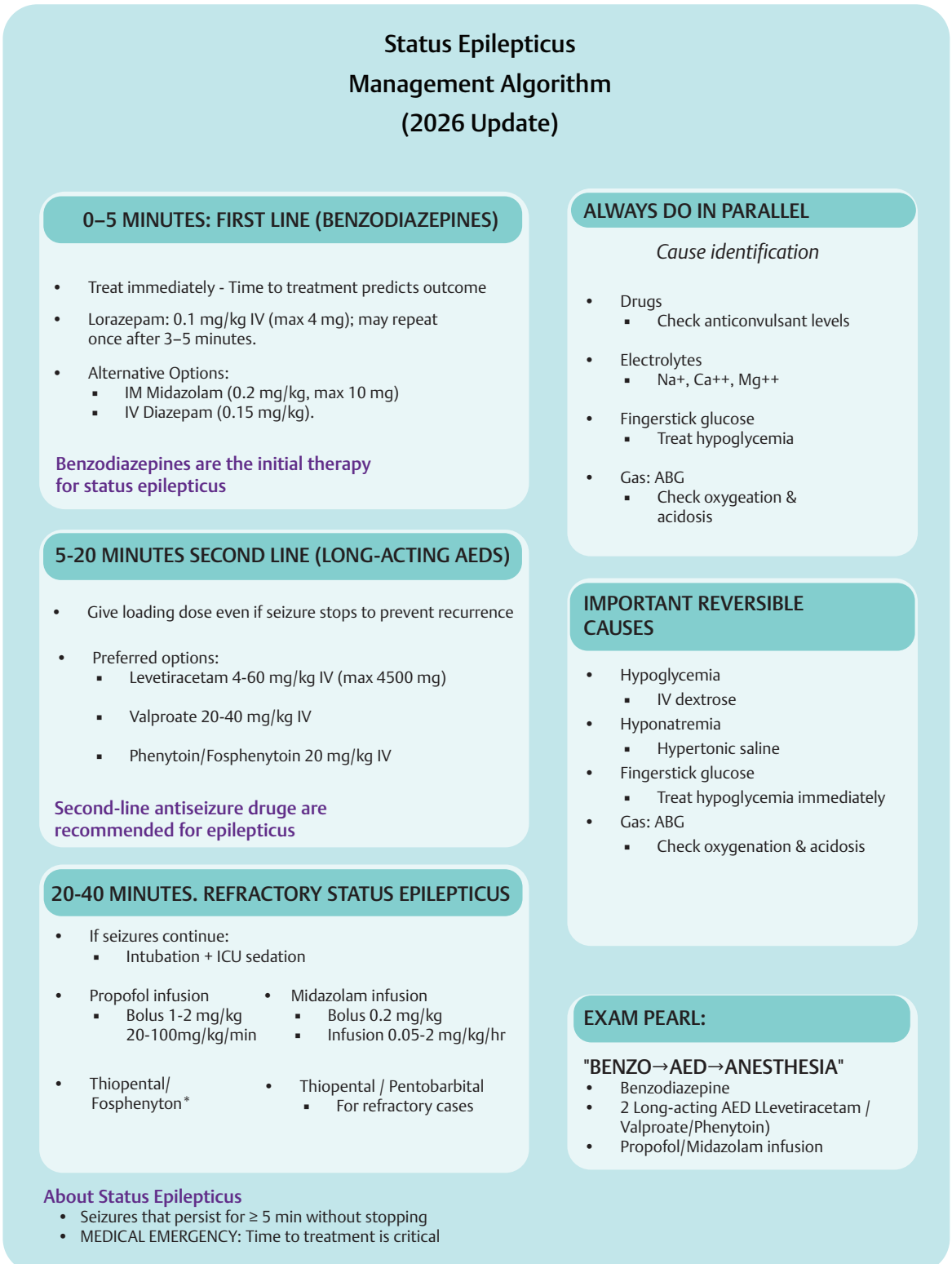


Fig. 3.6 Management of status epilepticus.

