CHAPTER 10

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

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INTRODUCTION

To facilitate the understanding of the pharmacological and unwanted effects of CNS drugs, the physiological functions of the main CNS neurotransmitters are discussed briefly.

Noradrenaline: Noradrenergic transmission is important in control of mood (functional deficiency resulting depression) controlling wakefulness, and alertness.

Dopamine: Dopamine is involved in motor control (Parkinsonism is caused by a lack of dopamine), has behavioural effects (excessive dopamine activity has been linked to schizophrenia), is involved in hormone release (prolactin, GH), and causes nausea and vomiting when present in the chemoreceptor trigor zone.

5-HT: Feeding behaviour, behavioural response (hallucinatory behaviour), mood and emotion control, body temperature control, and vomiting are all physiological functions associated with 5-HT pathways.

Acetylcholine (Ach): Arousal, learning, and short-term memory are all affected by Ach. Abnormalities in cholinergic pathways are linked to dementia and Parkinsonism.

GABA: It is an inhibitory neurotransmitter in the central nervous system

Glycine: is an inhibitory neurotransmitter that acts on the spinal cord's GABA-like receptor.

GENERAL ANESTHETICS

The physiological changes that occur during general anaesthesia include reversible loss of response to painful stimuli, loss of consciousness, and loss of motor and autonomic reflexes. The inhibition of reticular formation activity is linked to loss of consciousness. Inhalation or intravenous anaesthetics are used to administer general anaesthetics. They are divided into two categories based on how they are administered: inhalation and intravenous anaesthetics.

Anesthetics for inhalation

Halothane, nitrous oxide, enflurane, and ether are the main agents.

1. **Halothane:** Is the most widely used agent; it is highly lipid soluble and effective. If used frequently, it causes arrhythmia, hangovers, and a high risk of liver damage.

2. **Nitrous oxide:** Gas that is odourless and colourless. It has a quick onset of action and is an effective analgesic. Because of its low potency, it must be combined with other agents. It is relatively free of serious negative consequences.

3. **Enflurane:** Ether halogenated (similar to halothane). It is less toxic than halothane because it is poorly metabolised in the liver. When compared to halothane, it has a faster action and is less likely to accumulate in body fat. During induction and recovery from anaesthesia, it causes seizures.

4. **Ether:** It acts as an analgesic and a muscle relaxant. It's highly explosive, irritates the respiratory tract, and causes nausea and vomiting after surgery. It is currently not widely used.

INTRAVENOUS ANESTHETICS

Intravenous anaesthetics work much faster, causing unconsciousness in as little as 20 seconds after the drug reaches the brain from the injection site. These agents are used to induce anaesthesia before administering an inhalation agent. Thiopentone, etomidate, propofol, ketamine, and short-acting benzodiazepine are the most commonly used induction agents today (midazolam).

Thiopentone: It is a barbiturate with a high solubility in lipids. The drug enters tissues with a high blood flow (liver, kidneys, brain, etc.) quickly after intravenous administration and enters muscle more slowly. Due to the low blood flow to this tissue, uptake into body fat is slow, which could result in a prolonged effect if given repeatedly. It depresses the cardiovascular system.

Etomidate: When compared to thiopentone, it is more quickly metabolised and has a lower risk of cardiovascular depression. Etomidate suppresses the adrenal cortex, which has been linked to a higher risk of death in critically ill patients.

Ketamine: Dissociative anaesthesia is characterised by a marked sensory loss and analgesia, as well as amnesia and movement paralysis, without actual loss of consciousness. During recovery, ketamine causes dysphoria and hallucinations.

Benzodiazepines: In general anaesthetic procedures, diazepam, lorazepam, and midazolam are used. Benzodiazepines have a slower onset of central nervous system effects than intravenous barbiturates. Benzodiazepines not only prolong the recovery period after anaesthesia, but they also cause a high rate of amnesia for events that occurred after the drug was administered. Premedication and intraoperative sedation with benzodiazepines are useful in anaesthesia.

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Opioid analgesic anesthesia: Fentanyl and derivatives of fentanyl are commonly used for general anaesthesia in patients undergoing cardiac surgery.

