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PHARMACOLOGY - I

UNIT 5

TOPIC :

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

  a. Psychopharmacological agents: Antipsychotics, antidepressants, anti-anxiety agents, anti-manics and hallucinogens.

  b. Drugs used in Parkinsons disease and Alzheimer's disease.

  c. CNS stimulants and nootropics.

  d. Opioid analgesics and antagonists

  e. Drug addiction, drug abuse, tolerance and dependence.

Antipsychotic Agents

Antipsychotic agents are drugs used to manage psychotic disorders by modulating neurotransmission in the brain, mainly through dopamine receptor antagonism and serotonin modulation.

Psychosis

- A severe mental disorder where a person loses contact with reality, showing distorted thinking, perception, emotions, and behavior.
- **Key Symptoms:**
  - **Delusions:** Fixed, false beliefs not based on reality (e.g., belief of persecution).
  - **Hallucinations:** Perceptions without external stimuli (commonly auditory, e.g., hearing voices).
  - **Disorganized Thinking/Speech:** Illogical, incoherent thoughts and communication.
- **Common Example:** Schizophrenia (most prevalent psychotic disorder).

Schizophrenia

- "Splitting of the mind," a chronic psychotic disorder with loss of contact with reality.
- **Features:** Hallucinations, delusions, abnormal behavior, and impaired thought processes.
- **Epidemiology:** More common in men than women.
- **Causes:**
  - Genetic predisposition (family history)
  - Prenatal/perinatal complications
  - Social/environmental stressors
  - Neurotransmitter imbalance (dopamine, serotonin, glutamate)

Symptoms

- **Positive Symptoms:** Hallucinations, delusions, disorganized speech/behavior
- **Negative Symptoms:** Emotional blunting, apathy, social withdrawal, loss of motivation

Pathogenesis

- **Not fully understood**; involves a combination of genetic, neurobiological, and environmental factors.
- **Dopamine Hypothesis:**
  - Hyperactivity of dopamine in mesolimbic pathway → positive symptoms
  - Dopamine dysfunction in mesocortical pathway → negative symptoms
- **Other factors:** Neurodevelopmental abnormalities, brain dysfunction, neurotransmitter imbalance.

Treatment Approaches

- **Psychotherapy**
- **Antipsychotic drugs** (mainstay of treatment)
- **Adjuncts:** Antidepressants, mood stabilizers
- **Lifestyle modifications**

Classification of Antipsychotics

1. Typical (First-Generation Antipsychotics, FGAs)

- **Examples:**
  - *Phenothiazines:* Chlorpromazine, Triflupromazine, Trifluoperazine, Fluphenazine
  - *Thioxanthenes:* Flupentixol
  - *Butyrophenones:* Haloperidol, Droperidol
  - *Others:* Pimozide, Loxapine

2. Atypical (Second-Generation Antipsychotics, SGAs)

- **Examples:** Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, Asenapine

1. Typical Antipsychotics (FGAs)

Mechanism of Action

- Primarily block D_2 receptors in mesolimbic pathway → reduce positive symptoms
- Additional receptor actions:
  - α_1-adrenergic blockade → hypotension
  - Muscarinic blockade → anticholinergic effects
  - H_1-histamine blockade → sedation

Pharmacokinetics

- Absorption: Oral, also IM/depot forms available
- Distribution: Lipophilic, cross BBB, high protein binding
- Metabolism: Hepatic (CYP450 enzymes), active metabolites possible
- Excretion: Urine and feces

Uses

- Schizophrenia (mainly positive symptoms)
- Acute psychosis
- Mania (bipolar disorder)
- Nausea/vomiting (e.g., prochlorperazine)

Adverse Effects

- **Extrapyramidal Symptoms (EPS):** Dystonia, Parkinsonism, akathisia, tardive dyskinesia
- **Neuroleptic Malignant Syndrome (NMS):** Rare, life-threatening
- **Hyperprolactinemia:** Galactorrhea, amenorrhea, gynecomastia
- **Sedation:** (H_1 blockade)
- **Orthostatic hypotension:** (α_1 blockade)
- **Anticholinergic effects:** Dry mouth, blurred vision, constipation, urinary retention

2. Atypical Antipsychotics (SGAs)

Mechanism of Action

- **Dual action:**
  1. Dopamine D_2 receptor antagonism → reduces positive symptoms
  2. Serotonin 5-HT_2A receptor antagonism → improves negative symptoms, lowers EPS risk
- Additional receptor activity:
  - H_1 blockade → sedation, weight gain
  - Muscarinic blockade → anticholinergic effects
  - α_1 blockade → hypotension

Pharmacokinetics

- Well absorbed orally, some affected by food (e.g., ziprasidone better absorbed with food)
- Highly protein-bound, wide distribution
- Extensive hepatic metabolism (CYP450 system)
- Excreted via urine and feces