glutamate release at the synaptic cleft. It is currently the DOC for epilepsy in pregnancy.
  - **Lamotrigine:** VG-Na^+ channel blocker; also used as the first-line agent.
- When a pregnant woman is on any antiepileptic agent, it should not be stopped or changed.
- Upon sudden stopping or changing the AED, there is risk of sudden precipitation of seizure. This epileptic episode during pregnancy has a higher risk of birth defects than drugs.
- To reduce the risk of NTDs in pregnant patients on AEDs, prophylactic folic acid supplementation is recommended.
  - In the second and third trimester with a dose of 400 µg/d in normal pregnancy.
  - If there is a history of NTD in a previous pregnancy, 4,000 µg/d is advised. In addition to that, it is also advised to add vitamin K in the last month of pregnancy in order to reduce the risk of NTDs and bleeding tendencies.
- However, if a woman is planning to conceive and is on an AED like valproate, carbamazepine, or phenytoin, she should be shifted to a safer AED like levetiracetam or lamotrigine plus folic acid. She should be advised to conceive after 3 months of folic acid intake.
- Another option to conceive in a patient on AED is to discontinue the drug and allow a drug-free interval. If there is no seizure during this interval, then she can plan a pregnancy.

12. What are the antiepileptic drugs acting at the GABA-mediated chloride channel? Enumerate five differences between barbiturates and benzodiazepines.

- **GABA** is a neuroinhibitory neurotransmitter that acts by ion channel receptors. It facilitates chloride influx into the neurons, causing neuronal hyperpolarization.
- The GABA-mediated chloride channel is a pentameric structure, having three components: 2α, 2β, and 1γ subunits arranged alternatively (**Fig. 3.7a**).
- GABA binds at the α-β subunit and increases the duration of chloride channel opening.
- The agents that act at the GABA-mediated chloride channel are barbiturates and benzodiazepines.
- Barbiturates act similarly to GABA, that is, bind at the α-β subunit and increase the duration of chloride channel opening (**Fig. 3.7b**).

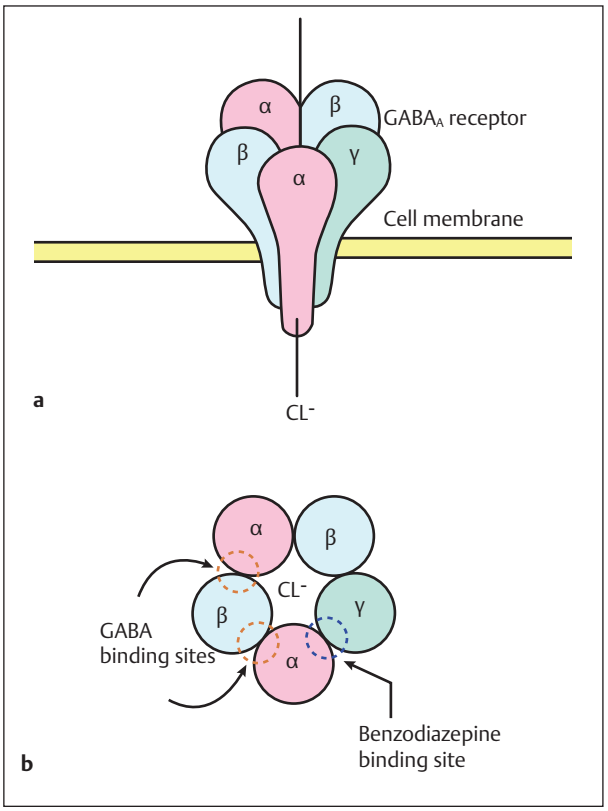


Fig 3.7 **(a, b)** Structure of GABA-mediated chloride channel, MOA of GABA-mediated chloride channel

Although both barbiturates and benzodiazepines are GABAergic drugs, their site of action and outcomes vary.

Difference between Barbiturates and Benzodiazepines

These are summarized in **Table 3.2**.

13. Discuss the drugs acting at the GABA-mediated chloride channel. What are the advantages of benzodiazepines over barbiturates?

Drugs Acting on GABA-Mediated Chloride Channel

Benzodiazepines

- Also known as the GABA facilitator, which increases the frequency of GABA-mediated chloride channel

