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PHARMACOLOGY - I

UNIT 4

TOPIC :

- **Pharmacology of drugs acting on central nervous system**

  a. Neurohumoral transmission in the C.N.S. special emphasis on importance of various

  neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.

  b. General anesthetics and pre-anesthetics.

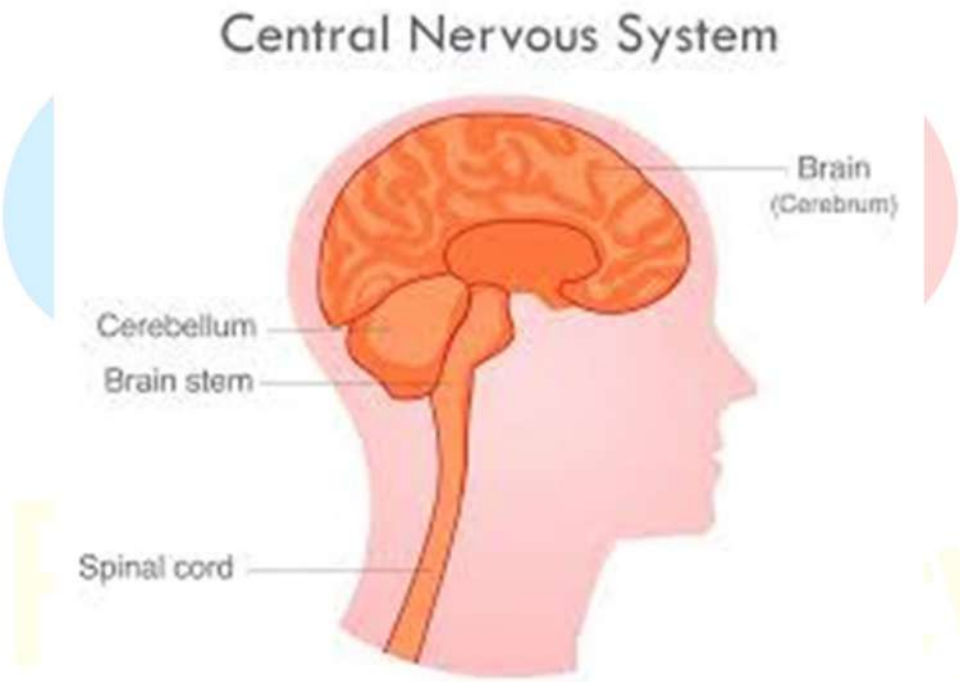
  c. Sedatives, hypnotics and centrally acting muscle relaxants.

  d. Anti-epileptics

  e. Alcohols and disulfiram

Central Nervous System (CNS)

The central nervous system (CNS) is the main part of the nervous system, consisting of the brain and spinal cord. It functions as the control center of the body, responsible for receiving sensory input, processing and interpreting information, and generating appropriate responses.



Structure of CNS

1. **Brain**
   - The largest and most complex organ of the CNS.
   - Protected by the skull, meninges, and cerebrospinal fluid (CSF).
   - Divided into major parts: cerebrum, cerebellum, and brainstem.
   - Controls higher functions such as memory, emotions, intelligence, and voluntary movements.
2. **Spinal Cord**
   - Extends downward from the brainstem.
   - Protected by vertebral column and CSF.
   - Serves as a conduction pathway for signals between the brain and body.
   - Involved in reflex actions.

Vertebral Column Segments Protecting the Spinal Cord

- **Cervical Vertebrae (C_1 – C_7)**
- **Thoracic Vertebrae (T_1 – T_{12})**
- **Lumbar Vertebrae (L_1 – L_5)**
- **Sacrum (S_1 – S_5; fused bones)**
- **Coccyx (tailbone)**

(Note: Spinal nerves emerge from each segment to connect the CNS with the peripheral nervous system.)

Main Functions of CNS

1. **Sensory Input** – Receives information from sensory organs (eyes, ears, skin, etc.) via peripheral nerves.
2. **Information Processing & Integration** – Interprets and integrates sensory data to form responses.
3. **Motor Output** – Sends commands to muscles and glands to perform actions.
4. **Reflex Actions** – Provides rapid, involuntary responses for protection and survival.
5. **Homeostasis Regulation** – Maintains balance in body functions like heart rate, respiration, temperature.
6. **Higher Functions** – Controls thought, reasoning, emotions, memory, and consciousness.

