Unit-4
Pharmacology-I

B.Pharma 4st Sem Notes

UNIT- IV

Pharmacology of drugs acting on central nervous system

- Neurohumoral transmission in the C.N.S. special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.
- General anesthetics and pre-anesthetics.
- Sedatives, hypnotics and centrally acting muscle relaxants.
- Anti-epileptics
- Alcohols and disulfiram

Pharmacology of drugs acting on central nervous system

Neurohumoral transmission in the C.N.S:

- Neurotransmitters are chemical messenger that transmit signals from a neuron to a target cell across a synapse.
- Target cell may be a neuron or some other king of cell like a muscle or gland cell.
- Necessary for rapid communication in synapse.
- Neurotransmitters are packaged into synaptic vesicle presynaptic side a synapse.

1. Some important neurotransmitters and their roles include:

- **Gamma-aminobutyric acid (GABA):** Acts as the primary inhibitory neurotransmitter, reducing neuronal excitability. Drugs that enhance GABAergic activity, such as benzodiazepines and barbiturates, have sedative, anxiolytic, and muscle-relaxant effects.
- **Glutamate:** Functions as the primary excitatory neurotransmitter in the CNS. Drugs that modulate glutamatergic activity may have effects on cognition, memory, and synaptic plasticity.
- **Glycine:** Acts as an inhibitory neurotransmitter in the spinal cord and brainstem, playing a role in motor control and sensory processing.
- **Serotonin (5-HT):** Regulates mood, appetite, sleep, and various other functions. Drugs that affect serotonin transmission are used in the treatment of depression, anxiety, and other psychiatric disorders.
- **Dopamine:** Involved in reward, motivation, motor control, and other functions. Drugs that modulate dopamine activity are used in the treatment of Parkinson's disease, schizophrenia, and other conditions.

General anesthetics:

- General anaesthetics (GAS) are drugs which produce reversible loss of all sensation and consciousness.

The cardinal features of general anesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

Stage of General anaesthetics:

- General anaesthetics cause an irregularly descending depression of the CNS.

- The higher functions are lost first and progressively lower areas of the brain are involved but in the spinal cord lower segments are affected somewhat earlier than the higher segments.
- The description of these stages still serves to define the efforts of light and deep anesthesia.

Important features of different stages are -

Stage I

- Analgesia state: Patient is conscious and rational, with decreased perception of pain.

Stage-II

- Delirium stage: Patient is unconscious; body responds reflexively; irregular breathing pattern with breath holding.

Stage-III

- Surgical anesthesia: Increasing degrees of muscle relaxation; unable to protect airway.

Stage IV

- Medullary depression: There is depression of cardiovascular and respiratory centers.

Properties of an ideal anesthetic:

A. For the patient

- It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. For the surgeon

- It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and non-explosive so that cautery may be used.

C. For the anesthetist

- Its administration should be easy, controllable and versatile.
- Margin of safety should be wide-no fall in BP. Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anesthesia should be possible.
- It should be cheap, stable and easily stored. It should not react with rubber tubing or soda lime.

Classification of General anaesthetics:

- **Inhalational**
  - **Gas-** Nitrous Oxide
  - **Volatile Oil Liquid-** Halothane
- **Parenteral anaesthetic**
  - **Benzodiazepines-** Diazepam, Lorazepam
  - **Opioid Analgesia-** Remifentanil,
  - **Dissociative Analgesia-** Ketamine

Mechanism of General Anesthesia:

- General anesthetics, particularly, inhibit the presynaptic voltage-gated sodium channels in glutamatergic synapse, which inhibits the excitation of the neuron by blocking the release of presynaptic neurotransmitters.

Halothane (Fluothane):

- It is a volatile liquid with sweet odor, nonirritant and non in flammable. Solubility in blood is moderate induction is reasonably quick and pleasant.
- It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.
- Halothane causes direct depression of myocardial contractility by reducing intracellular Ca2+ concentration. Moreover, sympathetic activity fails to increase reflex.
- Cardiac output is reduced with deepening anesthesia.