Table 3.2 Differences between barbiturates and benzodiazepines

Barbiturates	Benzodiazepines
▪ Act at alpha-beta subunit *(mnemonic: BArbi = AB)*	▪ Act at alpha-gamma subunit *(mnemonic: Benz car—AG laga degi)*
▪ Increases the duration of chloride channel opening	▪ Increases the frequency of chloride channel opening
▪ Known as a GABA mimetic	▪ Known as a GABA facilitator
▪ Narrow therapeutic index: unsafe	▪ Wide therapeutic index: safe
▪ Less commonly used	▪ More commonly used
▪ Potent enzyme inducer	▪ No enzyme induction activity
▪ Can precipitate AIP (acute intermittent porphyria)	▪ No AIP precipitation risk
▪ Associated with severe anterograde amnesia	▪ Associated with anterograde amnesia
▪ Overdose treatment: no antidote available ▪ Treated with forced alkaline diuresis using (sodium bicarbonate) $Na^+HCO_3^-$ or carbonic anhydrase inhibitor	▪ Overdose: treated with antidote—flumazenil
▪ Example of barbiturates: ○ Phenobarbitone ○ Thiopentone Na^+	▪ Example: Diazepam, midazolam, lorazepam

opening → more influx of chloride causing hyperpolarization of neurons.

- The hyperpolarization of neurons causes sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties. It is useful in alcohol dependence, seizures, anxiety disorders, panic, agitation, and insomnia.

Barbiturates

- It is also known as GABA mimetic, which increases the duration of chloride channel opening. Increased duration of chloride channel opening leads to more influx of chloride, which also causes hyperpolarization of neurons.
- It acts as a CNS depressant. These are effective as anxiolytics, hypnotics, and anticonvulsants but have physical and psychological addiction potential.

Z-Compounds (Zolpidem, Zaleplon, Zopiclone)

These are a class of psychoactive drugs that are benzodiazepine-like in nature.

Advantages of Benzodiazepines

- Benzodiazepines are preferred because they have a wider therapeutic index, and their liability for abuse is lower than that of barbiturates.
- Benzodiazepines cause less neuronal depression as compared with barbiturates. Also, benzodiazepines have no effect on rapid eye movement (REM) sleep and cause less distortion of the normal hypnogram.
- In case of **benzodiazepine overdose**, its antidote, **flumazenil,** is readily available. But in cases of **barbiturate overdose**, the treatment option is **forced alkaline diuresis**.

14. Discuss the management of barbiturate poisoning.

There is no specific antidote for barbiturates.

Management of Barbiturate Poisoning

- **Gastric lavage:** Cleaning out the content of the stomach by leaving a suspension of activated charcoal in the stomach to prevent drug absorption in the intestine.
- **Supportive measures:** These include maintenance of the patient's airway, respiration, oxygen, BP, blood volume by fluid infusion, and use of vasopressors—**dopamine** may be preferred for its vasodilating action.
- **Alkaline diuresis:** Using sodium bicarbonate with or without mannitol only in case of long-acting barbiturates, which are eliminated primarily by renal excretion.
- **Hemodialysis and hemoperfusion:** Highly effective in long- and short-acting barbiturates.

Note Flumazenil is used in benzodiazepine overdose. It is a competitive benzodiazepine receptor antagonist.

15. Classify the antiparkinsonian drugs. Explain the mechanism of action and adverse drug reactions of levodopa.

- Parkinson's disease is a neurodegenerative disorder. It occurs due to the degeneration of dopaminergic neurons in the specific area of the basal ganglia named the substantia nigra pars compacta (SnPC).
- This degeneration of dopaminergic neurons causes an imbalance between the levels of dopamine and acetylcholine (**Fig. 3.8**).
- Treatment is targeted toward bringing a balance between these neurotransmitters.
- As a treatment modality, dopaminergic drugs (like levodopa) can be given or centrally acting anticholinergics are also effective, which bring the balance between the two.

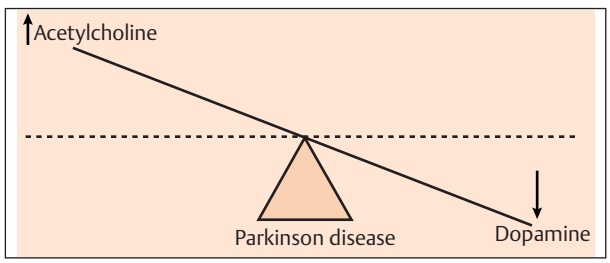


Fig. 3.8 Degeneration of dopaminergic neuron causing imbalance between acetylcholine and dopamine.

Drugs Used in Pharmacotherapy of Parkinson's Disease

The antiparkinsonian drugs are summarized in **Table 3.3**.

Levodopa: Mechanism of Action and ADRs

Mechanism of Action

- Levodopa is a prodrug of dopamine, which is metabolized to give the active metabolite dopamine by the enzyme DOPA decarboxylase (DDC).

