UNIT-IV

Central Nervous System (CNS)

Drugs Affecting The CNS

Drugs acting on CNS may be CNS depressants or CNS stimulants. Depressants are more important pharmacologically and therapeutically than stimulants. Most drugs that affect the CNS act by altering some step in the neurotransmission process.
Drugs affecting the CNS may act presynaptically by influencing the production, storage, release or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors.

However, we will discuss prototype drugs used in different CNS related diseases.

1. **Neurodegenerative Diseases**
2. **Anxiolytic And Hypnotic Drugs**
3. **CNS Stimulants**
4. **Antidepressant**
5. **Neuroleptics Drugs**
6. **Antiepileptic Drugs**

Neurodegenerative Diseases

Levodopa (Antiparkinson)

Levodopa is a metabolic precursor of dopamine. It decreases the rigidity, tremors and other symptoms of Parkinsonism. Because Parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to restore the dopamine deficiency.

Available Brands in the Market

Larodopa Tab. (Levodopa)

Mechanism Of Action

Dopamine itself does not cross the blood brain barrier, but its precursor Levodopa is actively transported into the CNS and is converted to dopamine in the brain.

Therapeutic Uses

Levodopa in combination with carbidopa is currently available to treat Parkinson's disease. It reduces the severity of the disease for the first few years of treatment.

Pharmacokinetics

The drug is absorbed rapidly from the small intestine. Levodopa should be taken on an empty stomach. Levodopa has an extremely short half-life (1 to 2 hours).

Adverse Effects

- **Peripheral Effects**

Trachycardia, Nausea, vomiting, hypotension, brownish color of saliva and urine.

- **CNS Effect**

Abnormal involuntary movements, mood change, depression

Anxiolytic And Hypnotic Drugs

Benzodiazepines

Barbiturates
➔Phenobarbitone

Other Anxiolytic drugs
➔Buspirone

Available Brands in the Market

Xanax Tab. (Benzodiazpines)
Valium Tab. (Benzodiazpines)
Busron Tab. (Buspirone)
Phenobarbitone Tab. (Phenobarbitone)

Benzodiazepines

Benzodiazepines are the most widely used Anxiolytic drugs. These are safer and effective than others like barbiturates.

Mechanism Of Action

The targets of benzodiazepine actions are GABAa receptors. Benzodiazepine modulate the GABA effects by binding to a specific site, these binding sites are sometimes labeled benzodiazepine receptors.

Actions Of Benzodiazepine

Reduction Of Anxiety
At low doses, the benzodiazepines are Anxiolytic. They reduce anxiety by selectively enhancing GABAergic transmission in neurons.

Sedative And Hypnotic Action
Benzodiazepines also have sedative properties and some can produce hypnosis (artificially produced sleep) at higher doses.

Muscle Relaxant
At high doses, the benzodiazepines relax the skeletal muscle.

Therapeutics Uses

Anxiety Treatment
Benzodiazepines are effective for the treatment of the anxiety disorder, social anxiety disorder, performance anxiety etc. The drug should not be used to reduce the normal stress of everyday life. They should be used for short periods of time.

Muscular Disorders
These agents are useful in the treatment of skeletal muscle spasms.

Seizures
These agents are also used in the treatment of certain types of epilepsy.

Sleep Disorders
Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. These agents are also used in the treatment of insomnia.

Pharmacokinetics

The benzodiazepines are lipophilic and they are rapidly and completely absorbed after oral administration and distribute throughout the body.

Adverse Effects
Drowsiness and confusion early morning insomnia

Barbiturates

Mechanism Of Action
The sedative-hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAnergic transmission.

Actions

Depression of CNS
At low doses, the barbiturates produce sedation (Have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose.

Respiratory Depression
Barbiturates suppress the hypoxic and chemoreceptor response to CO_2 and over dosage is followed by respiratory depression and death.

Therapeutic Uses

Anesthesia
Selection of a barbiturate is strongly influenced by the desired duration of action. The ultra short-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

Anticonvulsant
Barbiturates are used in long-term management of seizures, status epilepticus, and eclampsia.

Anxiety
Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.

Pharmacokinetics
Barbiturates are absorbed orally and distributed widely throughout the body. These agents are metabolized in the liver, and inactive metabolites are excreted in urine.

Adverse Effects
Drowsiness, impaired concentration, and mental and physical sluggishness tremors, anxiety, weakness, restlessness, nausea and vomiting, death can occur due to overdoses for many decades.

Buspirone (Other Anxiolytic Agents)

Buspirone is useful in the treatment of generalized anxiety disorder. Buspirone lack the anticonvulsant and muscle relaxant property. Most common adverse effects are headache, dizziness, and nervousness.

CNS Stimulants

Large number of drugs may stimulate different parts of brain and in large doses they may stimulate all parts of brain. CNS stimulants have diverse clinical uses and are important as drugs of abuse.

Following prototype drugs are used as CNS stimulants.

Psychomotor Stimulants
➔Cocaine
➔Nicotine

Hallucinogens
➔Lysergic Acid Diethylamide (LSD)

Available Brands in the Market

Coramin-G Cap. (Nicotine)

Cocaine (Psychomotor Stimulants)

Cocaine is a widely available and highly addictive drug that is currently abused daily by more than 3million people.