Neurohumoral Transmission

Neurohumoral transmission refers to the process by which neurons communicate with other neurons or effector cells (muscle, gland) using chemical messengers (neurotransmitters) that are released at synapses.

Steps of Neurohumoral Transmission

1. **Synthesis of Neurotransmitters**
    - Neurotransmitters (NTs) are synthesized in the neuron's cell body or axon terminal.
    - Enzymes and precursors are required (e.g., Tyrosine → Dopamine).
2. **Storage**
    - NTs are stored in synaptic vesicles in the axon terminal until a signal arrives.
3. **Arrival of Action Potential**
    - An electrical impulse (action potential) travels along the axon to the terminal.
4. **Opening of Ca^{2+} Channels**
    - Depolarization of the terminal membrane opens voltage-gated calcium channels.
    - Influx of Ca^{2+} triggers vesicle fusion with the presynaptic membrane.
5. **Release of Neurotransmitters**
    - NTs are released into the synaptic cleft via exocytosis.
6. **Binding to Receptors**
    - NTs bind to specific receptors on the postsynaptic membrane.
    - Two receptor types:
        - **Ionotropic receptors** – fast response.
        - **Metabotropic receptors** (G-protein coupled) – slow, modulatory response.
7. **Postsynaptic Response**
    - Depending on the NT and receptor:
        - **Excitatory Postsynaptic Potential (EPSP)** → depolarization.

        - **Inhibitory Postsynaptic Potential (IPSP)** → hyperpolarization.

Classification of Neurotransmitters

1. Inhibitory Neurotransmitters

Suppress generation of an action potential by causing hyperpolarization.

- **GABA (Gamma-Aminobutyric Acid)**
    - Major inhibitory NT in CNS.
    - Opens Cl^- channels → hyperpolarization.
    - Functions: promotes relaxation, reduces neuronal excitability, regulates sleep & muscle tone.
- **Glycine**
    - Inhibitory NT mainly in spinal cord & brainstem.
    - Opens Cl^- channels.
    - Functions: inhibits motor neurons, regulates reflexes and motor control.

2. Excitatory Neurotransmitters

Promote action potential generation by causing depolarization.

- **Glutamate**
    - Major excitatory NT in CNS.
    - Opens Na^+ and Ca^{2+} channels.
    - Functions: involved in learning, memory, cognition.
- **Dopamine** (can be excitatory or inhibitory depending on receptor type)
    - Monoamine NT.
    - Acts on:
        - D1 receptors → excitatory.
        - D2 receptors → inhibitory.
    - Functions: mood regulation, reward, motivation, motor control (deficiency causes Parkinson's disease).
- **Serotonin (5-HT)**

- Mostly excitatory, some inhibitory effects depending on receptor subtype.
- Acts on various 5-HT receptors.
- Functions: regulates mood, appetite, sleep, pain perception.

General Anesthetics

General anesthetics are central nervous system (CNS) depressant drugs that produce a reversible state of**:**

- Loss of consciousness,
- Analgesia (pain relief),
- Amnesia (loss of memory),
- Skeletal muscle relaxation,
- Suppression of reflexes.

These agents are used to perform surgical and medical procedures painlessly and without psychological trauma.

General Mechanism of Action

The exact mechanism of anesthesia is complex and not fully understood. However, the general principles include:

1. **Enhancement of Inhibitory Pathways**
   - Most general anesthetics enhance the effect of inhibitory neurotransmitters, especially GABA at GABA-A receptors.
   - This results in:
     - Increased Cl^- influx → hyperpolarization of neurons
     - Reduced neuronal excitability
     - Sedation, amnesia, unconsciousness
2. **Inhibition of Excitatory Pathways**
   - Some anesthetics inhibit excitatory neurotransmission.
   - Example: Ketamine blocks NMDA (N-methyl-D-aspartate) receptors, producing dissociative anesthesia.
3. **Modulation of Ion Channels**

- Some anesthetics act directly on ion channels:
  - Promote K^+ efflux → hyperpolarization
  - Inhibit Na^+ influx → reduced action potential generation

Stages of General Anesthesia

When general anesthetic agents are administered, the patient passes through four classical stages**.** These stages guide physicians in monitoring depth of anesthesia and safety.

Stage I – Analgesia (Pain Relief Stage)

- Begins immediately after administration.
- Patient is conscious but experiences reduced pain.
- May feel drowsy, relaxed, or sleepy.
- Reflexes (blinking, coughing) are still present.
- Used for minor procedures or as induction before deeper anesthesia.