Uses

- Schizophrenia (positive & negative symptoms)
- Bipolar disorder (mania & depression)
- Major depressive disorder (as adjunct therapy)

Examples

Clozapine, Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole

Adverse Effects

- Lower risk of EPS compared to FGAs
- Metabolic syndrome: weight gain, hyperglycemia, dyslipidemia
- Sedation, dizziness
- Orthostatic hypotension
- Constipation, dry mouth
- Tachycardia, insomnia

Antiparkinsonian Drugs

Parkinson's Disease (PD)

- A chronic, progressive neurodegenerative movement disorder caused by degeneration of dopaminergic neurons in the substantia nigra pars compacta.
- **Neurochemical Basis:**
  - ↓ Dopamine (DA) in basal ganglia
  - Imbalance between dopamine (inhibitory) and acetylcholine (excitatory) → abnormal motor control

Clinical Features

- **Cardinal Symptoms:**
  - Resting tremor ("pill-rolling tremor")
  - Rigidity ("cogwheel rigidity")
  - Bradykinesia (slowness of movement)
  - Postural instability
- **Other Symptoms:**
  - Reduced facial expression ("masked face")
  - Speech disorder (low, monotonous voice)
  - Depression, anxiety, sleep disturbances

Complications

- Social isolation
- Dementia or cognitive decline
- Sexual dysfunction
- Severe mobility issues

Causes / Etiology

- Degeneration of dopaminergic neurons in substantia nigra
- **Contributing factors:**
  - Genetic mutations
  - Environmental toxins
  - Mitochondrial dysfunction
  - Neuroinflammation
  - Head injury
  - Drugs (antipsychotics, reserpine)

Pathogenesis

1. Genetic & environmental triggers
2. Mitochondrial dysfunction & oxidative stress
3. α-synuclein accumulation → Lewy body formation
4. Progressive degeneration of nigrostriatal dopaminergic neurons
5. Deficiency of dopamine in basal ganglia
6. Imbalance between dopamine (↓) **&** acetylcholine (↑)
7. Motor dysfunction (tremors, rigidity, bradykinesia)

Treatment Principles

- No permanent cure; focus on symptom management
- Goals: restore dopamine function, inhibit excess acetylcholine activity, improve quality of life

General Measures

- Lifestyle modification
- Physiotherapy
- Psychological support

Drugs Used in Parkinson's Disease

1. Drugs Affecting Brain Dopaminergic System

(a) Dopamine Precursor

- **Levodopa:**
  - Most effective drug for PD
  - Crosses blood-brain barrier (BBB) → converted to dopamine in CNS
  - **Problem:** converted to dopamine peripherally → side effects (nausea, arrhythmia)
  - **Solution:** combine with peripheral decarboxylase inhibitors (carbidopa, benserazide)

(b) Peripheral Decarboxylase Inhibitors

- **Carbidopa, Benserazide**
- Inhibit peripheral metabolism of Levodopa → ↑ CNS availability
- ↓ Peripheral side effects (nausea, vomiting, CV effects)
- Always used in combination with Levodopa

(c) Dopamine Receptor Agonists

- **Examples:** Bromocriptine, Ropinirole, Pramipexole
- Directly stimulate dopamine receptors in brain
- Used in early PD or with Levodopa in advanced cases
- Fewer motor fluctuations than Levodopa
- **Side effects:** nausea, hypotension, hallucinations

(d) MAO-B Inhibitors

- **Selegiline, Rasagiline**
- Inhibit MAO-B enzyme → prevent dopamine breakdown
- ↑ Dopamine availability in brain
- Used in early PD or with Levodopa to prolong action
- **Side effects:** insomnia, headache, hypertensive crisis (with tyramine-rich foods in high doses)

(e) ***COMT Inhibitors***

- **Entacapone, Tolcapone**
- Inhibit COMT enzyme → prevent peripheral metabolism of Levodopa
- Prolong duration of action of Levodopa
- Used in **combination therapy (Levodopa + Carbidopa + COMT inhibitor)**
- **Side effects:** diarrhea, hepatotoxicity (tolcapone)

(f) ***Dopamine Facilitator / NMDA Antagonist***

- **Amantadine**
- Increases dopamine release and inhibits reuptake
- Also acts on **NMDA receptors** → reduces Levodopa-induced dyskinesia
- Used for mild PD or as add-on therapy
- **Side effects:** livedo reticularis (skin mottling), ankle edema, confusion

2. Drugs Affecting Brain Cholinergic System

- In PD, dopamine ↓, acetylcholine ↑ → excess cholinergic activity contributes to tremors
- **Mechanism:** Block muscarinic receptors in CNS → restore DA-ACh balance

(a) ***Central Anticholinergics***

- **Examples:** Trihexyphenidyl, Procyclidine, Biperiden
- Reduce tremor and rigidity (less effective on bradykinesia)
- **Uses:** Young patients, tremor-dominant PD, drug-induced parkinsonism
- **Side effects:** Dry mouth, blurred vision, constipation, urinary retention, confusion (elderly)