Pharmacology Action:

- Halothane causes general anaethesia due to its actions on multiple ion channels, which ultimately depresses nerve conduction, breathing, cardiac contractility.
- Its immobilizing effects have been attributed to its binding to potassium channels in cholinergic neurons.
- Halothane's effect are also likely due to binding to NMDA and calcium channels, causing hyperpolarization.

Benzodiazepines (BZDs):

- In addition to pre-anaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'.

Pharmacological actions:

- Benzodiazepines Benzodiazepines work by enhancing a very important neurotransmitter called GABA (gammaaminobutyric acid) at the GABA A receptor.
- This results in the sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.

Isoflurane:

- It is a structure derivative of enflurance. If is also a muscle relaxant is a potent coronary vasodilator.

Nitrous Oxide:

- It has a mild sweetish smell. It is used to maintain surgical anaesthesia with 50% oxygen and other volatile anaesthetics like halothane, isoflurane and a muscle relaxant if required.

Pre-Anesthetics:

- Pre-anesthesia drug that is given to a patient before anesthesia for surgery.
- The aim of pre-anesthetics medication is to ensure comfort to the patient and minimize adverse effects of anaesthesia.
- Pre-anesthetic drugs are prescribed by doctors to patients for the following purposes:
- Sedation, sedation, calming and reducing anxiety of the patient. Reduce pain, reduce metabolism, reduce harmful reflexes.

Sedative- Hypnotics:

- In addition to BZDs, promethazine is widely used. It is an antihistamine with sedative antiemetic, and anticholinergic actions.
- It cause negligible respiratory depression and useful of children.

Opioid analgesics:

- Morphine can pethidine is used. Fentanil may also be used.

Sedatives, hypnotics and centrally acting muscle relaxants.

Sedative & Hypnotic

Sedatives:

- A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced.
- Sedation refers to decreased responsiveness to stimulation; is associated with some decrease in alertness, ideation and motor activity.

Or

- **Sedative:-** These are the drug which reduce excitement or slow down the current physical activity.

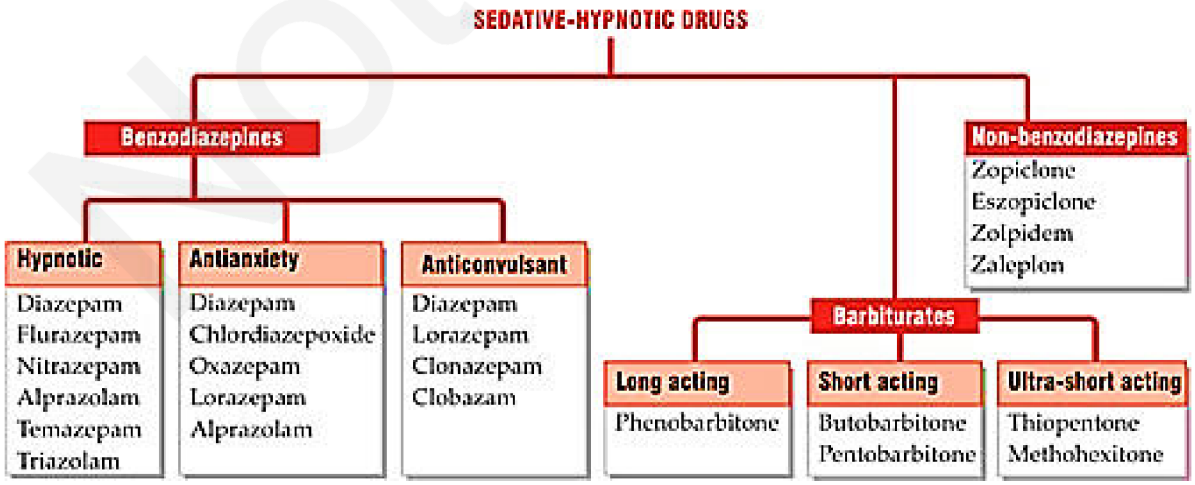
Hypnotics:

- A drug that induces and/or maintains sleep, similar to normal arousable sleep.
- This is not to be confused with 'hypnosis' meaning a trans-like state in which the subject becomes passive and highly suggestible.

