DRUGS AFFECTING CENTRAL NERVOUS SYSTEM

27. General Anaesthetics

General Anaesthetics are drugs that induce a reversible loss of consciousness and sensation. They are divided into inhalational and intravenous agents.

Mechanism of Action:

- Inhalational Anaesthetics: Work primarily by enhancing GABA-A receptor-mediated inhibition, reducing synaptic transmission.
- GABA-A Receptor Modulation: Increasing the duration of chloride channel opening, leading to hyperpolarization and neuronal inhibition.
- Other Effects: Nitrous oxide and xenon also inhibit NMDA receptors.

Classification:

1. Inhalational Anaesthetics:

- Examples: Halothane, Isoflurane, Sevoflurane, Nitrous Oxide.
- Uses: Maintenance of anaesthesia.
- Adverse Effects:
    - Halothane: Hepatotoxicity (especially in females and obese patients), arrhythmias, hypotension, and respiratory depression.
    - Isoflurane: Lower hepatotoxicity but can cause hypotension due to peripheral vasodilation.
    - Sevoflurane: Least hepatotoxic; used in pediatric anaesthesia but may cause nephrotoxicity.
    - Nitrous Oxide: Diffusion hypoxia, inhibits B12-dependent enzymes, leading to megaloblastic anemia with chronic use.

2. Intravenous Anaesthetics:

- Examples: Propofol, Ketamine, Thiopental, Etomidate.
- Uses: Induction of anaesthesia, conscious sedation.
- Adverse Effects:
    - Propofol: Hypotension, respiratory depression, and pain on injection.
    - Ketamine: Dissociative anaesthesia; side effects include emergence reactions (delirium, hallucinations), increased intracranial pressure.
    - Thiopental: Rapid onset but can cause respiratory depression and hypotension.
    - Etomidate: Preferred in patients with cardiovascular instability but can cause adrenal suppression.

Key Points for Exams:

- Minimum Alveolar Concentration (MAC): Inhaled agents are compared based on their MAC; lower MAC indicates higher potency.
- Induction and Recovery: Drugs with lower blood-gas partition coefficients (e.g., Nitrous oxide) provide rapid induction and recovery.
- Stages of Anaesthesia: Four stages from analgesia to respiratory paralysis (useful in viva questions).

28. Ethyl and Methyl Alcohols

Ethyl Alcohol (Ethanol):

- Mechanism of Action: Ethanol enhances GABA-A receptor-mediated inhibition and reduces excitatory NMDA receptor activity.
- Pharmacokinetics: Zero-order kinetics; the body metabolizes ethanol at a constant rate (regardless of concentration).
- Clinical Uses:
    - Treatment of methanol poisoning: Competes with methanol for alcohol dehydrogenase, preventing the formation of toxic metabolites.
    - Antiseptic: Used in disinfection.
- Chronic Effects:
    - Liver cirrhosis, pancreatitis, cardiomyopathy, neuropathy, Wernicke-Korsakoff syndrome (due to thiamine deficiency).
    - Withdrawal Management: Benzodiazepines (e.g., Diazepam) are used to prevent seizures during alcohol withdrawal. Thiamine is given to prevent neurological damage.

Methyl Alcohol (Methanol):

- Mechanism of Toxicity: Methanol is metabolized to formaldehyde and formic acid, leading to metabolic acidosis and damage to the optic nerve (blindness).

Treatment of Methanol Poisoning:

- Fomepizole: Inhibits alcohol dehydrogenase, preventing methanol metabolism.
- Ethanol: Competes with methanol for alcohol dehydrogenase.
- Supportive Care: Sodium bicarbonate to correct acidosis and dialysis in severe cases.

Key Points for Exams:

- Ethanol Metabolism: Involves alcohol dehydrogenase and acetaldehyde dehydrogenase. Excessive acetaldehyde can cause hangover symptoms.
- Fomepizole: Competitive inhibitor of alcohol dehydrogenase and is a standard treatment in methanol poisoning.

29. Sedative-Hypnotics

Classification:

1. Benzodiazepines (BZDs): Diazepam, Lorazepam, Alprazolam.

- Mechanism: Bind to the GABA-A receptor at the BZD site, increasing the frequency of chloride channel opening and hyperpolarizing the cell.
- Uses: Anxiety, insomnia, seizures, muscle relaxation, premedication in anesthesia.
- Adverse Effects: Sedation, dependence, withdrawal symptoms, cognitive impairment, paradoxical agitation in some patients.
- Toxicity Management: Flumazenil is a BZD antagonist used in overdose situations.