*(b) **Antihistaminics with Anticholinergic Activity***

- **Examples:** Orphenadrine, Promethazine
- H_1 antihistamines with central anticholinergic properties
- **Uses:** Mild PD, drug-induced parkinsonism (e.g., due to antipsychotics)
- **Side effects:** Sedation, dry mouth, dizziness, blurred vision

Alzheimer's Disease & Anti-Alzheimer Drugs

- Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder characterized by loss of memory, cognitive decline, and behavioral disturbances.
- It is the most common cause of dementia in the elderly.
- First described by Alois Alzheimer in 1907.
- The disease gradually worsens over time, impairing the patient's ability to perform daily tasks, communicate, and maintain independence.

Causes and Risk Factors

The exact cause is unknown, but multiple factors contribute:

- **Genetic factors** (mutations in APP, presenilin-1, presenilin-2 genes).
- **Family history** of Alzheimer's.
- **Age** (most important risk factor; prevalence increases after 65 years).
- **Down syndrome** (trisomy 21 → excess amyloid precursor protein).
- **Head trauma**.
- **Vascular risk factors**: hypertension, myocardial infarction, diabetes, obesity, smoking.
- **Environmental factors**: viral infections, toxins.

Pathogenesis

Two hallmark pathological changes explain AD neurodegeneration:

1. **Senile (Amyloid) Plaques**
    - Formed by extracellular deposition of β-amyloid (Aβ) peptides.
    - Result from abnormal cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase.
    - Aggregated Aβ → neurotoxicity, inflammation, and synaptic dysfunction.
2. **Neurofibrillary Tangles (NFTs)**
    - Intracellular aggregates of hyperphosphorylated tau protein.

- Cause microtubule destabilization → impaired neuronal transport → cell death.

Overall Effect:

- Neuronal dysfunction and degeneration.
- Loss of synaptic connections.
- Progressive cognitive decline.

Symptoms

- Progressive memory loss (short → long term).
- Poor judgment and decision-making.
- Confusion and disorientation.
- Personality and behavior changes.
- Depression, anxiety.
- Speech and communication difficulties.

Complications

- Inability to perform activities of daily living (ADL).
- Loss of mobility.
- Malnutrition and dehydration.
- Secondary infections (e.g., pneumonia).
- Death (advanced stages).

Treatment Approach

- No permanent cure available.
- Goal = symptom control + slowing progression + supportive care.
- Strategies:
  - Pharmacological (Cholinesterase inhibitors, NMDA antagonists).
  - Non-pharmacological (counseling, physiotherapy, occupational therapy).
  - Lifestyle modifications (mental stimulation, exercise, diet control).

Anti-Alzheimer Drugs

1. Cholinesterase Inhibitors (Mainstay for mild–moderate AD)

- Rationale: In AD, acetylcholine deficiency in the brain impairs memory and cognition.
- Mechanism of Action: Inhibit acetylcholinesterase enzyme, preventing breakdown of ACh → ↑ ACh concentration in synapses → improved neurotransmission.

Drug	Absorption / Route	Metabolism	Remarks
Donepezil	Well absorbed orally	Liver (CYP450 enzymes)	Used in mild, moderate & severe AD
Rivastigmine	Oral / Transdermal patch	Hydrolyzed by esterases (non-CYP)	Fewer drug interactions
Galantamine	Oral	Liver (CYP2D6, CYP3A4)	Also modulates nicotinic receptors

- Therapeutic Uses: Mild to moderate AD (Donepezil also for severe AD).
- Adverse Effects: Nausea, vomiting, diarrhea, dizziness, bradycardia, insomnia, muscle cramps.

2. NMDA Receptor Antagonist

- **Drug: Memantine**.
- **Rationale:** In AD, excess glutamate overactivates NMDA receptors → excitotoxicity → neuronal death.
- **MOA:** Blocks NMDA receptor channels → prevents glutamate-induced neurotoxicity.
- **Pharmacokinetics:**
  - Given orally, well absorbed.
  - Low hepatic metabolism.

    - Excreted largely unchanged in urine.
    - Long half-life (60–80 hrs).
- **Uses:** Moderate to severe AD (alone or with cholinesterase inhibitors).
- **Adverse Effects:** Dizziness, headache, confusion, constipation, rarely hallucinations/agitation.

3. Other / Investigational Approaches

- Nicotinic receptor agonists.
- Antioxidants (Vitamin E, selegiline).
- PPAR-γ agonists.
- γ-secretase inhibitors.
- 5-HT6 antagonists.
- Statins (cholesterol-lowering drugs).

Depression & Antidepressants

- Depression is a mood disorder characterized by persistent sadness, loss of interest/pleasure, feelings of hopelessness, and impaired daily functioning.
- It is a serious mental illness and a major risk factor for suicide.
- Affects emotions, thoughts, physical health, and social life.
- Globally, it is one of the leading causes of disability.