Or

- Hypnotic:- These are the agent that induce sleep resembling natural sleep.

Classification of Sedative and Hypnotics



Barbiturates:

- Barbiturates are substituted derivatives of barbituric acid. These possess sedative hypnotic properties and anticonvulsant sedative action.

Mechanism of action:

- Barbiturates act on the channel modulatory site of $GABA_A$ receptor and potentiate the GABA mediated inhibitory effects by increasing the duration of chloride channel opening.
- At high doses, barbiturates directly

Method of Action:

- Barbiturates act on the channel modulatory site of $GABA_A$ receptor and potentiate the GABA mediated inhibiting effects by increasing the duration of Chloride channel opening.
- At high doses barbiturates directly increase chloride ion conductance and exhibit GABA mimetic action and not a GABA facilitatory action.

Pharmacokinetics:

- The rate of absorption of barbiturates depends on their lipid solubility.
- They are widely distributed depending on lipid solubility and regional blood flow.
- They are metabolized bath by phase-I and Phase II processes.
- Phase-I involves microsomal oxidation while phase-II involves glucuronyl conjugation.
- The are excreted through urine but are readily reabsorbed from renal tubules.

Pharmacological Effects:

- The ultra-short acting barbiturates exhibit dose dependent CNS depressant action.
- The long acting barbiturates possess sedative anticonvulsant actions.
- They may show hyperalgesia action ie, they may increase reaction to painful stimuli.
- Sedative – Hypnotic doses have no effect on cardiovascular system.
- High Dose decrease blood pressure heart rate and depress myocardium.

Uses:

- Used in Sedative and Hypnotics.
- To treat Hyperbilirubinemia.
- This medication is a benzodiazepine, prescribed for anxiety.
- It is also used for muscle spasms and seizures.
- It works by acting on receptors in the brain called GABA receptors.
- Chronic insomnia
- Anxiety

Benzodiazepines (BZDs):

These were introduced after barbiturates they are preferred drugs for hypnotic and sedative activities because…

a. BZDs produce a lower degree of neuronal depression than barbiturates.
b. Hypnotic doses do not affect respiration or cardiovascular functions.
c. BZDs have practically no action on other body systems. Only on I.V injection the BP falls & cardiac contractility decreases.
d. BZDs cause less distortion of sleep architecture.

Mechanism of Action:

- Benzodiazepines are a group of CNS depressants which induce feelings of calm (anxiolysis), drowsiness and sleep. They act by facilitating the binding of the inhibitory neurotransmitter GABA at various GABA receptors throughout the CNS.

Uses:

- To treat insomnia.
- To Treat Anxiety neuroses
- Treatment of alcohol withdrawal.
- As anti-consultants.

Non-benzodiazepine Hypnotics:

- Non-benzodiazepine hypnotics, also sometimes referred to as "Z-drugs" due to many of their names starting with "Z", are a class of medications used to treat insomnia. Unlike benzodiazepines, they are not chemically related but share some similar mechanisms of action and effects.

Mechanism of Action:

- Non-benzodiazepine hypnotics work by enhancing the action of a brain chemical called gamma-aminobutyric acid (GABA). GABA acts as a calming neurotransmitter in the central nervous system, and by increasing its activity, these medications promote sleepiness.

Uses:

- The primary use of non-benzodiazepine hypnotics is for the short-term treatment of insomnia, particularly difficulty falling asleep (sleep latency).