Stage II – Excitement / Delirium Stage

- Patient becomes unconscious.
- May show **involuntary movements**, talking, shouting, or crying.
- Breathing is irregular and may be rapid.
- Reflexes are still present and sometimes exaggerated.
- Nausea, vomiting, and risk of choking may occur.
- This stage is **dangerous** → anesthetists try to **pass quickly** into the next stage.

Stage III – Surgical Anesthesia (Safe Stage for Surgery)

- Patient is completely unconscious.
- Muscles are relaxed.
- Breathing becomes regular.
- Reflexes are absent.

- This stage is subdivided into 4 planes**:**

1. **Plane I – Light anesthesia** → eyelid reflex lost.
2. **Plane II – Moderate anesthesia** → corneal reflex lost (ideal for surgery).
3. **Plane III – Deep anesthesia** → intercostal muscle relaxation.
4. **Plane IV – Very deep anesthesia** → breathing weakens (dangerous).

Note: Surgical operations are usually performed in Plane II or III**.**

Stage IV – Medullary Paralysis (Overdose / Danger Stage)

- Occurs if too much anesthetic is given.
- Vital centers in medulla (respiration and cardiovascular control) are depressed.
- Breathing stops, blood pressure falls drastically.
- This stage is life-threatening and may cause death if not treated immediately.

Classification of General Anesthesia

1. **Inhalational Anesthetics**
    - **Gaseous agent:** Nitrous oxide (N_2O)
    - **Volatile liquids:** Ether, Halothane, Isoflurane, Desflurane, Sevoflurane
2. **Intravenous Anesthetics**
    - **Fast-acting drugs:** Thiopentone sodium, Methohexitone sodium, Propofol, Etomidate
    - **Benzodiazepines:** Diazepam, Lorazepam, Midazolam
    - **Dissociative anesthetics:** Ketamine
    - **Opioid analgesics:** Fentanyl, Morphine

1. Inhalational Anesthetics

Drugs administered via inhalation (lungs), absorbed into blood, and acting on CNS to induce/maintain anesthesia.

Mechanism of Action

- Enhance inhibitory neurotransmission (mainly GABA-A).
- Some (e.g., Nitrous oxide, Ketamine) inhibit excitatory NMDA receptors.
- Also act on K^+ and glycine channels.

Gaseous Agent: Nitrous Oxide (N_2O)

- **MOA:** NMDA receptor antagonist → inhibits excitatory transmission.
- **Effect:** Analgesia + sedation, but no muscle relaxation.

Pharmacokinetics

- Absorption: Rapid (low blood:gas partition coefficient).
- Onset/Recovery: Almost immediate.
- Distribution: Highly diffusible, quickly reaches CNS.
- Metabolism: Not metabolized.
- Elimination: Exhaled unchanged.

Uses

- As adjuvant with other anesthetics.
- Dental & obstetric analgesia.
- Minor procedures (e.g., dressing changes).

Adverse Effects

- Diffusion hypoxia, neuropathy, megaloblastic anemia (prolonged use).
- Nausea, vomiting, mild respiratory depression.

Volatile Liquids (Ether, Halothane, Isoflurane, Desflurane, Sevoflurane)

MOA

- Potentiate GABA-A receptors.
- Cause CNS depression, unconsciousness, and variable muscle relaxation.
- Some act on K^+ and glycine channels.

Pharmacokinetics (Comparative)

Agent	Onset/Recovery	Metabolism	Elimination	Notes
Ether	Very slow	Negligible	Exhaled	Obsolete, irritant
Halothane	Moderate	~20% liver	Exhaled	Risk: hepatotoxicity, arrhythmia
Isoflurane	Fast	Negligible	Exhaled	Safe, widely used
Desflurane	Very rapid	<0.02%	Exhaled	Day-care surgeries
Sevoflurane	Fast	3–5% liver	Exhaled	Preferred in children (non-irritant)

Uses

- Induction & maintenance of anesthesia.
- Sevoflurane: preferred in children.
- Desflurane: rapid recovery → day-care surgery.
- Often combined with IV agents.

2. Intravenous General Anesthetics

Drugs administered directly into the bloodstream for rapid induction of anesthesia. Commonly combined with inhalational agents ("balanced anesthesia").