Table 3.3 Classification of antiparkinsonian drugs

Type	Sub-type	Drugs
Drugs affecting the brain's dopaminergic system	▪ Dopamine precursor	▪ Levodopa
	▪ Peripheral dopa decarboxylase inhibitor	▪ Carbidopa ▪ Benserazide
	▪ Dopaminergic agonists	▪ **Ergot:** bromocriptine, cabergoline ▪ **Nonergot:** ropinirole, pramipexole, rotigotine, apomorphine
	▪ Monoamine oxidase-B (MAO-B) inhibitors	▪ Selegiline ▪ Rasagiline ▪ Safinamide
	▪ COMT (catechol-O-methyltransferase) inhibitors	▪ Entacapone ▪ Tolcapone ▪ Opicapone
	▪ Glutamate (NMDA receptor) agonist (dopamine facilitator)	▪ Amantadine
Drugs affecting the brain's cholinergic system	▪ Centrally acting cholinergic	▪ Benztropine ▪ Benzhexol ▪ Trihexyphenidyl ▪ Procyclidine ▪ Biperiden
	▪ Antihistaminic (with centrally acting anticholinergic action)	▪ Orphenadrine ▪ Promethazine

- "DDC" converts levodopa into dopamine in peripheral circulation as well as in the CNS after levodopa has crossed the BBB.
- Since dopamine cannot cross the BBB, we use dopamine precursor (levodopa) for the treatment of Parkinson's disease. Levodopa can cross the BBB and improve the symptoms of Parkinson's disease.
- Along with levodopa, peripheral DDC inhibitors are given so that dopamine availability in the brain can be increased and systemic side effects can be minimized.

ADRs of Levodopa Therapy

At the initiation of therapy:

- Nausea and vomiting: A very common side effect with levodopa therapy.
- On–off phenomenon: It is an unpredictable fluctuation between mobility and immobility due to the short half-life of levodopa.
- Postural hypotension: Due to vasodilation caused by dopamine (D1 receptor).
- Cardiac arrhythmias: Due to the β_1 activity of dopamine.
- Exacerbation of angina: Due to the β_1 activity.
- Altered taste.

After prolonged therapy:

- Dyskinesia (abnormal movements).
- Behavioral effects.
- Fluctuation in motor performance.

16. What is the on–off phenomenon with levodopa therapy? List drugs used in the management of the on–off phenomenon.

- Levodopa is converted to dopamine in the peripheral circulation and CNS after crossing the BBB.
- Activation of the central dopamine receptor improves the symptoms of parkinsonism, whereas peripheral dopamine receptor activation causes side effects like nausea, vomiting, and cardiac side effects. To avoid such peripheral side effects and increase central effects, carbidopa is added along with levodopa (**Fig. 3.9**).
- Carbidopa prevents levodopa from being converted into dopamine in the bloodstream, which allows more of the medication to get to the brain. This also means that lower doses of levodopa can be given. The addition of carbidopa also reduces the risk of side effects caused by dopamine in the rest of the body such as nausea and vomiting.
- Upon levodopa therapy, the patients' symptom like bradykinesia improves (on phase), but due to the short half-life of the drug (~2 hours), the parkinsonian symptoms recur (off phase). This unpredictable fluctuation between mobility and immobility due to the short half-life of the drug is called the **on–off phenomenon**.
- Drugs in the management of the on–off phenomenon:
  - **COMT inhibitor:** Entacapone, opicapone.
  - **MAO-B inhibitors:** Safinamide.
  - **Dopamine agonist:** Apomorphine.

17. What is secondary parkinsonism? What are the drugs used in its management?

- When Parkinson's disease occurs secondary to drug intake like dopamine receptor blockers (typical antipsychotics/D_2 blockers), the condition is called secondary parkinsonism.
- These symptoms include tremors, rigidity, bradykinesia (slow movements), voice changes, decreased facial expression, and stiffness of arms and legs. It may be caused by brain injury, diffuse