Mechanism Of Action

Cocaine inhibits the reuptake of monoamines (nor epinephrine, serotonin and dopamine). The inhibition of reuptake of monoamine by the cocaine potentiates and prolongs the CNS and peripheral action of these monoamines.

Actions

CNS

The behavioral effects of cocaine result from powerful stimulation of cortex and brainstem. It also causes tremors and convulsions.

Hyperthermia

Hyperthermia can also cause by cocaine.

Therapeutics Uses

Cocaine has a local anesthetic action. Cocaine is applied topically as a local anesthetic during eye, ear, nose and throat surgery. Cocaine is the only local anesthetic that causes vasoconstriction.

Pharmacokinetics

Cocaine is often self-administered by chewing, intranasal, smoking or intravenous onset of action is most rapid.

Adverse Effects

Anxiety, depression, seizures, cardiac aarrhythmias.

Nicotine (Psychomotor Stimulants)

Nicotine is the active ingredient in tobacco. It is most widely used CNS stimulant.

Mechanism Of Action

In low doses, nicotine causes ganglionic stimulation by depolarization. At high doses, nicotine causes ganglionic blockade.

Action

CNS
Nicotine is highly lipid soluble and readily cross the blood brain barrier. It improves attention, learning, problem solving and reaction time.

Peripheral Effects
The peripheral effects of nicotine are complex. It increases blood pressure and heart rate. Use of tobacco is harmful in hypertensive patients.

Pharmacokinetics
Because nicotine is highly lipid soluble absorption readily occur via oral mucosa, lungs, GIT and skin. Clearance of nicotine involves metabolism in the lung and the liver and urinary excretion.

Adverse Effects
High blood pressure trachycardia, diarrhea, tremors

Hallucinogens (Lysergic Acid Diethylamide, LSD)

Mechanism Of Actions
Multiple sites in the CNS are affected by lysergic acid diethylamide (LSD). The drug shows serotonin agonist activity at presynaptic receptor in the midbrain.

Pharmacological Effects
Activation of the sympathetic nervous system causes pupillary dilation, increased blood pressure and increased body temperature.

Adverse Effects
Adverse effects include hyper-reflexia, nausea and muscular weakness.

Antidepressants

Depression is a serious disorder and its symptoms are intense feeling of sadness, hopelessness and inability to experience pleasure in usual activities.

Here is the list of Prototype Antidepressant

Selective Serotonin Re-uptake Inhibitors
➔Fluoxetine

Serotonin/norepinephrine Re-uptake Inhibitors
➔Duloxetine

Atypical Antidepressant
➔Mirtazapine

Tricyclic Antidepressants
➔Amitriptyline

Monoamine Oxidase Inhibitors
➔Phenelzine

Available Brands in the Market

Depex Tab. (Fluoxetine)
Depricap Tab. (Fluoxetine)
Dulan Tab. (Duloxetine)
Zeubar Tab. (Duloxetine)
Mirtazep Tab. (Mirtazapine)
Mipine Tab. (Mirtazapine)
Tryptanol Tab. (Amitriptyline)

Fluoxetine (Selective Serotonin Re-Uptake Inhibitors)

Selective serotonin re-uptake inhibitors are a group of antidepressant drugs that specifically inhibit serotonin uptake.

Mechanism Of Action

The SSRI block the reuptake of serotonin, leading to increased concentration of the neurotransmitter in the synaptic cleft and increased postsynaptic neuronal activity

Therapeutic Uses

SSRI are used for the treatment of depression. It also used for generalized anxiety disorder, panic disorder.

Pharmacokinetics

All SSRI are well absorbed after oral administration. All agents are well distributed. Their half-life range between 16 to 36 hours

Adverse Effects

Headache, sweating, sleep disturbance, sexual dysfunction

Duloxetine (Serotonin/ Norepinephrine Re-Uptake Inhibitors)

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It metabolized in the liver. Duloxetine should not be administered to patients with hepatic insufficiency. Metabolites are excreted in the urine. Food delays the absorption of the drug. The half-life is 12 hours.

Mirtazapine (Atypical Antidepressants)

This drug enhances serotonin and norepinephrine neurotransmission. Via mechanism related to its ability to block presynaptic ALPHA2 receptors. It does not cause the antimuscarinic side effects. It increased appetite and weight gains frequently occur. Mirtazapine is sedating, which may be used in sleeping disorder.

Amitriptyline (Tricyclic Antidepressants)

Mechanism Of Action

The Tricyclic antidepressants block serotonin and norepinephrine reuptake into the neuron.
Tricyclic antidepressants also block serotonergic, alpha adrenergic, histaminic and muscarinic receptors.

Actions

Tricyclic antidepressants elevate mood, improve mental alertness, and increase physical activity.

Therapeutics Uses

Tricyclic antidepressants are effective in treating moderate to severe major depression. Some patients with panic disorder also respond to these agents.