Preanesthetic medication: It is the administration of drugs prior to the administration of an anaesthetic agent with the goal of making anaesthesia safer and more pleasant for the patient. Opioid analgesics, barbiturates, anticholinergics, antiemetics, and glucocorticoids are all commonly used drugs.

SEDATIVE AND HYPNOTIC DRUGS

Anxiolytic drugs are used to treat anxiety symptoms, whereas hypnotic medications are used to treat insomnia. Both purposes are served by the same drugs.

Classes of anxiolytic and hypnotic drugs: The main groups of the drugs are:

1. Benzodiazepines. The most common class of drugs is benzodiazepines, which are used as sedatives and hypnotics.
2. 5- HT_{1A} receptor agonist (e.g. buspirone). It is recently introduced anxiolytic.
3. Barbiturates (phenobarbitone). They are nowadays less commonly used as sedative- hypnotics.
4. Adrenoceptor antagonists (e.g. propranolol). They are used to treat anxiety that is accompanied by physical symptoms such as sweating, tremor, and tachycardia. They aren't used to induce sleep.
5. Miscellaneous drugs (chloral hydrate, paraldehyde, and diphenhydramine). These medications are rarely prescribed for anxiety or insomia.

Benzodiazepines

Orally administered benzodiazepines are well absorbed. They bind tightly to plasma proteins, but many of them accumulate in body fat over time (i.e. they are highly lipid soluble). The liver inactivates benzodiazepines, which are then excreted in the urine.

Short acting (flurazepam, triazolam), medium acting (alprazepam, lorazepam), and long acting compounds are classified according to their duration of action (diazepam, chlordiazepoxide, clonazepam).

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Pharmacodynamics

Act by binding to a specific regulatory site on the GABAA receptor, thereby amplifying GABA's inhibitory effects. Benzodiazepines have the following central nervous system effects:

1. Benzodiazepines have the following central nervous system effects
2. Sedation and sleep induction
3. Muscle tone and coordination are reduced.
4. Anti-convulsant properties.

Clinical Uses

- Treatment insomnia
- As anticonvulsants
- Anxiety
- Acute alcohol withdrawal
- Chronic muscle spasm and spasticity
- Preoperative mediations

Unwanted effects

- Acute overdosage causes toxic effects, which result in prolonged sleep.
- Drowsiness, confusion, amnesia, and impaired motor coordination are some of the unwanted effects that can occur during normal therapeutic use.
- Dependence and tolerance: Physical dependence is caused by pharmacokinetic and tissue tolerance. Stopping benzodiazepine treatment after weeks or months results in an increase in anxiety symptoms.

5 - HT_{1A} receptor agonist

Buspirone is a strong agonist for the 5-HT1A receptor. The effects of anxiolytics take days to weeks to manifest. Sedation, motor incoordination, or withdrawal symptoms are not caused by buspirone. Nausea, dizziness, headache, and restlessness are the most common side effects.

Barbiturates

They're non-selective CNS depressants that can cause anything from sedation to anxiety reduction to unconsciousness and death from respiratory and cardiovascular failure.

Barbiturates are less specific than benzodiazepines in that they enhance GABA action. They are strong inducers of hepatic drug metabolising enzymes, which means they are likely to cause drug interactions. More than benzodiazepines cause tolerance and dependence.

ANTIEPILEPTIC DRUGS

The episodic high frequency discharge of impulses by a group of neurons in the brain is linked to seizures.

Depending on the location and spread of the abnormal neuronal discharge, seizures can be partial or generalised. The majority of the symptoms are motor, sensory, or behavioural.

Partial seizures are frequently linked to brain damage, whereas generalised seizures occur for no apparent reason. Grand mal and petit mal seizures are two types of generalised seizures.

Mechanism of action

Anticonvulsant drugs work in two ways: they reduce cell membrane electrical excitability and they increase GABA-mediated synaptic transmission.

The important drugs used in the treatment of epilepsy are **phenytoin, carbamazepine, valproate, ethosuximide and phenobarbitone.**

Phenytoin

It is a commonly prescribed antiepileptic medication. It works against various types of partial and generalised seizures, but not absence seizures.