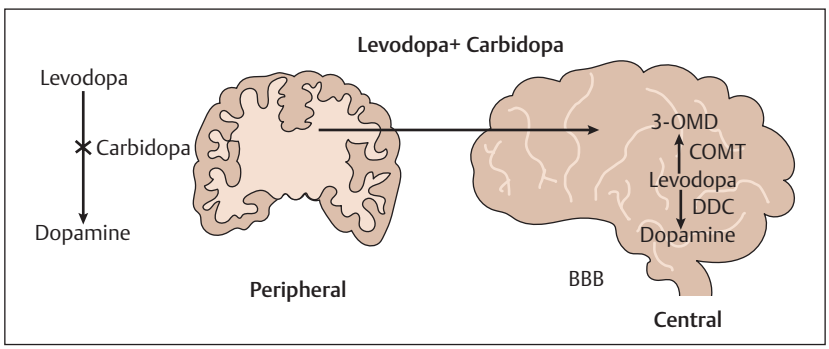


Fig. 3.9 Action of dopamine and levodopa.

Lewy body disease, encephalitis, meningitis, stroke, Wilson's disease, carbon monoxide poisoning, narcotics overdose, etc.

Drugs for the Management of Secondary Parkinsonism

- Centrally acting anticholinergics like **benzhexol, benztropine, trihexyphenidyl, and biperiden** are effective in drug-induced parkinsonism or secondary parkinsonism.
  - They act by reducing centrally acting cholinergic activity in the striatum of the parkinsonian patient.
  - This class of drugs provides symptomatic improvement, but their efficacy is much lower than that of levodopa. However, they are inexpensive and produce fewer side effects than levodopa.

18. Discuss the dopamine agonist used in the management of parkinsonism. List their ADRs.

Dopamine Agonists in the Management of Parkinsonism

Bromocriptine and Cabergoline

- They are ergoline derivatives and dopamine agonists used in the treatment of Parkinson's disease, pituitary tumors, hyperprolactinemia, neuroleptic malignant syndrome, and type 2 diabetes mellitus.
- **ADRs:** Vomiting, hallucinations, hypotension, hyperprolactinemia, fibrotic reaction, nasal stuffiness, and conjunctival injection.

Ropinirole and Pramipexole

- They are nonergoline dopamine agonists used in the treatment of Parkinson's disease, restless leg syndrome, and extrapyramidal symptoms (EPS).
- **ADRs:** Vomiting, dizziness, pathological gambling, postural hypotension, and hallucination.

Rotigotine

It is also a nonergoline dopamine agonist used to treat parkinsonism. It is available as a transdermal patch.

Apomorphine

A newly approved dopamine receptor agonist for the off-phase of the on–off phenomenon occurring secondary to levodopa therapy.

19. Write a short note on typical antipsychotics. List the ADRs of haloperidol.

- Typical antipsychotics or first-generation antipsychotic drugs were first developed in the 1950s. **Haloperido**l and **thioridazine** are best known typical antipsychotics.
- Drugs in typical antipsychotics are the following:
  - **Phenothiazines:**
    - Chlorpromazine.
    - Thioridazine.
    - Trifluoperazine.
    - Fluphenazine.
    - Perphenazine.
  - **Butyrophenone:**
    - Haloperidol.
    - Droperidol.
    - Benperidol.
  - **Thioxanthenes:**
    - Thiothixene.
    - Flupenthixol.
    - Zuclopenthixol.

Mechanism of Action

D_2 receptor blockers.

Uses

- Treatment of severe psychosis and behavioral problems until the newer drugs were ineffective.
- Effective in the treatment of only positive symptoms.
- Tourette's syndrome.
- Intractable hiccups.

Side Effects

EPS, hyperprolactinemia, and sedation.

ADRs of Haloperidol (Typical Antipsychotics)

- **EPS:** Most common side effect.
- **Hyperprolactinemia:** Can cause gynecomastia in males and galactorrhea and irregular menstrual cycle in females.

(Continued–The remaining content is available in the book.)

Antiepileptic Drugs

Na^+ channel

Phenytoin
- Prodrug : FOSPHENYTOIN
- Zero-order (nonlinear) kinetics at high doses
- Potent CYP45O inducer
- ADR: Gingival hyperplasia (most common), hirsutism, nystagmus, ataxia, teratogenic (fetal hydantoin syndrome), SJS/TEN
- C/I: Absence and myoclonic seizure

Carbamazepine
- Potent CYP450 auto-inducer
- DOC: Partial/focal seizure; Benign rolandic epilepsy of childhood; trigeminal and glossopharyngeal neuralgia
- ADRs: Aplastic anemia, agranulocytosis, SIADH (hyponatremia), SJS/TEN (esp. HLA – **B*1502** allele in Asians)
- C/I: Absence and myoclonic seizure