Pharmacokinetics

Tricyclic antidepressants are well absorbed upon oral administration because of their lipophilic nature. They are widely distributed in body. These drugs have variable half-lives from 4 to 17 hours metabolism occurs in liver and excreted from urine.

Adverse Effects

Blurred vision, dry mouth, urinary retention, and constipation

Phenelzine (Monoamine Oxidase Inhibitors)

Monoamine oxidase (MAO) is mitochondrial enzyme found in nerve and other tissues. In the neuron, MAO functions a safety valve as MAO inactivate any excess neurotransmission.

Mechanism Of Action

Most MAO inhibitors form a stable complex with the enzyme to increase the storage of norepinephrine. Serotonin and dopamine within the neuron.

Actions

These drugs are used to inhibit the action of MAO and enhance the activity of neurotransmitters.

Therapeutics Uses

MAO inhibitors are used for the treatment of depression. Patients with low psychomotor activity may also use these agents.

Pharmacokinetics

These drugs are well absorbed after oral administration. MAO inhibitors are metabolized and excreted rapidly in the urine.

Adverse Effects

Headache, stiff neck, tachycardia, hypertension are common adverse effects of MAO inhibitors.

Neuroleptics Drugs OR Antipsychotic Drugs

Neuroleptics drugs are used primarily to treat schizophrenia. They are also used in other psychotic states such as manic states.

Schizophrenia

Schizophrenia is caused by increased dopamine activity in mesolimbic pathway and mesocortical pathway. During schizophrenia, glutamic acid activity in mid brain is decreased and now there is a new emergence of role of serotonin in the development of schizophrenia.

Prototype Neuroleptics Drugs

Typical Neuroleptics (Low Potency)
➔Chlorpromazine

Typical Neuroleptics (High Potency)
➔Haloperidol

Atypical Neuroleptics
➔Clozapine

Available Brands in the Market

Chlorotil Tab. (Chlorpromazine)
Halodol Tab. (Haloperidol)
Clozaril Tab. (Clozapine)

Here is the general introduction of Neuroleptics drugs

Mechanism Of Action

Dopamine Receptor Blocking In The Brain

All of the older and new Neuroleptics drugs block dopamine receptor in the brain and the periphery. The Neuroleptics drugs bind to these receptors to varying degrees.

Serotonin Receptor Blocking Activity In The Brain

Some of these drugs also inhibit serotonin receptors.

Actions

Antipsychotic Actions

All of the Neuroleptics drugs can reduce the symptoms of schizophrenia by blocking dopamine receptors in the brain.

Antiemetic Effects
Most of the drugs have antiemetic effects.

Antimuscrinic Effects
Some of the Neuroleptics produce anticholinergic effects

Therapeutics Uses
The Neuroleptics are considered to be the only efficacious treatment for schizophrenia.

Prevention Of Severe Nausea And Vomiting
Old Neuroleptics are useful in the treatment of drug-induced nausea and vomiting.

Other Uses
The Neuroleptics drugs can be used as tranquilizers. These drugs with combination also used for treatment of chronic pain and severe anxiety.

Pharmacokinetics
After oral administration the Neuroleptics show variable absorption. These agents readily pass into the brain.

Adverse Effects
Movement disorder, tremors, constipation, urinary retention, confusion, sexual dysfunction

Antiepileptic Drugs

Epilepsy

In epilepsy there is a sudden excessive and rapid discharge in grey matter of the brain. Epilepsy is not a single entity it is collection of different seizure types and syndromes originating from several mechanisms. This abnormal electrical activity may result in variety of events including loss of consciousness, abnormal movements, and odd behavior.
Seizures have been classified into two groups.

1. **Partial or focal seizures**
2. **Generalized seizures**

Partial Or Focal Seizures
Partial seizures involve one portion of the brain. Partial seizures may progress, becoming generalized seizures.

Generalized Seizures
Generalized seizures may begin locally, producing abnormal electrical discharge throughout both hemisphere of the brain.

Mechanism Of Action Of Antiepileptic Drugs
These drugs inhibit the neuronal discharge or its spread, by altering cell permeability to ions and by enhancing the activity of natural inhibitory neurotransmitter such as GABA.

Prototype Antiepileptic Drugs

Benzodiazepines
(See In Anxiolytic And Hypnotic Drugs)

GABA Analogues
➔Gabapentin

Phenytoin

Available Brands in the Market

Xanax Tab. (Benzodiazpines)
Valium Tab. (Benzodiazpines)
Neogab Tab. (Gabapentin)
Epinat Tab. (Phenytoin)

Gabapentin (GABA Analogues)

Gabapentin is an analog of GABA. However it does not act at GABA receptors nor enhance GABA actions, nor it converted into GABA. Its precise mechanism of action is not known. Gabapentin does not bind to plasma protein and is excreted unchanged through kidneys.

Phenytoin

Mechanism of Action
Phenytoin blocks voltage-gated sodium channels. At very high concentration, Phenytoin can block voltage-dependent calcium channel.

Therapeutic Uses
Phenytoin is used in the treatment of partial seizures and generalized seizures.

Adverse Effects
The side effects may include gum hypertrophy, skin rashes.