When taken orally, it is well absorbed. It is broken down by the liver. It is a liver enzyme inducer, which means it speeds up the metabolism of other drugs. Sedation, confusion, gum hyperplasia, skin rash, anaemia, nystagmus, and diplopia are the most common side effects.

Carbamazepine

It's a tricyclic antidepressant derivative. Its pharmacological action is similar to that of phenytoin, but it is primarily used to treat partial seizures. Trigeminal neuralgia and manic-depressive illness are also treated with it.

It increases the metabolism of phenytoin, warfarin, oral contraceptives, and corticosteroids by inducing liver microsomal enzymes.

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Sedation, mental disturbances, and water retention are all side effects of carbamazepine.

Valproate

Valproate is not related to the other antiepileptic drugs chemically. The action mechanism is unknown. In grand mal, partial, petit mal, and myoclonic seizures, it is used.

It has a low number of side effects, but it is potentially hepatotoxic. It has no sedative properties.

Ethosuximide

It is used to treat absence seizures and has fewer side effects.

Phenobarbitone

It is well absorbed and widely distributed after oral administration. Acidification of the urine promotes renal excretion. Because phenobarbitone stimulates liver enzymes, it speeds up the metabolism of many drugs, including oral contraceptives and warfarin.

Phenobarbitone is used in the same way as phenytoin in clinical practise. Sedation is the most significant side effect.

Benzodiazepines: Clonazepam and related compounds, such as clobazam, are antiepileptic drugs that are said to be relatively selective. The most common side effect of these drugs is sedation, but there's also the possibility of withdrawal syndrome, which causes seizures to worsen if the drug is stopped.

MANAGEMENT OF PARKINSONISM

Parkinsonism: Rigidity, bradykinesia, tremor, and postural instability are all symptoms of Parkinson's disease. It's caused by an imbalance in the basal ganglia's cholinergic and dopaminergic influences. The goal of treatment is to either increase dopaminergic activity (using a dopamine agonist) or to reduce cholinergic influence on the basal ganglia (using antimuscarinic drugs).

Levodopa: The immediate metabolic precursor of dopamine, levodopa, does pass through the blood-brain barrier and is decarboxylated into dopamine. The small intestine absorbs levodopa very quickly. The appearance of levodopa in the plasma is delayed by eating. Because peripheral dopa decarboxylase metabolises it extensively, it is given in combination with carbidopa, a peripheral dopa decarboxylase inhibitor.

When given without carbidopa, levodopa causes vomiting (due to dopamine stimulation of the emetic centre) and CVS disorder (tachycardia, ventricular extrasystoles, atrial fibrillation and due to increased catecholamine formation peripherally).

Dopamine agonists: Because the enzymes that synthesise dopamine are depleted in Parkinson's patients' brains, drugs that act directly on dopamine receptors may have a beneficial effect in addition to levodopa. A number of dopamine agonists have antiparkinsonism properties.

e.g: Bromocryptine: Monoamine Oxidase Inhibitors: **Selegiline** (deprenyl), As a selective inhibitor of monoamine oxidase B, it prevents dopamine breakdown and thus prolongs levodopa's antiparkinsonism effect. When given alone, selegiline has only a minor therapeutic effect on Parkinsonism. It may slow the progression of disease.

Amantadine: Antiviral amantadine was discovered to have antiparkinsonian properties by chance. Its exact mechanism of action in Parkinsonism is unknown, but it could enhance dopaminergic function by influencing dopamine synthesis, release, or reuptake.

Acetylcholine Blocking Drugs (Benztropine, Trihexyphenidyl)

There are several centrally acting antimuscarinic preparations available, each with varying potencies and efficacy in different patients. Treatment usually begins with a low dose of one of these drugs, which is gradually increased until benefit is obtained or adverse effects prevent further increases. Antimuscarinic drugs may help with Parkinson's tremor and rigidity, but they have little effect on bradykinesia.

Adverse Effects: Drowsiness, mental slowness, inattention, restlessness, and confusion, as well as agitation, delusions, hallucinations, and mood changes, are all side effects of antimuscarinic drugs. Dry mouth, blurred vision, mydriasis, urinary retention, nausea and vomiting, constipation, tachycardia, tachypnea, increased intraocular pressure, palpitations, and cardiac arrhythmias are all common side effects.