Oxcarbazepine
- Prodrug (metabolite: eslicarbazepine). Less CYP induction than carbamazepine
- ADR: Higher risk of SIADH/hyponatremia than carbamazepine

Zonisamide
- Also # Ca^{2+} channel
- ADR: Renal stone, weight loss

(A) Inhibition of excitation

Topiramate
- MOA:
  - # Na^+ channel
  - Activate GABA-A
  - # AMPA/kainate
- ADR: Cognitive slowing ("dopamax"), weight loss, renal stones (carbonic anhydrase inhibitor), angle closure glaucoma

Lamotrigine
- Also # N-type Ca^{2+} channel
- DOC: GTCS
- ADR: **R**ash (SJS/TEN), **A**taxia, **I**nsomnia, **D**iplopia
- Requires slow titration to minimize SJS risk
- Valproate inhibits its metabolism (↑ SJS risk); carbamazepine induces it

Lacosamide
- Inhibit CRMP release → ↓ BDNF
- ADR: ↑ PR interval

Rufinamide
- Also mGluR 5#

SJS/TEN: Carbamazepine > lamotrigine

Ca^{2+} channel

Ethosuximide (T-type)
- Use: Absence Seizures ONLY (1st line)
- ADR: GI distress (common), SJS
- Can worsen GTC seizures

Gabapentin and pregabalin ($\alpha_2\delta$ subunit)
- DOC: Neuropathic pain (diabetic neuropathy, postherpetic neuralgia, sciatica)
- ADR: Ataxia, tremor, weight gain
- C/I: Absence and myoclonic seizures

Glutamate receptor antagonist

Felbamate
- Dual mechanism: ↓ excitation (NMDA #) and ↑ inhibition (GABA enhancement)

Perampanel
- AMPA#

Voltage-gated K^+ channel opener (Kv7 type)

Retigabine
- ADR: Bluish pigmentation of the retina

(Continued)

(Continued)

Antiepileptic Drugs

(B) Enhancement of inhibition

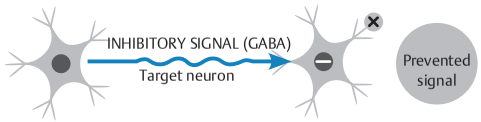
Positive allosteric modulators of GABA-A receptor

Benzodiazepines

- MOA: ↑ **frequency** of Cl^- channel opening
- Safe (**wide** therapeutic index)
- DOC: Febrile seizures - intranasal midazolam >> per rectal diazepam
- DOC: Status epilepticus – IV lorazepam
- Antidote: Flumazenil
- ADR: Sedation, tolerance, dependence

Barbiturates

- MOA: ↑ **duration** of Cl^- channel opening
- Unsafe (**narrow** therapeutic index)
- Potent CYP450 inducer
- Rx for overdose: Forced alkaline diuresis
- Phenobarbitone-DOC: Neonatal seizures
- ADR: Profound sedation, cardiorespiratory depression, precipitate porphyria



↑ GABA availability

Vigabatrin

- MOA: Irreversible **inhibitor of GABA transaminase**
- DOC: Infantile spasm a/w tuberous sclerosis
- ADR: Peripheral retinopathy atrophy
- C/I: Absence and myoclonic seizure

Tiagabine

- MOA: Inhibits GABA reuptake **(GAT-1 inhibitor)**
- C/I: Absence seizures

(C) Multiple/unique mechanism

Valproate

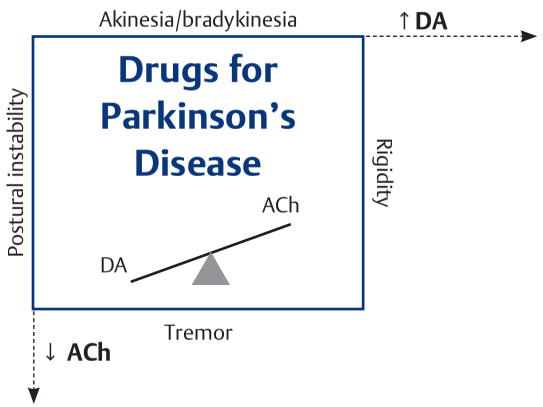
- MOA:
  - # Na^+ channel
  - # T-type Ca^{2+} channels
  - Inhibits GABA Transaminase (↑ GABA)
- DOC: GTCS, atonic, clonic, myoclonic seizure, juvenile myoclonic epilepsy (JME), Lennox–Gastaut syndrome (LGS), Dravet syndrome, atypical absence seizure, bipolar disorder–rapid cycler, Sydenham's chorea
- Potent CYP450 **inhibitor**
- ADR: Fulminant hepatitis, **most teratogenic** (neural tube defects), pancreatitis, weight gain–PCOS, tremor