Types of Depression

1. **Major Depressive Disorder (MDD)**
    - Most common and severe type.
    - Persistent sadness, hopelessness, and inability to enjoy daily activities.
2. **Persistent Depressive Disorder (Dysthymia)**
    - Chronic depression lasting ≥ 2 years.
    - Symptoms are milder than MDD but long-lasting.
3. **Bipolar Depression**
    - Also called manic-depressive illness.
    - Alternating episodes of mania (highs) and depression (lows).
4. **Seasonal Affective Disorder (SAD)**
    - Depression during **winter months** due to reduced sunlight.
    - Improves in spring/summer.
5. **Psychotic Depression**
    - Severe depression with psychotic features: hallucinations, delusions.
6. **Postpartum Depression**
    - Occurs after childbirth (up to 1 year).
    - Related to hormonal and psychological changes.
7. **Premenstrual Depression (PMDD)**
    - Emotional and physical symptoms before menstruation.
    - Improves after onset of menses.

Causes & Risk Factors

- **Genetic factors** (family history).
- **Neurotransmitter imbalance** (↓ serotonin, norepinephrine, dopamine).
- **Neuroendocrine dysfunction** (HPA axis → ↑ cortisol).
- **Environmental stress** (social isolation, financial issues, trauma).
- **Medical conditions** (thyroid disorders, chronic illness).
- **Drugs/medications** (e.g., corticosteroids, alcohol, illicit drugs).

Pathogenesis

1. **Monoamine Hypothesis**
    - Depression is due to deficiency of monoamines (serotonin, norepinephrine, dopamine) in the brain.
2. **Neuroendocrine Hypothesis**
    - Overactivity of hypothalamic-pituitary-adrenal (HPA) axis.
    - ↑ Cortisol → neuronal damage, mood disturbances.

Overall: Stress + genetic predisposition → ↓ monoamines + ↑ cortisol → impaired mood regulation.

Signs & Symptoms

- Persistent sadness, hopelessness.
- Loss of interest in activities.
- Low self-esteem, guilt, worthlessness.
- Sleep disturbances (insomnia / hypersomnia).
- Fatigue, lack of energy.
- Poor concentration, forgetfulness.
- Irritability.
- Suicidal thoughts/behavior.

Complications

- Suicide.
- Social and occupational dysfunction.
- Relationship and family problems.
- Substance abuse.
- Physical health decline (malnutrition, cardiovascular risk).

Treatment

1. **Non-pharmacological**
    - Counseling (CBT, psychotherapy).
    - Lifestyle modifications (exercise, diet, sleep hygiene).
    - Mindfulness and meditation.
    - Social support.
2. **Pharmacological (Antidepressants)**
    - Correct neurotransmitter imbalance.
    - Main classes discussed below.

Antidepressants

Antidepressants restore monoamine balance, improving mood and reducing depressive symptoms.

1. Reversible Inhibitors of MAO-A (RIMAs)

- **Examples:** Moclobemide, Clorgyline.
- **MOA:** Reversibly inhibit **MAO-A enzyme**, preventing breakdown of serotonin (5-HT) & norepinephrine → ↑ levels in brain.
- **ADME:** Well absorbed orally; metabolized in liver; short duration due to reversible binding.
- **Uses:** Atypical depression, social phobia.
- **Adverse Effects:** Insomnia, dizziness, less risk of "cheese reaction" than older MAOIs.

2. Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Examples:** Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram, Dapoxetine.
- **MOA:** Block serotonin reuptake → ↑ serotonin in synaptic cleft → improved mood.
- **ADME:** Well absorbed orally, hepatic metabolism. Fluoxetine has long half-life (once daily).
- **Uses:** Major depression, anxiety, OCD, panic disorder.
- **Adverse Effects:** Nausea, insomnia, sexual dysfunction, headache.
- **Note:** First-line therapy due to safety & tolerability.

3. Tricyclic Antidepressants (TCAs)

- **Examples:** Amitriptyline, Imipramine, Clomipramine, Nortriptyline, Desipramine.
- **MOA:** Inhibit **reuptake of serotonin & norepinephrine** → ↑ neurotransmission.
- **ADME:** Lipophilic, well absorbed orally, hepatic metabolism.
- **Uses:** Depression, neuropathic pain, nocturnal enuresis.
- **Adverse Effects:** Sedation, dry mouth, weight gain, anticholinergic effects, cardiotoxicity (arrhythmias).
- **Note:** Effective but limited by side effects → used in resistant cases.

4. Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

- **Examples:** Venlafaxine, Duloxetine.
- **MOA:** Block reuptake of both serotonin and norepinephrine.
- **ADME:** Oral absorption, hepatic metabolism, short half-life.
- **Uses:** Depression, anxiety, neuropathic pain, fibromyalgia.
- **Adverse Effects:** Nausea, increased blood pressure (esp. venlafaxine), sexual dysfunction.
- **Note:** Safer than TCAs.