Fast-Acting IV Agents

- Thiopentone sodium, Propofol, Etomidate, Ketamine, Midazolam

MOA:

- Thiopentone, Propofol, Etomidate → enhance GABA-A activity.
- Ketamine → NMDA antagonist, dissociative anesthesia.
- Midazolam → potentiates GABA-A, sedation + anxiolysis.

Pharmacokinetics:

- Onset: 10–30 sec (very rapid).
- Duration: 5–10 min (redistribution).
- Metabolism: Mainly hepatic.
- Excretion: Renal.

Uses:

- Induction of anesthesia.
- Short procedures (endoscopy, cardioversion).
- ICU sedation.
- **Ketamine:** emergency anesthesia, asthmatic patients (bronchodilator).
- **Etomidate:** cardiac patients (minimal CV depression).

Slower-Acting IV Agents

- Benzodiazepines (Midazolam, Diazepam, Lorazepam)
- Opioids (Morphine, Fentanyl)
- Dissociative anesthetic (Ketamine, also fast acting)

MOA:

- Benzodiazepines → enhance GABA-A (sedation, amnesia).
- Opioids → μ-opioid receptor agonists (analgesia, sedation).
- Ketamine → NMDA antagonist (analgesia, dissociative anesthesia).

Pharmacokinetics:

Drug class	Onset	Duration	Metabolism	Uses
Benzodiazepines	1–3 min	Midazolam: short	Hepatic	Premedication, sedation, status epilepticus
Opioids	Fentanyl: 1 min	10–15 min anesthesia (longer analgesia)	Hepatic	Analgesia in surgery, post-op pain, adjunct to G.A.
Ketamine	30 sec	10–15 min	Hepatic (CYP3A4 → norketamine)	Emergency anesthesia, children's short procedures, asthma, trauma cases

Pre-Anaesthetic Agents

- Pre-anaesthetic agents (also called *premedications*) are drugs given before the administration of general anaesthesia.
  Their main purpose is to prepare the patient for surgery, reduce the undesirable effects of anaesthetics, and ensure smooth induction, maintenance, and recovery from anaesthesia.
- They are usually given 30–60 minutes before anaesthesia either orally, intramuscularly, or intravenously.

Objectives of Pre-Anaesthetic Medication

1. **Anxiolysis** – Relieves fear, tension, and anxiety in the patient.
2. **Sedation** – Produces calmness and relaxation before induction.
3. **Analgesia** – Provides pain relief before and during surgery.
4. **Amnesia** – Prevents recall of unpleasant pre-operative events.
5. **Anti-secretory effect** – Reduces salivary, tracheobronchial, and gastric secretions, which lowers the risk of aspiration.
6. **Anti-emetic effect** – Prevents post-operative nausea and vomiting.
7. **Hemodynamic stability** – Helps maintain stable blood pressure and heart rate.
8. **Decrease anaesthetic dose requirement** – Allows use of lower and safer doses of general anaesthetics.
9. **Facilitates smooth induction and intubation** during surgery.

Common Classes of Pre-Anaesthetic Agents

Class	Example Drugs	Purpose/Action
Sedative-Hypnotics / Anxiolytics	Diazepam, Midazolam, Lorazepam	Provide sedation, reduce anxiety, induce amnesia, smooth induction
Opioid Analgesics	Morphine, Pethidine, Fentanyl	Relieve pain, provide pre-operative analgesia, potentiate anaesthesia
Anticholinergics	Atropine, Glycopyrrolate, Scopolamine	Reduce salivary & bronchial secretions, prevent vagal bradycardia, decrease aspiration risk
H_2-Receptor Blockers / Proton Pump Inhibitors (PPI)	Ranitidine, Famotidine, Omeprazole, Pantoprazole	Reduce gastric acid secretion, lower aspiration pneumonitis risk
Anti-emetics	Ondansetron, Metoclopramide	Prevent nausea and vomiting during/after surgery
Neuromuscular Blocking Agents (given just before induction)	Succinylcholine, Vecuronium	Facilitate tracheal intubation and provide muscle relaxation
Others	Dexamethasone (anti-emetic, anti-inflammatory), Antihistamines (Diphenhydramine)	Additional supportive roles in special cases

Sedatives & Hypnotics

- **Sedatives**: Drugs that calm the patient, reduce anxiety, tension, and excitement, and induce relaxation.
- **Hypnotics**: Drugs that induce and maintain sleep when given in higher doses.
- Both are CNS depressants, but the effect depends on dose:
  - Low dose → sedation
  - High dose → hypnosis

Classification of Sedative-Hypnotics

1. Benzodiazepines (BZDs)

- Examples: Diazepam, Lorazepam, Alprazolam, Clonazepam, Temazepam, Midazolam, Flurazepam, Triazolam, Clobazam.
- Uses: Sedative, hypnotic, anxiolytic, anticonvulsant, muscle relaxant.
- Safer than barbiturates.