Levetiracetam, brivaracetam

- Synaptic vesicle protein 2A (SV2A) inhibitor → GABA ↑
- DOC: Epilepsy in pregnancy
- ADR: Behavioral/psychiatric (irritability, agitation, depression, anger, aggression)
- Least teratogenic

DOC: Eclamptic seizure – $MgSO_4$

Video 3.1 Antiepileptic drug.
Scan the QR code to access the video.



in combination with

LEVODOPA

- Prodrug→ cross BBB→ dopamine→ CNS
- Most effective (improve bradykinesia 1st)

S/E:
- ON–OFF phenomenon (d/t short $t_{1/2}$ = 2 hours) (Rx: COMT inhibitor)
- Wearing-off phenomenon (Rx: add COMT- I/MAO-B-I)
- Arrhythmia
- Postural hypotension
- Mydriasis (can ppt. glaucoma)
- Dyskinesia

C/I: Melanoma, angle closure glaucoma, psychosis

Drug–drug interactions:
- Nonspecific MAO inhibitors→ HTN crisis, hyperpyrexia
- Pyridoxine→ ↓ efficacy
- Enzyme inhibitors →↑ toxicity

PERIPHERAL DOPA-DECARBOXYLASE INHIBITOR

- Carbidopa/benserazide
- ↑ CNS availability of DA
- ↓ Peripheral S/E

CENTRAL ANTICHOLINERGICS

- # Muscarinic receptors in striatum
- Improve tremor
- Rx of drug-induced parkinsonism
- Trihexyphenidyl (benzhexol), benztropine, orphenadrine
- S/E: Impaired cognition, blurred vision, urinary retention (♂), dryness of mouth

DOPAMINE AGONIST

Also used for restless leg syndrome

- Stimulate D_2/D_3 receptor
- Longer $t_{1/2}$
- Preferred in young
- Non-ergot (pref.): Pramipexole, ropinirole, rotigotine (patch)
- Ergot: Bromocriptine (risk of fibrosis)
- S/E: Impulse control disorders (gambling, hypersexuality), somnolence

NMDA GLUTAMATE RECEPTOR ANTAGONIST

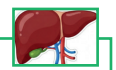
- Amantadine (dev. as antiviral for influenza A2)
- ↑DA release; ↓DA uptake
- Rx of L-Dopa-induced dyskinesia
- S/E: Insomnia, confusion, hallucination, ankle edema, livedo reticularis

MAO-B INHIBITORS

Serotonin syndrome: Risk with SSRIs, TCAs, meperidine

- Action: Brain
- Adjuvant drug
- Selegiline (↓wearing off) S/E: anxiety & insomnia d/t active metabolite—amphetamine)
- Rasagiline (more potent, no active metabolite, preferred)
- Safinamide (for "OFF" phase)

COMT INHIBITORS



- Action: Periphery
- Adjuvant drug, ↑ $t_{1/2}$ of levodopa
- Entacapone, opicapone, tolcapone
- ↓ "OFF" time
- S/E: Dyskinesia, diarrhea, orange urine

Tolcapone-hepatotoxic

Drug-induced Parkinsonism:
- First-generation/typical antipsychotics: Haloperidol, chlorpromazine, fluphenazine
- Second-generation/atypical antipsychotics: Risperidone, aripiprazole
- Antiemetics: Metoclopramide, prochlorperazine, domperidone

Video 3.2 Drugs for Parkinson's Disease.
Scan the QR code to access the video.

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Over the years, he has mentored more than 50,000 medical students, guiding them in pharmacology for both university examinations and national competitive entrance tests. He has also contributed internationally as a guest faculty of pharmacology, delivering academic sessions for medical students in countries such as the Philippines, Ukraine, China, Kyrgyzstan, Uzbekistan, Kazakhstan etc. He has authored various book chapters as well as publications on COPD.

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