5. Atypical Antidepressants

- **Examples & MOA:**
  - **Mirtazapine:** α2-blocker → ↑ serotonin & norepinephrine release.
  - **Bupropion:** Inhibits dopamine & norepinephrine reuptake.
  - **Trazodone:** 5-HT2 antagonist + weak SSRI + H1 blocker.
  - **Atomoxetine:** Selective norepinephrine reuptake inhibitor (NRI).
- **ADME:** Orally absorbed, metabolized in liver, variable half-life.
- **Uses:** Major depression, anxiety disorders, insomnia (trazodone).
- **Adverse Effects:**
  - Mirtazapine → sedation, weight gain.
  - Bupropion → insomnia, seizures.
  - Trazodone → sedation.
  - Atomoxetine → appetite loss, insomnia.

Anti-Anxiety Drugs (Anxiolytics)

Anti-anxiety drugs, also called anxiolytics, are a group of agents used to reduce excessive anxiety, nervousness, and associated physical symptoms (like restlessness, tremors, palpitations, sweating) without causing major sedation or loss of consciousness.

Classification of Anti-anxiety Drugs

1. **Benzodiazepines**
    - Lorazepam
    - Diazepam
    - Alprazolam
    - Chlordiazepoxide
2. **Azapirones**
    - Buspirone
    - Gepirone
    - Ipsapirone
3. **Sedative Antihistaminics**
    - Hydroxyzine
4. **β-Adrenergic Blockers**
    - Propranolol

1. Benzodiazepines

- **Examples:** Diazepam, Lorazepam, Alprazolam, Chlordiazepoxide.

Mechanism of Action (MOA):

- Enhance the effect of **GABA (γ-aminobutyric acid)**, the major inhibitory neurotransmitter in CNS.
- Bind to **GABA-A receptor complex**, increase the frequency of chloride (Cl^-) channel opening.
- Hyperpolarization → CNS inhibition → reduced anxiety, sedation, and muscle relaxation.

Pharmacological Effects

- Anxiolytic (reduce anxiety)
- Sedative-hypnotic (dose dependent)
- Muscle relaxant
- Anticonvulsant

Adverse Effects

- Drowsiness, dizziness
- Ataxia, confusion
- Risk of dependence and tolerance (with long-term use)
- Withdrawal symptoms if stopped suddenly

2. Azapirones

- **Example:** Buspirone

Mechanism of Action:

- Partial agonist at **5-HT1A serotonin receptors** in the brain.
- Modulates serotonin activity → reduces anxiety gradually.
- No effect on GABA receptors.

Special Features

- Onset of action is **slow (1–2 weeks)** → not useful for acute anxiety.
- No sedation, hypnosis, muscle relaxation, or dependence.
- Safer in long-term use.

Adverse Effects

- Headache
- Nausea
- Dizziness

3. Sedative Antihistaminics

- **Example:** Hydroxyzine

Mechanism of Action:

- Blocks **H1 histamine receptors** in the CNS.
- Produces sedation and mild anxiolytic effect.

Uses

- Short-term relief of anxiety
- Pre-anesthetic medication

Adverse Effects

- Drowsiness
- Dry mouth

4. β-Adrenergic Blockers

- **Example:** Propranolol

Class: Non-selective β-adrenergic receptor blocker (blocks both β1 and β2).

Mechanism of Action:

- Blocks **β1 receptors in heart** → ↓ heart rate, ↓ cardiac output.
- Blocks **β2 receptors in blood vessels and lungs**.
- In anxiety: reduces **physical symptoms** like palpitations, tremors, sweating (especially in performance anxiety).

Pharmacokinetics

- Absorption: Well absorbed orally
- Distribution: Lipid soluble, crosses BBB
- Metabolism: Extensive first-pass metabolism in liver
- Excretion: Mainly via urine

Uses

- Performance anxiety
- Hypertension
- Angina pectoris

Adverse Effects

- Bradycardia
- Hypotension
- Fatigue, dizziness

ANTI-MANIC DRUGS

Anti-manic drugs are medications used to control manic episodes in patients with bipolar disorder (also called manic-depressive illness). They reduce symptoms like excessive excitement, overactivity, irritability, impulsiveness, and insomnia.

Classification of Anti-Manic Drugs

1. Mood Stabilizers

- **Lithium carbonate** (most commonly used, gold standard).
- **Anticonvulsants used as mood stabilizers**:
  - Valproic acid
  - Carbamazepine
  - Lamotrigine

2. Atypical Antipsychotics

- Olanzapine
- Risperidone
- Quetiapine
- Aripiprazole

Mechanism of Action (MOA)

- **Lithium:**
  - Alters sodium transport across nerve and muscle cells.
  - Modulates neurotransmitters (↓ dopamine, ↑ serotonin).
  - Stabilizes mood by affecting intracellular signaling pathways (e.g., IP_3, DAG).
- **Valproic Acid & Carbamazepine:**
  - Anticonvulsants that stabilize neuronal membranes and reduce excitatory neurotransmission (especially glutamate).
- **Atypical Antipsychotics:**

- Block **dopamine D2** and **serotonin 5-HT2A receptors** → reduce manic symptoms.