Mechanism of Action

Benzodiazepines (BZDs)

- Bind to GABA-A receptor complex (benzodiazepine site).
- Enhance GABA action by increasing frequency of Cl^- channel opening.
- Leads to hyperpolarization of neurons → CNS depression.

2. Barbiturates

- Examples: Phenobarbitone, Pentobarbitone, Butobarbitone, Thiopentone, Methohexitone.
- Uses: Sedation, hypnosis, anaesthesia, seizure control.
- Rarely used today due to high risk of overdose, tolerance & dependence.

Based on Duration of Action

- **Ultra-short acting**: Thiopentone, Methohexitone → IV anaesthesia
- **Short acting**: Pentobarbitone, Butobarbitone → Hypnotics (obsolete)
- **Long acting**: Phenobarbitone → Seizures, epilepsy

Mechanism of Action

Barbiturates

- Also act on GABA-A receptors.
- Increase duration of Cl^- channel opening.
- At high doses → can directly open GABA channels (more dangerous).

3. **Non-benzodiazepines (Z-drugs)**

- Examples: Zolpidem, Zaleplon, Zopiclone, Eszopiclone
- Uses: Mainly for insomnia (short-term use)
- Mechanism: Selectively act on BZD site of GABA-A receptor → enhance GABA inhibition
- Advantages: Less dependence, safer side-effect profile

Mechanism of Action

Non-Benzodiazepines (Z-drugs)

- Selectively bind to BZD site of GABA-A receptors.
- Produce mainly sedative-hypnotic effect with less anxiolytic/muscle relaxant action.

4. **Other CNS Depressants**

- **Chloral hydrate** – old hypnotic, rapid sleep induction, gastric irritation
- **Triclofos** – used in children for sedation (ECG, MRI)
- **Paraldehyde** – anticonvulsant, formerly used in alcohol withdrawal seizures
- **Glutethimide** – barbiturate-like, risk of dependence (rare now)
- **Methaqualone** – formerly used for insomnia, withdrawn due to abuse

- **Meprobamate** – anxiolytic, sedative, rarely used today
- **Promethazine** – sedative antihistamine, also for nausea & allergies
- **Chlorpromazine** – antipsychotic with sedative effect, used in agitation & pre-op sedation
- **Amitriptyline** – tricyclic antidepressant with sedative effect (due to antihistamine action)
- **Morphine** – opioid analgesic, causes sedation & CNS depression

Pharmacokinetics (General)

- **Absorption** – Well absorbed orally.
- **Distribution** – Lipid soluble → rapid brain entry.
- **Metabolism** – Liver (CYP450 enzymes).
- **Excretion** – Kidneys (urine, often as metabolites).

Therapeutic Uses

1. Anxiety disorders
2. Insomnia & other sleep disorders
3. Seizures, epilepsy (e.g., diazepam, phenobarbitone)
4. Pre-operative sedation
5. Muscle relaxation (e.g., diazepam)
6. Induction of anaesthesia (thiopentone, midazolam)

Adverse Effects

- Drowsiness, sedation, dizziness
- Confusion, impaired coordination, memory disturbance
- Respiratory depression (especially barbiturates, opioids)
- Tolerance & dependence on long-term use
- Withdrawal symptoms (insomnia, anxiety, seizures)
- Overdose: coma, respiratory failure, death (esp. barbiturates)

Centrally Acting Muscle Relaxants

- Centrally acting muscle relaxants are drugs that **r**educe muscle tone and spasms by acting mainly on the CNS (brainstem & spinal cord) rather than directly on skeletal muscle fibers.
- They are widely used in the management of muscle spasticity, musculoskeletal pain, and neurological disorders**.**

Examples

- Baclofen
- Tizanidine
- Methocarbamol
- Chlorzoxazone
- Cyclobenzaprine
- Carisoprodol
- Diazepam (benzodiazepine with muscle relaxant action)

Mechanism of Action

- Depress polysynaptic reflexes at the spinal cord and brainstem level.
- Reduce excitability of α-motor neurons, leading to decreased muscle tone.
- Many agents enhance GABAergic inhibition (e.g., baclofen, diazepam).
- Tizanidine acts as an α2-adrenergic agonist, reducing presynaptic excitatory neurotransmitter release.