2. Non-Benzodiazepine Hypnotics (Z-drugs): Zolpidem, Zaleplon.

- Mechanism: Act on the BZD binding site of GABA-A receptors, but more selective for the α1 subunit, causing sedation without significant muscle relaxation or anticonvulsant effects.
- Uses: Insomnia (short-term use).
- Adverse Effects: Sleepwalking, complex behaviors during sleep.

3. Barbiturates: Phenobarbital, Pentobarbital.

- Mechanism: Potentiate GABA-A action and increase the duration of chloride channel opening, as well as direct GABA-mimetic activity at higher doses.
- Uses: Seizure control, anesthesia (Thiopental), and sedation.
- Adverse Effects: Respiratory depression, hypotension, drug interactions due to CYP450 induction.
- Overdose Treatment: Supportive care (no specific antidote).

Key Points for Exams:

- Difference in Action between Benzodiazepines and Barbiturates: BZDs increase the frequency of chloride channel opening, whereas barbiturates increase the duration.

- Flumazenil: Often asked as an antidote for BZD overdose but not recommended in chronic users due to risk of precipitating seizures.

30. Antiepileptic Drugs (AEDs)

Classification:

1. Sodium Channel Blockers: Phenytoin, Carbamazepine.

- Mechanism: Stabilizes the inactive state of voltage-gated sodium channels, preventing repetitive firing.
- Uses: Focal and generalized tonic-clonic seizures.
- Adverse Effects:
- Phenytoin: Gingival hyperplasia, hirsutism, megaloblastic anemia, and Stevens-Johnson syndrome.
- Carbamazepine: Aplastic anemia, agranulocytosis, hyponatremia.
- Kinetics of Phenytoin: Follows zero-order kinetics at therapeutic doses.

2. GABA Enhancers:

- Benzodiazepines (Diazepam, Lorazepam): Used for status epilepticus.
- Valproate: Increases GABA levels by inhibiting GABA transaminase. Used for generalized seizures.
- Adverse Effects: Hepatotoxicity, pancreatitis, teratogenic (spina bifida).

3. T-type Calcium Channel Blockers: Ethosuximide.

- Mechanism: Inhibits T-type calcium channels in the thalamus, reducing the hyperexcitability seen in absence seizures.
- Uses: Drug of choice for absence seizures.
- Adverse Effects: GI upset, headache, and lethargy.

Key Points for Exams:

- Phenytoin's Non-linear Kinetics: Important concept, especially regarding dosing adjustments.
- Ethosuximide: Drug of choice for absence seizures. This is a frequent question in both theory and viva.

31. Antiparkinsonian Drugs

- Parkinson's disease (PD) is caused by the degeneration of dopaminergic neurons in the substantia nigra, leading to dopamine deficiency in the basal ganglia and relative cholinergic overactivity.
- Goals of Therapy:
- Restore dopaminergic activity.
- Reduce excessive cholinergic activity.

Classification:

1. Dopaminergic Drugs:

Levodopa (combined with Carbidopa or Benserazide):

- Mechanism: Levodopa is a precursor of dopamine that crosses the blood-brain barrier (BBB) and is converted to dopamine. Carbidopa/Benserazide inhibits peripheral dopa decarboxylase, reducing the peripheral metabolism of levodopa, allowing more levodopa to reach the brain.
- Adverse Effects:
    - Early: Nausea, vomiting, orthostatic hypotension.
    - Late: Dyskinesias (involuntary movements), motor fluctuations (on-off phenomenon), hallucinations, and psychosis.
    - Management of "On-Off" Phenomenon: Adjusting levodopa dosage, adding dopamine agonists or COMT inhibitors, or using continuous infusions.
    - Drug Interactions: Pyridoxine (Vitamin B6) increases peripheral metabolism of levodopa unless given with carbidopa.

2. Dopamine Agonists:

- Examples: Pramipexole, Ropinirole, Rotigotine, Apomorphine.
- Mechanism: Directly stimulate dopamine receptors (mainly D2 receptors).
- Uses: As monotherapy in early PD or in combination with levodopa in advanced stages to reduce motor fluctuations.
- Adverse Effects: Nausea, hallucinations, impulse control disorders (gambling, hypersexuality), somnolence, and orthostatic hypotension.

3. MAO-B Inhibitors:

- Examples: Selegiline, Rasagiline.