Uses

- Treatment of acute mania.
- Prevention of recurrent manic and depressive episodes in bipolar disorder.
- Sometimes used along with antidepressants to prevent mood swings.

Adverse Effects

- **Lithium:** Tremors, hypothyroidism, polyuria (nephrogenic diabetes insipidus), nausea, toxicity (narrow therapeutic index).
- **Valproic acid:** Hepatotoxicity, weight gain, teratogenicity.
- **Carbamazepine:** Blood dyscrasias, ataxia.
- **Atypical antipsychotics:** Weight gain, metabolic syndrome, sedation.

HALLUCINOGENS

Hallucinogens are psychoactive drugs that cause hallucinations — i.e., false perceptions such as seeing, hearing, or feeling things that are not real. They also alter thoughts, emotions, and perception of time and space.

Classification of Hallucinogens

Natural

- Psilocybin (from *magic mushrooms*).
- Mescaline (from *peyote cactus*).
- Cannabis (in high doses).

Synthetic

- LSD (Lysergic acid diethylamide).
- Phencyclidine (PCP).
- MDMA (Ecstasy; mixed stimulant-hallucinogen effect).

Mechanism of Action (MOA)

- Most hallucinogens stimulate serotonin (5-HT2A) receptors in the brain.
- This alters sensory perception, cognition, and mood.
- Some (like PCP) act on NMDA glutamate receptors.

Effects (Temporary, Dose-Dependent)

Psychological

- Visual and auditory hallucinations.
- Altered sense of time and space.
- Distorted thinking and emotions.
- Euphoria or intense anxiety ("bad trip").

Physiological

- Dilated pupils.
- Increased heart rate and blood pressure.
- Sweating, tremors.

Adverse Effects / Risks

- Acute anxiety or panic reactions.
- Flashbacks (recurrence of hallucinations even without drug use).
- Psychosis (in susceptible individuals).
- Dependence is rare but possible with repeated use.

CNS STIMULANTS

CNS stimulants are a group of drugs that increase activity of the central nervous system, leading to enhanced alertness, wakefulness, attention, mood elevation, and physical energy.
They act mainly by increasing neurotransmitters (dopamine, norepinephrine, serotonin, or blocking adenosine).

Classification of CNS Stimulants

1. **Respiratory Stimulants (Analeptics)**
   - Doxapram
   - Nikethamide
2. **Psychomotor Stimulants**
   - Amphetamines (e.g., Amphetamine, Methylphenidate)
   - Cocaine
   - Methylxanthines (Caffeine, Theophylline, Theobromine)
3. **Convulsants (Experimental / Toxicological importance)**
   - Pentylenetetrazol (Leptazol)
   - Strychnine

1. Respiratory Stimulants (Analeptics)

- **Mechanism of Action:** Stimulate respiratory centers in the medulla and carotid body chemoreceptors.
- **Examples:**
  - **Doxapram:** Activates carotid body chemoreceptors → increases breathing.
  - **Nikethamide:** Weak CNS stimulant, previously used for respiratory depression but obsolete now.
- **Uses:** Emergency treatment of respiratory depression due to anesthetics, opioids, or premature babies (historical use).

2. Psychomotor Stimulants

These drugs increase mental alertness, wakefulness, reduce fatigue, improve mood, and physical performance.

a. Amphetamines

- **MOA:** Increase release of dopamine & norepinephrine in CNS.
- **Uses:**
  - ADHD (Attention-Deficit Hyperactivity Disorder).
  - Narcolepsy (uncontrollable daytime sleep attacks).
- **Adverse effects:** Hypertension, insomnia, addiction, anxiety.

b. Cocaine

- **MOA:** Inhibits reuptake of dopamine, norepinephrine, serotonin → prolonged neurotransmitter action.
- **Effects:** Strong euphoria, local anesthetic (blocks sodium channels).
- **Adverse effects:** Addiction, hallucinations, cardiovascular toxicity (arrhythmias, hypertension).

c. Methylxanthines (Naturally Occurring Stimulants)

- **Examples:**
  - **Caffeine** (coffee, tea, cola).
  - **Theophylline** (tea; bronchodilator).
  - **Theobromine** (cocoa).
- **Mechanism of Action:**
  - Inhibit **phosphodiesterase (PDE)** → ↑ cAMP.
  - Block **adenosine receptors** → prevent drowsiness.
- **Pharmacological Effects:**
  - CNS stimulation (↑ alertness, ↓ fatigue).
  - Bronchodilation (Theophylline useful in asthma, COPD).
  - Mild diuretic effect.
  - Cardiac stimulation (tachycardia).
  - ↑ Gastric acid secretion.
- **Therapeutic Uses:**
  - **Caffeine:** Relieve fatigue, drowsiness, mild stimulant.
  - **Theophylline:** Bronchial asthma, COPD.
  - **Theobromine:** Mild, mainly of historical interest.