Overall effect = Muscle relaxation & relief from spasm**.**

Pharmacokinetics

Parameter	General Information
Absorption	Well absorbed orally
Distribution	Crosses blood-brain barrier (acts centrally)
Metabolism	Mostly hepatic metabolism
Excretion	Primarily renal (urine)

Therapeutic Uses

- Relief of acute muscle spasms (e.g., lower back pain, neck pain).
- Treatment of spasticity due to multiple sclerosis, cerebral palsy, spinal cord injury.
- Muscle relaxation in orthopedic procedures.
- Relief of musculoskeletal pain due to strain, trauma, or injury.
- Supportive therapy in neurological diseases with hypertonia.

Adverse Effects

- Sedation & drowsiness
- Dizziness, fatigue, weakness
- Blurred vision
- Hypotension (esp. with tizanidine)
- Hepatotoxicity (chlorzoxazone, tizanidine)
- Dependence & withdrawal symptoms (carisoprodol, diazepam)

Epilepsy and Antiepileptic Drugs

- Epilepsy is one of the most common chronic neurological disorders, characterized by recurrent and unpredictable seizures due to abnormal electrical activity of brain cells.
- A seizure is a sudden, uncontrolled electrical disturbance in the brain leading to changes in behavior, movements, sensation, or consciousness.
- It is a paroxysmal disorder (appears suddenly, in episodes).
- Usually results from excessive neuronal excitation **or** reduced neuronal inhibition**.**

Types of Epilepsy

1. **Generalized Epilepsy**
    - Involves abnormal electrical activity in both hemispheres of the brain.
    - Subtypes:
        - **Tonic–Clonic (Grand Mal):**
            - Loss of consciousness.
            - *Tonic phase*: muscle stiffening.
            - *Clonic phase*: rhythmic jerking of limbs.
            - Followed by post-seizure depression**.**
        - **Absence (Petit Mal):**
            - Brief loss of consciousness (30–60 sec).
            - "Blank stare" or absent-mindedness.
            - More common in children.
        - **Tonic:** Sustained muscle stiffness (arms, legs, back).
        - **Clonic:** Repeated jerking movements (face, neck, arms).
        - **Atonic:** Sudden loss of muscle control → fall or collapse.
        - **Myoclonic:** Sudden, brief muscle contractions (localized or generalized).
2. **Focal (Partial) Epilepsy**
    - Abnormal activity is limited to a specific brain region**.**
    - Subtypes:

- **Simple Partial Seizure:**
  - No loss of consciousness.
  - Localized symptoms: tingling, abnormal sensations, emotional changes.
- **Complex Partial Seizure:**
  - Loss of consciousness with automatisms (repetitive, purposeless acts).
  - Amnesia for the seizure episode.

Etiology (Causes)

- Genetic factors.
- Head injury / trauma.
- Brain tumors.
- Infections (e.g., meningitis, encephalitis).
- Neurodegenerative diseases (e.g., Alzheimer's).
- Stroke.
- Metabolic causes: hypoglycemia, electrolyte imbalance.
- Idiopathic (unknown cause).
- Certain drugs or medications.

Pathogenesis

1. Etiological factors (trauma, tumor, genetics, etc.).
2. Altered neuronal membrane activity.
3. Imbalance between excitatory (Glutamate, Aspartate) and inhibitory (GABA, Glycine) neurotransmission.
4. Hyperexcitation of neurons & neuronal networks.
5. Repeated rapid generation of action potentials.
6. Lowered seizure threshold.
7. Seizure episode → Epilepsy.

Symptoms of Epilepsy

- Temporary confusion.
- Muscle stiffening (tonic).
- Uncontrolled jerking (clonic).
- Sudden loss of consciousness.
- Sudden rapid eye movements.
- Sudden mood or behavioral changes.
- Post-ictal (after seizure) depression or fatigue.