Contraindications: Patients with prostatic hyperplasia, obstructive gastrointestinal disease, or angle-closure glaucoma should avoid acetylcholine-blocking drugs.

ANTIPSYCHOTIC AGENTS

Delusions, hallucinations, thought disorder, social withdrawal, and flattering of emotional response are all symptoms of psychotic illness. Antipsychotics are a class of medications used to treat schizophrenia.

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Atypical neurolopitics (chlorpromazine, thioridazine, haloperidol, flupenthixol) and typical neuroleptics (chlorpromazine, thioridazine, haloperidol, and flupenthixol) are two (clozapine, sulpiride).

The majority of antipsychotic drugs are absorbed quickly but insufficiently. Many of these drugs are subjected to extensive first-pass metabolism. Because these drugs are almost completely metabolised into more polar substances, very little of them is excreted unchanged. The antipsychotic drugs known as phenothiazine have a wide range of central nervous system, autonomic, and endocrine effects, with chlorpromazine serving as the prototype. It inhibits dopamine and alpha-adrenoceptor receptors, as well as muscarinic, H1 histaminic, and serotonin (5-HT2) receptors. The effects of dopamine receptors were quickly identified as the most interesting.

Clinical uses

- Mania
- Schizophrenia
- Vomiting

Adverse Reactions

- Extrapyramidal reactions
- Autonomic nervous system effects (antimuscarinic effects, orthostatic hypotension)
- Seizures
- Metabolic and Endocrine Effects (weight gain, hyperprolactinemia, infertility, loss of libido and impotence)

ANTIDEPRESSANT AGENTS

One of the most common mental illnesses is depression. Antidepressants are medications that are primarily used to treat depression.

Types of antidepressant drugs

1. Tricyclic antidepressants (TCAs)
2. 5-HT uptake inhibitors
3. Atypical antidepressants
4. Monoamine oxidase inhibitors (MAOI)

Pharmacokinetics

The majority of tricyclics are poorly absorbed and undergo extensive first-pass metabolism. Protein binding and lipid solubility are both high. Fluoxetine (SSRIs) absorbs well. MAO inhibitors are easily absorbed through the digestive tract.

Mechanisms of action

The most commonly used antidepressants are tricyclic antidepressants (imipramine, amitriptyline), which are structurally similar to phenothiazines. TCAs compete for the carrier transport system and block the uptake of amines (noradrenaline and 5-HT) by nerve terminals. TCAs also inhibit 1-adrenoceptors, muscarinic receptors, histamine (H1) receptors, and 5-HT receptors.

Monoamine oxidase inhibitors (MAOI): Tranylcypromine inhibits MAO-A specifically. The substrate preference of MAO-A is 5 –HT. MAOI raises 5-HT, noradrenaline, and dopamine levels quickly and consistently.

Fluvoxamine and other selective 5-HT uptake inhibitors have no antimuscarinic or cardiovascular effects.

Atypical antidepressants have no common mechanism of action; some are monoamine reuptake inhibitors, while others have unknown mechanisms of action.

Clinical Indications: Endogenous depression, panic attacks, phobic and obsessional states (clomipramine), and bedwetting in children are the most common side effects of TCAs. MAOIs are used to treat severe depression and phobias that have not responded to other treatments.

Adverse Effects: TCAs' most common side effects include postural hypotension, dry mouth, blurred vision, constipation, urine retention, and sedation. MAOIs cause restlessness, tremor, and insomnia by causing postural hypotension, atropine-like effects, weight gain, and CNS stimulation.

Atropine-like effects and postural hypotension are caused by TCA and MAO inhibitors. MAOI causes weight gain and excessive central stimulation.

ANALGESICS

Opioid Analgesics

Any substance with morphine-like effects is classified as an opioid. The juice of the poppy Papaver somniferum is used to extract opium. Many alkaloids found in opium are similar to those found in morphine. Morphine analogues and synthetic

derivatives are the two main types of drugs discussed in this section. Analogs of morphine Morphine-like compounds. They can be either agonists (codeine and heroin) or antagonists (nalorphine) (naloxone). Derivatives of synthetics Synthetic derivatives include phencyclidine, fentanyl, methadone, and pentazocine.