- Mechanism: Inhibit monoamine oxidase-B (MAO-B), the enzyme responsible for the breakdown of dopamine in the brain, thus increasing dopamine levels.
- Uses: Early PD as monotherapy or in combination with levodopa to reduce motor fluctuations.
- Adverse Effects: Insomnia (selegiline is metabolized to amphetamine), headache, and dyskinesias.

4. COMT Inhibitors:

- Examples: Entacapone, Tolcapone.
- Mechanism: Inhibit catechol-O-methyltransferase (COMT), an enzyme that metabolizes levodopa in the periphery, increasing the amount of levodopa reaching the brain.
- Uses: Used as an adjunct to levodopa to reduce "off" time.
- Adverse Effects: Dyskinesias, diarrhea, and hepatotoxicity (Tolcapone).

5. Anticholinergic Drugs:

- Examples: Trihexyphenidyl, Benztropine.
- Mechanism: Block muscarinic cholinergic receptors to reduce cholinergic activity, which is increased in PD.
- Uses: More effective for tremor and rigidity than bradykinesia. Used mainly in younger patients.
- Adverse Effects: Dry mouth, constipation, blurred vision, urinary retention, cognitive impairment, and hallucinations (especially in elderly patients).

6. Amantadine:

- Mechanism: Increases dopamine release and inhibits dopamine reuptake; also has NMDA receptor antagonist properties, reducing dyskinesias.
- Uses: Early mild PD and levodopa-induced dyskinesias.
- Adverse Effects: Livedo reticularis (a mottled skin discoloration), peripheral edema, and confusion.

Key Points for Exams:

- Levodopa-Carbidopa remains the most effective treatment for PD, but long-term use is associated with motor complications.
- Impulse control disorders with dopamine agonists are a commonly asked question.
- COMT inhibitors: Entacapone is preferred over Tolcapone due to the latter's hepatotoxicity.

32. Drugs Used in Mental Illness: Antipsychotic and Antimanic Drugs

Antipsychotic Drugs:

- Used to treat schizophrenia, bipolar disorder, and psychotic symptoms in other disorders.

Classification:

1. Typical Antipsychotics (First-Generation):

- Examples: Chlorpromazine, Haloperidol, Fluphenazine.
- Mechanism: Block dopamine D2 receptors in the mesolimbic and mesocortical pathways, reducing positive symptoms (e.g., hallucinations, delusions).
- Adverse Effects:
    - Extrapyramidal Symptoms (EPS): Parkinsonism, akathisia, dystonia (acute), and tardive dyskinesia (chronic).
    - Neuroleptic Malignant Syndrome: Life-threatening muscle rigidity, hyperthermia, autonomic instability.
    - Sedation and Weight Gain: Due to histamine H1 receptor blockade.
    - Hypotension: Due to α1 adrenergic receptor blockade.

2. Atypical Antipsychotics (Second-Generation):

- Examples: Clozapine, Risperidone, Olanzapine, Aripiprazole, Quetiapine.
- Mechanism: Block both D2 and serotonin 5-HT2A receptors, addressing both positive and negative symptoms (e.g., apathy, social withdrawal).
- Adverse Effects:
    - Metabolic Syndrome: Weight gain, diabetes mellitus, dyslipidemia (especially with Olanzapine and Clozapine).
    - Agranulocytosis: Clozapine requires regular monitoring of WBC count.
    - Prolonged QT Interval: Especially with Ziprasidone.
    - Lower Risk of EPS compared to typical antipsychotics.

Antimanic Drugs:

- Used for acute mania and maintenance treatment in bipolar disorder.

1. Lithium:

- Mechanism: Alters sodium transport in nerve and muscle cells, affects neurotransmitter reuptake, and second messenger systems (cAMP and IP3).
- Uses: First-line for acute mania and as a mood stabilizer in bipolar disorder.
- Adverse Effects:
    - Tremor, hypothyroidism, nephrogenic diabetes insipidus, renal impairment.
    - Lithium Toxicity: Narrow therapeutic window; signs of toxicity include tremors, confusion, seizures, and coma. Managed by stopping lithium and providing supportive care; hemodialysis in severe cases.
- Drug Interactions: NSAIDs, diuretics, and ACE inhibitors increase lithium levels.

2. Valproate:

- Mechanism: Increases GABA levels, stabilizes neuronal membranes by blocking sodium channels.
- Uses: Acute mania, bipolar disorder, and seizure disorders.
- Adverse Effects: Hepatotoxicity, teratogenicity, weight gain, and thrombocytopenia.