Classification of Antiepileptic Drugs (AEDs)

1. **Barbiturates** – Phenobarbitone.
2. **Hydantoins** – Phenytoin, Fosphenytoin.
3. **Succinimides** – Ethosuximide.
4. **Benzodiazepines** – Diazepam, Lorazepam, Clonazepam, Clobazam.
5. **Iminostilbenes** – Carbamazepine, Oxcarbazepine.
6. **Carboxylic acids** – Valproic acid, Divalproex.
7. **Phenyltriazines** – Lamotrigine.
8. **Cyclic GABA analogues** – Gabapentin, Pregabalin, Vigabatrin, Tiagabine.
9. **Newer AEDs** – Topiramate, Levetiracetam, Lacosamide, Zonisamide.

Commonly Used Antiepileptic Drugs

1. Phenytoin

- **MOA:** Blocks voltage-gated Na^+ channels → stabilizes neuronal membranes → prevents repetitive firing.
- **ADME:**
  - Absorption: Variable; saturable kinetics.
  - Distribution: Highly protein bound.
  - Metabolism: Hepatic (CYP450); shows zero-order kinetics at high doses.
  - Excretion: Renal (metabolites).
- **Uses:** Generalized tonic-clonic seizures, focal seizures, status epilepticus (IV form).

2. Carbamazepine

- **MOA:** Blocks voltage-gated Na^+ channels → decreases synaptic transmission.
- **ADME:**
  - Absorption: Good oral bioavailability.
  - Distribution: High protein binding.
  - Metabolism: Hepatic; induces its own metabolism (autoinduction).
  - Excretion: Renal.
- **Uses:** Focal seizures, generalized tonic-clonic seizures, trigeminal neuralgia, bipolar disorder.

3. Valproic Acid

- **MOA:**
  - Blocks Na^+ channels.
  - Blocks T-type Ca^{2+} channels.
  - Increases GABA by inhibiting GABA transaminase.
- **ADME:**

    - Absorption: Well absorbed orally.
    - Distribution: Highly protein bound.
    - Metabolism: Hepatic (CYP + glucuronidation).
    - Excretion: Renal.
- **Uses:** Broad-spectrum AED: generalized, absence, myoclonic seizures; bipolar disorder; migraine prophylaxis.

4. Ethosuximide

- **MOA:** Blocks T-type Ca^{2+} channels in thalamic neurons.
- **ADME:**
    - Absorption: Good oral absorption.
    - Distribution: Low protein binding.
    - Metabolism: Hepatic.
    - Excretion: Renal.
- **Uses:** Drug of choice for absence seizures.

5. Benzodiazepines (Diazepam, Lorazepam, Clonazepam, Clobazam)

- **MOA:** Potentiate GABA action on GABA-A receptors → increased Cl^- influx → neuronal inhibition.
- **Uses:**
    - Status epilepticus (Diazepam, Lorazepam).
    - Absence and myoclonic seizures (Clonazepam).
    - Adjunct therapy in focal seizures (Clobazam).

Alcohol (Ethanol)

- Alcohol usually refers to Ethanol (C_2H_5OH), a psychoactive substance present in alcoholic beverages.
- It is a CNS depressant with dose-dependent effects ranging from sedation, euphoria, impaired coordination to respiratory depression and coma.
- Alcohol use can cause acute intoxication and with prolonged use, leads to tolerance, dependence, and organ damage.

Mechanism of Action (MOA)

Ethanol acts on multiple neurotransmitter systems**:**

1. **Enhances GABA-A receptor activity** → increases inhibitory neurotransmission → sedation, hypnosis.
2. **Inhibits NMDA (glutamate) receptors** → reduces excitatory neurotransmission → memory impairment.
3. **Increases dopamine release** in mesolimbic pathway → euphoria, rewarding effects (addiction potential).
4. **Modulates serotonin, endorphins, and cannabinoid systems** → mood alterations and reinforcement of alcohol use.

Pharmacokinetics

- **Absorption:** Rapid (20% from stomach, 80% from small intestine); food delays absorption.
- **Distribution:** Widely distributed in body water (Vd = 0.5–0.7 L/kg); crosses blood-brain barrier and placenta.
- **Metabolism:**
  - In liver by alcohol dehydrogenase (ADH) → acetaldehyde.
  - Acetaldehyde converted by aldehyde dehydrogenase (ALDH) → acetic acid.
  - Follows zero-order kinetics (fixed rate metabolism ~10–12 mL/hour).

- **Excretion:** 90–98% metabolized; 2–10% excreted unchanged in breath, urine, sweat.