Opioid receptors the main pharmacological effects of opiates are mediated by three receptors. Analgesic and major unwanted effects are mediated by mu receptors (respiratory depression, sedation and dependance). Delta is responsible for analgesia and opiates' peripheral effects, while kappa is responsible for analgesia and dysphoria at the spinal level.

Agonists and antagonists of opioid receptors pure agonists. They have similar mu receptor affinities but differ in their affinity for delta and kappa receptors (codeine, methadone, dextropropoxyphene).Partial antagonists and mixed agonist-antagonists: Nalorphine, and pentazocine.

Pharmacokinetics: Subcutaneous and intramuscular sites, as well as the mucosal surfaces of the nose and mouth, are all good sources of opioid analgesics. Although rapid absorption from the gastrointestinal tract, some opioids administered this way are subject to first-pass metabolism in the liver via glucuronidation. All opioids bind to plasma proteins with varying degrees of affinity; the drugs leave the bloodstream quickly and concentrate in highly perfused tissues. The opioids are mostly converted to polar metabolites, which are excreted easily by the kidneys.

Pharmacodynamics

A. Mechanism of Action: Analgesia is produced by opioid agonists binding to specific receptors in the brain and spinal cord that are involved in the transmission and modulation of pain.

Effects of morphine and its synthetic derivatives

1. **Central nervous system effects-**The central nervous system is the primary effect of opioid analgesics with affinity for mu receptors; the most important effects are analgesia, euphoria, sedation, and respiratory depression. Except for respiratory depression, all of these effects develop a high level of tolerance with repeated use. They also lead to dependency and addiction.

    1. Analgesia-Pain has sensory as well as affective (emotional) components. Opioids can alter both aspects of pain perception. These drugs have a relatively greater effect on the affective component in most cases.

2. Euphoria**-**A typical pain patient feels a pleasant floating sensation and is free of anxiety and distress after taking morphine. Dysphoria is a mood disorder characterised by restlessness and malaise.
3. Sedation**-**Drowsiness and a clouding of the mind are common opioid side effects.
4. Respiratory depression**-**By inhibiting brain stem respiratory mechanisms, all opioid analgesics can cause significant respiratory depression.
5. Cough suppression**-**Opioids have a well-known effect of suppressing the cough reflex. However, cough suppression with opioids may allow secretions to accumulate, resulting in airway obstruction and atelectasis. e.g. codeine
6. Miosis**-**Pupil constriction is seen with almost all opioid agonists.
7. Nausea and vomiting**-**The brain stem chemoreceptor trigger zone can be activated by opioid analgesics, causing nausea and vomiting.

2. Peripheral effects

i. **Biliary tract:** The opioids constrict the smooth muscle of the bile duct, causing biliary colic. The Oddi sphincter may constrict, causing biliary and pancreatic secretions to reflux and elevated plasma amylase and lipase levels.

ii. **Cardiovascular system:** Hypotension is caused by a variety of mechanisms, including central depression of vasomotor-stabilizing mechanisms and histamine release.

iii. **Gastrointestinal tract:** Constipation. Opioid receptors are abundant in the gastrointestinal tract, and opioids' constipating effects are mediated by actions on both the local enteric nervous system and the central nervous system.

iv. **Genitourinary tract:** Opioids have a negative effect on renal function. This is thought to be due to a decrease in renal plasma flow in humans.

v. **Neuroendocrine:** Antidiuretic hormone, prolactin, and somatotropin are all stimulated by opioid analgesics, but luteinizing hormone is inhibited.

vi. **Uterus:** Opioid analgesics may lengthen labour.

B. Effects of mixed agonist-antagonists: Opioid analgesics may lengthen labour..

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Clinical use of opioid analgesics

Opioids are used to treat severe, chronic pain, acute pulmonary edoema (pulmonary edoema caused by left ventricular failure), cough suppression, diarrhoea, and preanaesthetic medication.