They may be preferred over benzodiazepines due to potentially:

- Less disruption of normal sleep architecture
- Reduced risk of daytime drowsiness

- Lower risk of dependence and abuse
- Milder withdrawal symptoms

Centrally Acting Muscle relaxants:

- Centrally acting muscle relaxants, also known as spasmolytics, target the central nervous system (CNS) to reduce muscle tone and alleviate muscle spasms.
- These drugs reduce skeletal muscle tone by a selective action in the cerebrospinal axis without altering consciousness.
- Spasticity is characterized by an increase in tonic stretch reflexes and flexor muscle spasm along with muscle weakness.
- It is associated with disease like cerebral palsy and multiple sclerosis.

Benzodiazepine group:

- Benzodiazepines are a class of psychoactive drugs that are commonly prescribed for their anxiolytic (anti-anxiety), sedative, hypnotic (sleep-inducing), muscle relaxant, and anticonvulsant properties.
- Benzodiazepines exert their effects by enhancing the activity of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system.
- They are among the most widely prescribed medications globally due to their effectiveness in treating various conditions.

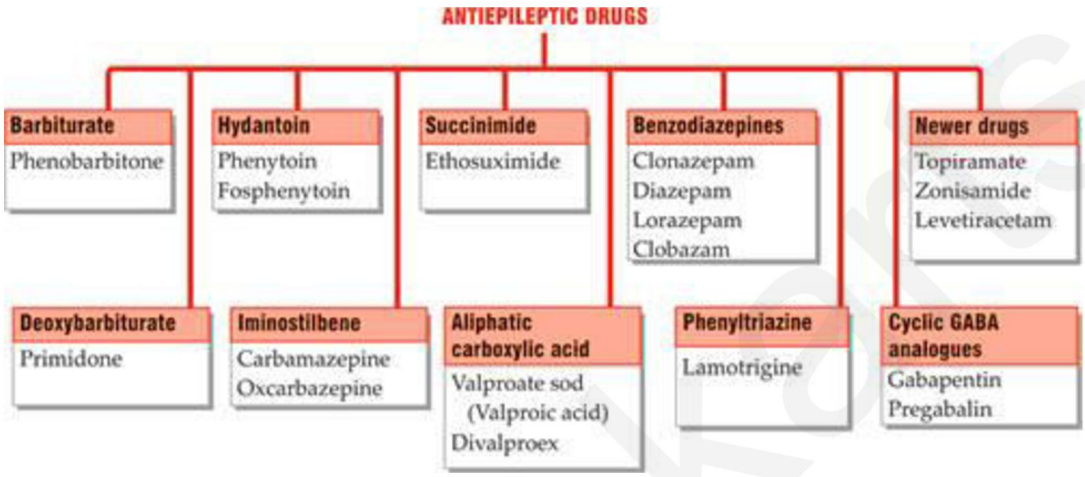
GABA derivative:

- Baclofen is an orally active GABA-mimetic drug which acts as a agonist on $GABA_B$ receptors.
- The receptors are G-protein coupled receptors which hyperpolarise neurons by increasing potassium ion conductance and reducing calcium ion conductance.
- At spinal level it inhibits both monosynaptic and polysynaptic responses.
- It is used to relieve painful spasticity and reduces pain associated with spastic conditons.

Anti-epileptics:

- Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures.
- Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain.

Classification of Anti-epileptics:



Phenytoin

- Phenytoin is in a class of medications called anticonvulsants.
- Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system.
- It works by decreasing abnormal electrical activity in the brain.

Pharmacological actions of Phenytoin

- Phenytoin is often described as a non-specific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes.
- More specifically, phenytoin prevents seizures by inhibiting the positive feedback loop that results in neuronal propagation of high frequency action potentials.

Alcohols and disulfiram

Alcohols:

Alcohols are a class of organic compounds characterized by the presence of a hydroxyl (-OH) group attached to a carbon atom. They can be classified based on the number of -OH groups they contain:

- **Monohydric alcohols**: Contain one -OH group (e.g., methanol, ethanol).
- **Polyhydric alcohols**: Contain multiple -OH groups (e.g., glycerol, ethylene glycol).