Pharmacodynamic Effects

1. Central Nervous System (CNS)

- **Acute:** Sedation, euphoria, impaired judgment, loss of motor coordination, cognitive dysfunction.
- **Chronic:** Tolerance, dependence, withdrawal syndrome, Wernicke–Korsakoff syndrome (thiamine deficiency → memory loss, confusion, ataxia).

2. Cardiovascular System

- **Acute:** Moderate intake causes vasodilation (warmth, flushing, mild hypotension).
- **Chronic:** Hypertension, arrhythmias, dilated cardiomyopathy, stroke risk.

3. Respiratory System

- **Acute:** High doses → respiratory depression → hypoventilation/coma.
- **Chronic:** Weakens pulmonary defenses → ↑ susceptibility to pneumonia, ARDS.

4. Gastrointestinal Tract

- **Acute:** Gastric irritation, ↑ gastric acid secretion, nausea, gastritis.
- **Chronic:** Esophagitis, peptic ulcer, malabsorption, ↑ risk of GI cancers.

5. Liver (Alcoholic Liver Disease)

- **Steatosis (Fatty liver):** Reversible with abstinence.
- **Alcoholic Hepatitis:** Inflammation, jaundice, impaired liver function.
- **Cirrhosis:** Irreversible scarring → liver failure, ↑ risk of hepatocellular carcinoma.

Adverse Effects of Chronic Alcohol Use

- Tolerance and dependence.
- Withdrawal syndrome: tremors, anxiety, seizures, delirium tremens.
- Organ damage: liver cirrhosis, cardiomyopathy, pancreatitis, brain atrophy.
- Nutritional deficiencies (thiamine, folate, vitamin B12).

Therapeutic Uses of Alcohol

- As antiseptic and disinfectant (70% ethanol).
- Solvent in pharmaceutical preparations.
- Used in methanol/ethylene glycol poisoning (competitively inhibits alcohol dehydrogenase).

Disulfiram

- Disulfiram is a drug used in the management of chronic alcohol dependence.
- It is an aversion therapy agent → causes unpleasant and potentially dangerous effects when alcohol is consumed, discouraging patients from drinking.
- Marketed under brand names such as Antabuse.

Mechanism of Action (MOA)

- Disulfiram irreversibly inhibits Aldehyde Dehydrogenase (ALDH), an enzyme in ethanol metabolism.
- Normal ethanol metabolism:
  - **Ethanol** → (via Alcohol Dehydrogenase, ADH) → Acetaldehyde → (via Aldehyde Dehydrogenase, ALDH) → Acetic acid.
- With disulfiram:
  - **ALDH inhibition** → Acetaldehyde accumulation.
  - Acetaldehyde causes toxic symptoms, making alcohol consumption highly unpleasant.

Reaction Flow:
Ethanol → (ADH) → Acetaldehyde ⊖(ALDH inhibited by Disulfiram) → ✕ Acetic acid

Result: ↑ Acetaldehyde → Adverse reactions:

- Throbbing headache
- Nausea & vomiting
- Flushing of face/neck
- Palpitations, chest pain
- Hypotension
- Sweating & anxiety
- Weakness, dizziness

Pharmacokinetics

- **Absorption:** Well absorbed orally.
- **Distribution:** Widely distributed; crosses the blood-brain barrier.
- **Metabolism:**
  - Metabolized in the liver to active metabolites.
  - Inhibits Aldehyde Dehydrogenase and also Dopamine β-hydroxylase**.**
- **Excretion:** Excreted in urine and feces.
- **Duration:** Effects may last 1–2 weeks after discontinuation due to irreversible enzyme inhibition.

Therapeutic Uses

1. **Primary Use:**
   - Treatment of chronic alcohol dependence (long-term therapy after detoxification).
   - Works best with supervised administration + counseling/psychotherapy**.**
2. **Other Uses (rare, investigational):**
   - Heavy metal chelation.
   - Potential role in cancer therapy research (experimental).

Adverse Effects

- **When alcohol is consumed:**
  - Disulfiram-ethanol reaction (DER): flushing, nausea, vomiting, palpitations, chest pain, hypotension, anxiety, headache.
  - Severe cases: cardiovascular collapse, arrhythmias, seizures.
- **Without alcohol:**
  - Drowsiness, fatigue.
  - Hepatotoxicity (liver damage).
  - Polyneuropathy (nerve damage, rare).

Contraindications

- Severe cardiovascular disease (risk of collapse during DER).
- Severe liver disease.
- Pregnancy and breastfeeding.
- Patients with psychosis or cognitive impairment.