Key Points for Exams:

- EPS vs. Metabolic Syndrome: Differentiating side effects of typical vs. atypical antipsychotics is frequently tested.
- Clozapine Monitoring: Requires regular WBC counts due to agranulocytosis risk.
- Lithium Toxicity: Commonly tested with interactions and symptoms.

33. Drugs Used in Mental Illness: Antidepressant and Antianxiety Drugs

Antidepressants:

- Used for major depressive disorder, anxiety disorders, and chronic pain syndromes.

Classification:

1. Selective Serotonin Reuptake Inhibitors (SSRIs):

- Examples: Fluoxetine, Sertraline, Escitalopram.
- Mechanism: Inhibit the reuptake of serotonin (5-HT) into presynaptic neurons, increasing serotonin levels in the synaptic cleft.
- Adverse Effects: Sexual dysfunction, nausea, weight gain, serotonin syndrome (agitation, hyperreflexia, fever), especially when combined with other serotonergic agents.

Key Exam Point:

- First-line agents for depression and anxiety due to their favorable side effect profile.

2. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):

- Examples: Venlafaxine, Duloxetine.
- Mechanism: Inhibit the reuptake of both serotonin and norepinephrine.
- Uses: Depression, generalized anxiety disorder (GAD), and neuropathic pain.
- Adverse Effects: Hypertension (due to increased norepinephrine), nausea, sexual dysfunction.

3. Tricyclic Antidepressants (TCAs):

- Examples: Amitriptyline, Nortriptyline.
- Mechanism: Inhibit the reuptake of serotonin and norepinephrine. Also block histamine, muscarinic, and α1 receptors.
- Uses: Depression, neuropathic pain, migraine prophylaxis.
- Adverse Effects: Sedation, weight gain, dry mouth, constipation, and risk of cardiotoxicity (QT prolongation, arrhythmias

Key Exam Point:

TCAs are no longer first-line due to their significant side effect profile and toxicity in overdose, especially cardiac arrhythmias.

4. Monoamine Oxidase Inhibitors (MAOIs):

- Examples: Phenelzine, Tranylcypromine.
- Mechanism: Inhibit monoamine oxidase, the enzyme responsible for the breakdown of serotonin, norepinephrine, and dopamine, thereby increasing their levels in the brain.
- Uses: Atypical depression, treatment-resistant depression.
- Adverse Effects: Hypertensive crisis when taken with tyramine-containing foods (e.g., cheese, wine), serotonin syndrome if combined with SSRIs, orthostatic hypotension.

5. Atypical Antidepressants:

- Examples:

- Bupropion: Inhibits dopamine and norepinephrine reuptake. Used in depression and smoking cessation. Adverse effects include insomnia, and it lowers the seizure threshold.
- Mirtazapine: Blocks α2 receptors, increasing norepinephrine and serotonin release. Adverse effects include weight gain and sedation.

Key Points for Exams:

- SSRIs and SNRIs are first-line for depression and anxiety, while TCAs and MAOIs are reserved for treatment-resistant cases.
- Serotonin syndrome is a key adverse effect of serotonergic agents and is commonly tested.
- MAOI and food interactions are high-yield exam topics, focusing on hypertensive crises.

Antianxiety Drugs:

Classification:

1. Benzodiazepines:

- Examples: Diazepam, Lorazepam, Alprazolam.
- Mechanism: Potentiate the action of GABA by binding to the GABA_A receptor, increasing the frequency of chloride channel opening, leading to CNS depression.
- Uses: Anxiety, insomnia, muscle relaxation, status epilepticus, alcohol withdrawal.
- Adverse Effects: Sedation, dependence, tolerance, withdrawal symptoms (e.g., rebound anxiety, seizures), respiratory depression when combined with other CNS depressants.

Key Exam Point:

- Benzodiazepines are used for acute anxiety, but long-term use is associated with dependence and tolerance.

2. Non-Benzodiazepine Anxiolytics:

Buspirone:

- Mechanism: Partial agonist at serotonin 5-HT1A receptors.
- Uses: Generalized anxiety disorder (GAD), but takes 2–4 weeks for full effect.
- Adverse Effects: Dizziness, headaches, but no sedation or dependence.

Key Exam Point:

- Buspirone is a non-sedating anxiolytic that does not cause dependence, unlike benzodiazepines.

3. Antidepressants for Anxiety:

- SSRIs and SNRIs are commonly used for long-term management of anxiety disorders (GAD, panic disorder, social anxiety disorder).