Pharmacological Effects of Alcohol:

Pharmacokinetics:

- Ethanol is rapidly absorbed from GIT.
- It crosses BBB as well as placental barrier, but the concentration in brain is very close concentration to that in blood.
- About 95% of absorbed alcohol is metabolized and remaining 5% is excreted through breath urine and sweat.
- A sizable fraction of ethanol is cleared by first-pass hepatic metabolism which follows zero-order kinetics.
- Ethanol is first metabolized to acetaldehyde and then to acetic acid.

Effect on organs: CNS, Heart, Smooth muscles and other effects

1. **Central Nervous System (CNS):**
    - Alcohol is a depressant that affects the central nervous system. It slows down brain function, altering neurotransmitter levels and impairing cognitive and motor skills.
    - Short-term effects include slurred speech, impaired judgment, decreased inhibition, and slowed reflexes.
    - Long-term alcohol consumption can lead to neurological disorders such as Wernicke-Korsakoff syndrome, characterized by memory loss, confusion, and coordination problems.
2. **Heart:**
    - Acute alcohol consumption can lead to temporary increases in heart rate and blood pressure.
    - Long-term heavy drinking is associated with an increased risk of cardiovascular diseases such as hypertension, arrhythmias, cardiomyopathy, and stroke.
    - Chronic alcohol abuse weakens the heart muscle, leading to conditions like alcoholic cardiomyopathy, which can ultimately result in heart failure.

3. **Liver:**
    - The liver metabolizes alcohol, but excessive alcohol consumption can lead to liver damage, ranging from fatty liver to more severe conditions like alcoholic hepatitis and cirrhosis.
    - Fatty liver occurs when fat accumulates in liver cells due to alcohol metabolism. It is reversible with abstinence.
    - Alcoholic hepatitis is inflammation of the liver caused by excessive alcohol consumption, leading to symptoms like jaundice, abdominal pain, and liver failure.
    - Cirrhosis is the late stage of liver disease characterized by irreversible scarring of the liver tissue, impaired liver function, and an increased risk of liver cancer.
4. **Pancreas:**
    - Alcohol can cause inflammation of the pancreas, known as pancreatitis. Acute pancreatitis is a sudden and severe condition, while chronic pancreatitis develops over time and can lead to permanent damage.
    - Pancreatitis can cause abdominal pain, nausea, vomiting, and potentially life-threatening complications if left untreated.
5. **Gastrointestinal Tract:**
    - Alcohol irritates the lining of the stomach and intestines, leading to inflammation and an increased risk of conditions like gastritis, ulcers, and gastrointestinal bleeding.
    - Chronic heavy drinking is associated with an increased risk of digestive cancers, including those of the esophagus, stomach, and colon.
6. **Muscles:**
    - Alcohol affects smooth muscles, leading to relaxation and dilation of blood vessels, which contributes to the flushing and warmth sensation often experienced after drinking.
    - Prolonged alcohol use can impair muscle function and contribute to muscle weakness and wasting.
7. **Immune System:**
    - Chronic alcohol abuse weakens the immune system, making individuals more susceptible to infections, including respiratory infections and pneumonia.
    - Long-term alcohol consumption can impair the body's ability to produce and utilize immune cells, leading to increased susceptibility to diseases and slower wound healing.

Disulfiram:

Disulfiram is a medication used to help manage alcohol dependence.

Mechanism:

- It inhibits the enzyme aldehyde dehydrogenase, which is responsible for breaking down acetaldehyde, a byproduct of alcohol metabolism.
- With this enzyme blocked, acetaldehyde levels rise in the bloodstream, leading to a disulfiram-alcohol reaction.

Adverse Effects:

- The reaction caused by disulfiram and alcohol consumption can range from mild to severe and may include symptoms such as flushing, nausea, vomiting, headache, sweating, chest pain, palpitations, and hypotension.
- In severe cases, it can lead to respiratory distress, cardiovascular collapse, or even death in rare instances.

Use in Alcohol Dependence Treatment:

- Disulfiram is used as a deterrent to drinking in individuals who have difficulty abstaining from alcohol.