CNS stimulants:

Stimulants of the central nervous system are less therapeutically useful than CNS depressants because they lack selectivity of action. Additionally, excessive CNS stimulation is followed by CNS depression.

CNS stimulant can be classified into

1. Convulsants and Respiratory Stimulants Eg. Srychnine Picrotoxin, Nikethaimide
2. Psychotomimetic Drug Eg. Lysergic And Diethylamide (Lsd) Psilocybin, Phencyclidine
3. Psychomotor stimulants Eg. Amphetamine, cocaine, caffeine

Convlsants and respiratory stimulants: These are a diverse group of drugs with limited clinical utility. In respiratory failure, short-acting respiratory stimulants such as doxapram and amiphenazole can be used. In experimental pharmacology, strychnine, picrotoxin, and leptazole are used as chemical tools in a variety of animal models.

Psychomotor stimulants: Due to the release of noradrerline and dopamine, drugs like amphetamine cause increased motor activity, euphoria, excitement, and anorexia.

Clinical uses: In children, amphaetamine is used to treat narcolepsy and attention deficit. Cocaine is used as a local anaesthetic in ophthalmology and minor nose and throat surgery on rare occasions.

Another drug in this group is khat, which is a major drug of abuse in Ethiopia. Amphetamine khat and cocaine, as abuse drugs, produce strong psychological dependence and a high risk of adverse effects.

Psycho mimetic drugs: Sensory changes, hallucinations, and delusions are common side effects of drugs like LSD, phencyclidine, and psilocybin, which are similar to the symptoms of acute schizophrenia. They are not used in clinical settings, but they are important as abuse drugs.

Drug dependence and drug abuse

Many drugs are taken by people because they want to, rather than because they are prescribed by doctors. In most cases, there is a social cost; in the case of certain

drugs, this is judged to outweigh the individual benefit, and their use is prohibited in many countries.

The main drugs of abuse are given in the following table.

Table 10.1: Main Drugs of Abuse

Type	Example	Dependence Liability
Narcotic Analgesics	Morphine	very strong
CNS Depressants Anxiolytic Drugs	Ethanol Barbiturates Benzodiazepines	strong strong moderate
Psychomotor Stimulants	Amphetamine Cocaine Nicotine Caffeine	strong very strong very strong weak
Psychomimetic Drugs	LSD Mescaline Phencyclidine Cannabis	weak or absent weak or absent moderate weak or absent

LOCAL ANESTHETICS

Procaine, dibucaine, benzocaine, and other esters and amides are used as local anaesthetics (lidocaine, prilocaine, bupivacaine, etc). Non-specific esterases usually inactivate ester-containing compounds in the plasma and tissues. Local anaesthetics prevent the voltage-dependent increase in Na+ conductance, which prevents the initiation of action potentials.

Minor surgery, dentistry, abdominal surgery, and painless childbirth all use local anaesthetics. CNS effects (agitation, confusion, respiratory depression, and convulsions), CVS effects (myocardial depression, hypotension), and occasional hypersensitivity reactions are all caused by LA entering systemic circulation.

Table10.2. shows the methods of administration and clinical uses of local aesthetics

Methods of Administration	Uses	Drugs
Surface Anaesthesia	Nose, mouth, urinary tract	Lidocaine
Infiltration Anaesthesia	Direct injection into tissues to reach nerve Braches and terminals. Minor surgery	Most
Regionanl Anaesthesia	LA injected IV distal to a pressure cuff, limb surgery	Mainly lidocaine

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Nerve Block Anaesthesia	LA injected close to nerve trunks. Dentistry	Most
Spinal Anaesthesia	LA injected into subarachinoid space. Pelvis surgery	Mainly lidocaine
Epidural Anaesthesia	LA injected into epidural space. Labour.	Mainly lidocaine

Questions

i. What are intravenous anaesthetics? Write about their clinical uses.

ii. Why levodopa is combined with carbidopa in the treatment of Parkinsonism

iii. Write about mechanism of action and adverse effects of Phenytoin and carbamazepine.

iv. Write about benzodiazepines and their therapeutic uses.

v. Write about tricyclic antidepressants and their clinical indications.

vi. List commonly abused drugs.

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