Key Points for Exams:

- Benzodiazepines are the most common drugs for acute anxiety but are associated with dependence and withdrawal symptoms.
- Buspirone is a non-sedating option for chronic anxiety management.

34. Opioid Analgesics and Antagonists

Opioids are the most potent class of analgesics used to manage moderate to severe pain, especially in palliative care.

Classification:

1. Natural Opioids: Morphine, Codeine.

2. Semi-synthetic Opioids: Oxycodone, Hydromorphone.

3. Synthetic Opioids: Fentanyl, Methadone, Tramadol.

- Mechanism of Action:
    - Opioids act primarily on mu (μ) receptors in the CNS to inhibit the transmission of pain signals by:
        - Decreasing presynaptic calcium influx, thereby reducing neurotransmitter release (e.g., glutamate, substance P).
        - Increasing postsynaptic potassium efflux, hyperpolarizing the membrane and reducing neuronal excitability.
- Effects:
    - 1. Analgesia: Effective in treating severe pain.
    - 2. Euphoria: Due to activation of the reward pathway, leading to potential abuse.
    - 3. Respiratory Depression: The main cause of death in opioid overdose, due to reduced brainstem sensitivity to CO2.

    - 4. Sedation: Synergistic with other CNS depressants.
    - 5. Miosis: Pinpoint pupils, a classic sign of opioid use.
    - 6. Cough Suppression: Mediated by suppression of the medullary cough center (e.g., Codeine).
    - 7. Constipation: Opioids reduce GI motility through action on the enteric nervous system.
- Adverse Effects:
    - Acute: Respiratory depression, sedation, nausea, vomiting, constipation.
    - Chronic: Tolerance, dependence, addiction, hyperalgesia.
- Overdose Management:
    - Naloxone: A pure opioid antagonist that reverses opioid overdose by competitively binding to opioid receptors.
    - Supportive care: Oxygen, ventilation.
- Opioid Antagonists:
    - Naloxone: Short-acting, used in emergency opioid overdose situations.
    - Naltrexone: Long-acting, used for maintenance therapy in opioid addiction.

Key Points for Exams:

- The respiratory depressant effects of opioids and the role of Naloxone in overdose reversal are crucial to understand.
- Morphine is commonly used in palliative care but has a high abuse potential due to its euphoric effects.
- Tolerance develops to most opioid effects except constipation and miosis

35. CNS Stimulants and Cognition Enhancers

CNS stimulants are used to treat conditions like ADHD and narcolepsy, while cognition enhancers are used in dementia.

CNS Stimulants:

1. Amphetamines:

- Examples: Dextroamphetamine, Methamphetamine.
- Mechanism: Increase the release of dopamine and norepinephrine by reversing their transporters (DAT and NET).
- Uses: ADHD, narcolepsy.
- Adverse Effects: Insomnia, hypertension, weight loss, increased risk of substance abuse.

2. Methylphenidate:

- Mechanism: Blocks the reuptake of dopamine and norepinephrine, increasing their levels in the synapse.
- Uses: ADHD.
- Adverse Effects: Similar to amphetamines, including anxiety, agitation, and insomnia.

3. Modafinil:

- Mechanism: Promotes wakefulness by increasing histamine and orexin levels in the hypothalamus.
- Uses: Narcolepsy, shift work sleep disorder.
- Adverse Effects: Headache, dizziness, and nausea, but has a lower abuse potential compared to amphetamines.

Cognition Enhancers:

1. Cholinesterase Inhibitors:

- Examples: Donepezil, Rivastigmine, Galantamine.
- Mechanism: Inhibit acetylcholinesterase, increasing acetylcholine levels in the brain, which is deficient in Alzheimer's disease.
- Uses: Mild to moderate Alzheimer's disease.
- Adverse Effects: Nausea, vomiting, diarrhea, bradycardia.

2. NMDA Receptor Antagonist:

- Example: Memantine.
- Mechanism: Inhibits NMDA receptors, reducing glutamate-mediated excitotoxicity, which contributes to neurodegeneration in Alzheimer's disease.
- Uses: Moderate to severe Alzheimer's disease.
- Adverse Effects: Dizziness, confusion, and hallucinations.

Key Points for Exams:

- CNS stimulants like Amphetamines and Methylphenidate are first-line for ADHD.
- Cholinesterase inhibitors are essential for symptomatic management in Alzheimer's, while Memantine is added in later stages.
- Abuse potential and long-term effects of stimulants are frequently tested topics.