3. Convulsants (Toxicological Interest)

These CNS stimulants produce convulsions and seizures by excessive stimulation of spinal cord and brain neurons.

- **Examples:**
  - **Pentylenetetrazol (Leptazol):** Used experimentally to induce seizures (no longer therapeutic).
  - **Strychnine:** Plant alkaloid; blocks glycine receptors in spinal cord → severe uncontrolled muscle spasms and convulsions.
- **Uses:** None clinically, only of toxicological and experimental importance.

NOOTROPICS (Smart Drugs / Cognitive Enhancers)

- Nootropics are drugs, supplements, or substances that enhance cognitive functions such as memory, learning, creativity, attention, and motivation without causing sedation or significant CNS stimulation.

Key Features of Nootropics

- Improve memory and learning ability.
- Enhance brain metabolism and neuronal communication.
- Increase mental performance and alertness.
- Do not cause sedation, dependence, or major side effects (ideally).
- Usually considered safe and non-addictive at therapeutic doses.

Examples of Nootropics and Their Actions

Drug Name	Mechanism / Action	Uses
Piracetam	Improves neuronal membrane fluidity, enhances neurotransmission, and brain metabolism.	Memory enhancement, learning disorders, cognitive decline in dementia.
Aniracetam	Analog of piracetam; modulates AMPA receptors; improves focus and attention.	Used for cognitive deficits, experimental in Alzheimer's disease.
Modafinil	Promotes wakefulness by modulating dopamine and orexin systems.	Narcolepsy, shift-work sleep disorder; off-label as cognitive enhancer.
Selegiline	MAO-B inhibitor; increases dopamine levels; has neuroprotective effects.	Parkinson's disease, age-related cognitive decline.
Caffeine (low dose)	Adenosine receptor antagonist → ↑ alertness, mild memory/attention enhancer.	Fatigue, drowsiness, mild cognitive boosting.

Mechanism of Action (General)

- Enhance neurotransmitter activity (acetylcholine, dopamine, glutamate).
- Increase cerebral blood flow and oxygen utilization.
- Improve synaptic plasticity and memory consolidation.
- Provide neuroprotection against age-related degeneration.

Therapeutic Uses

- Cognitive decline in Alzheimer's disease and dementia.
- Stroke rehabilitation (Piracetam).
- Narcolepsy and hypersomnia (Modafinil).
- Parkinson's disease (Selegiline).
- Age-related memory loss and attention deficits.

Adverse Effects

- Usually well tolerated.
- Mild effects may include:
    - Insomnia
    - Headache
    - Nausea
    - Anxiety (with stimulatory nootropics like Modafinil, Caffeine).

Opioid Analgesics

- Opioid analgesics are drugs that relieve moderate to severe pain by binding to opioid receptors (μ, κ, δ) in the CNS and PNS.
- They mimic the actions of endogenous opioids such as endorphins, enkephalins, and dynorphins.

Opioid Receptors

- **Type:** G-protein coupled receptors (GPCRs).
- **Location:** Brain, spinal cord, peripheral nerves, GIT.
- **Main Receptors and Functions:**

Receptor	Main Actions	Endogenous Ligand	Drugs Acting
μ (Mu)	Supraspinal & spinal analgesia, euphoria, sedation, respiratory depression, constipation, physical dependence	Endorphins	Morphine, Fentanyl, Methadone
κ (Kappa)	Spinal analgesia, dysphoria, sedation	Dynorphins	Pentazocine, Nalbuphine
δ (Delta)	Spinal analgesia, mood modulation	Enkephalins	(Few selective drugs clinically used)

Classification of Opioid Analgesics

1. **Natural Opium Alkaloids**
    - Morphine
    - Codeine
    - Pholcodine
    - Ethylmorphine
2. **Semisynthetic Opioids**
    - Diacetylmorphine (Heroin)
    - Hydromorphone

    - Oxymorphone
3. **Synthetic Opioids**
    - Pethidine (Meperidine)
    - Methadone
    - Fentanyl, Remifentanil
    - Tramadol, Tapentadol

Mechanism of Action

- Bind mainly to μ (mu) receptors in brain and spinal cord.
- Actions:
    - Inhibit release of pain neurotransmitters (Substance P, glutamate).
    - Hyperpolarize neurons → reduce excitability.
    - Result = analgesia, sedation, euphoria, respiratory depression, constipation.

Pharmacokinetics (General)

- **Absorption:** Well absorbed orally, IM, IV.
- **Distribution:** Cross blood–brain barrier (lipophilic opioids like fentanyl faster than morphine).
- **Metabolism:** Liver (Morphine → active metabolite morphine-6-glucuronide).
- **Excretion:** Renal (urine).

Therapeutic Uses of Opioids

- Relief of moderate to severe pain (trauma, MI, cancer, post-operative).
- Pre-anaesthetic medication (Fentanyl).
- Cough suppression (Codeine, Pholcodine).
- Diarrhea (Loperamide, diphenoxylate – peripheral opioids).
- Pulmonary edema (reduces anxiety & preload).

Adverse Effects

- Respiratory depression (dose-limiting).
- Constipation (due to ↓ GIT motility).
- Nausea & vomiting.
- Miosis (pin-point pupils – diagnostic sign).
- Physical dependence & tolerance.
- Sedation, dizziness.

Pharmacology of Morphine (Prototype Opioid)

- **Source:** Natural alkaloid from *Papaver somniferum*.
- **Mechanism:** Full agonist at μ receptors, weak action at κ and δ.
- **Effects:**
  - Analgesia (central + spinal).
  - Sedation, euphoria.
  - Depressed respiration.
  - ↓ GI motility → constipation.
- **Pharmacokinetics:**
  - Absorption: Oral, IM, IV (oral less effective due to first-pass).
  - Distribution: Crosses BBB slowly.
  - Metabolism: Liver → morphine-6-glucuronide (active metabolite).
  - Excretion: Urine.
- **Therapeutic Uses:** Severe pain, pulmonary edema, MI, rarely cough/diarrhea.
- **Adverse Effects:** Respiratory depression, constipation, nausea, dependence, sedation.

Opioid Antagonists

- Opioid antagonists are drugs that block opioid receptors (μ, κ, δ) without activating them.
- They reverse the effects of opioid agonists (e.g., morphine, heroin) in overdose or toxicity.
- They do not produce opioid-like effects themselves.

Examples and Uses

Drug Name	Duration	Uses
Naloxone	Short	Acute opioid overdose (IV only)
Naltrexone	Long	Opioid & alcohol dependence (maintenance therapy)
Nalmefene	Long	Alcohol dependence, opioid overdose (IV), opioid-induced constipation
Methylnaltrexone	Peripheral only	Opioid-induced constipation (acts only on gut)

Mechanism of Action

- **Competitive antagonism** at μ, κ, δ receptors in CNS and periphery.
- **Rapidly reverses**:
  - Respiratory depression
  - Sedation
  - Euphoria caused by opioid agonists
- **Peripheral selective agents** (e.g., Methylnaltrexone) do not cross BBB; only act on gut.

Pharmacokinetics

Drug	Route	Onset	Duration
Naloxone	IV/IM	Rapid	1–2 hours (may require repeat doses)
Naltrexone	Oral	30 min	Up to 24 hours
Methylnaltrexone	Subcutaneous	30–60 min	Peripheral action only

Therapeutic Uses

- **Naloxone:** Emergency treatment of opioid overdose.
- **Naltrexone:** Maintenance therapy for opioid addiction; also reduces alcohol craving.
- **Methylnaltrexone:** Treats opioid-induced constipation without affecting analgesia.
- **Nalmefene:** Used in alcohol dependence and some opioid overdose cases.

Adverse Effects

- Sweating
- Anxiety
- Vomiting
- Tachycardia
- Nausea
- Dizziness

Drug Addiction, Abuse, Dependence & Tolerance

Drug Addiction

- A chronic condition where a person loses control over drug use, leading to compulsive drug-seeking behavior and continued use despite harmful consequences.

Key Features:

- Strong psychological craving.
- Repeated, uncontrollable drug use.
- Commonly associated with opioids, cocaine, alcohol, nicotine, and other psychoactive substances.

Drug Abuse

- The intentional and inappropriate use of drugs for non-medical purposes, often to achieve euphoria or altered mental states.

Key Features:

- Use of illegal drugs or misuse of prescription drugs.
- Leads to social, occupational, or health-related problems.
- Can involve recreational or experimental use beyond therapeutic limits.

Drug Dependence

- A state in which the body or mind adapts to repeated drug use, causing withdrawal symptoms when the drug is reduced or stopped.

Types:

1. **Physical Dependence**

- Withdrawal symptoms: tremors, sweating, nausea, muscle pain, or seizures.

2. **Psychological Dependence**
   - Emotional or mental craving for the drug; persistent desire to use it.

Examples:

- Long-term use of benzodiazepines, opioids, alcohol can lead to dependence.

Drug Tolerance

- A condition in which increasing doses of a drug are required to achieve the same therapeutic or euphoric effect.

Mechanism:

- May occur due to metabolic adaptation (enhanced drug metabolism) or changes in receptor sensitivity.
- Leads to reduced response over time, even at the same dosage.

Examples:

- Common with morphine, alcohol, barbiturates, and other CNS-active drugs.