UNIT 9 DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

Structure

9.1 INTRODUCTION

The central nervous system consists of the brain and the spinal cord. It is the seat of the autonomic nervous system, consciousness, motor coordination, behaviour, thoughts and memory processes. Many neurotransmitters have been shown to be involved in the control of these processes in different parts of the brain. In most of the places there are pairs of neurotransmitters that oppose the actions of each other so as to coordinate and regulate the different processes. Any imbalance in the neurotransmitter functions can lead to the development of neurological or psychiatric disorders.

Objectives

After studying this unit, you should be able to:

- explain the causes of various neurological and psychological problems;
- classify the drugs used in various disorders of the CNS;
- describe the pharmacology and clinical use of various drug groups; and
- explain the adverse effects seen with the clinical use of various drugs.

9.2 SEDATIVES AND HYPNOTICS

Sedatives (anxiolytic) are the agents which reduce anxiety and exert a calming effect with little or no effect on motor or mental functions. **Hypnotics** are the drugs which produce drowsiness and encourage the onset and maintenance of sleep. They are discussed according to the broad groups as given in the following subsections.

9.2.1 Barbiturates

Barbiturates are the derivatives of barbituric acid. They are general CNS depressants. They can cause sedation, hypnosis and general anaesthesia depending upon the particular barbiturates used and its dose. Barbiturates produce depression of central nervous system in dose dependent manner. In small dose, barbiturates relieve anxiety and are generally used as sedative. In hypnotic dose, it produces sleep resembling normal physiological sleep. Hangover is especially seen with long acting barbiturates. They produce physical dependent and have abuse potential. The important therapeutic uses of this class of compounds are:

- To produce sedation and hypnosis.
- Anticonvulsant action: Phenobarbital is drug of choice.
- For general anaesthesia: Ultra short acting barbiturates are used.
- As preanaesthetic medication.
- As obstetrical analgesic.

9.2.2 Benzodiazepines

Benzodiazepines are commonly used anxiolytics in clinical practice because these agents exhibit good efficacy, are relatively safe and have minimum toxicity. They are indicated for short term relief of anxiety. Other uses of benzodiazepines are:

- As hypnotic
- As anticonvulsant
- As preanaesthetic medication

9.2.3 Newer Compounds

Zopiclone

It is useful in short term management of insomnia and has low abuse potential. Zopiclone exhibits anticonvulsant, muscle relaxant and sedative properties similar to benzodiazepines.

It is **indicated** in treatment of transient, situational and chronic insomnia, insomnia secondary to psychiatric disorders.

Zolpidem

Zolpidem is a non-benzodiazepine hypnotic. It is **indicated** in short term management of insomnia.

SAQ 1

a) Barbiturates produce _______________, ________________ and ______________ in a dose dependent manner.

b) Newer sedatives are indicated only in the management of __________.

9.3 NARCOTIC ANALGESICS

Analgesics are the drugs (natural or synthetic origin) which relieve pain by acting on CNS or peripheral pain mechanism without causing loss of consciousness. Analgesics can be divided into two main groups:

a) Opioid/narcotic/morphine like analgesics.

b) Non-opioid/non-narcotic/aspirin like analgesics.

Drugs obtained from morphine are known as opioids or narcotic analgesics.

The opium is obtained from the opium poppy *Papaver somniferum.* It contains two type of alkaloids e.g. phenanthrene derivatives (morphine, codeine & thebaine) and benzyl isoquinoline derivatives (papaverine and noscapine).

9.3.1 Opioids

Opium is the milky exudate obtained by incising the unripe seed capsule of the poppy plant and following are the analgesics associated with this.

Morphine

Morphine is the most important alkaloid in the exudate. Morphine produces analgesia through action in the brain and spinal cord that contain peptides possessing opioid like pharmacological action.

The main action of morphine is CNS depression which further results in analgesia, depression of respiratory centre, cough centre and sleep. In addition it causes euphoria or dysphoria and dependence. Morphine produces analgesia by elevation of pain threshold, thereby reducing the perception of pain. It also altered psychic reaction to pain which may be associated with feeling of well being e.g. euphoria. Morphine also produces a sense of anxiety, known as dysphoria. The morphine produces euphoria (which makes morphine as one of the main drugs of abuse) and analgesia by acting on higher centres and spinal cord. It is contraindicated in asthmatics as it can precipitate an attack by releasing histamine.

The main therapeutic uses of morphine are:

1. ***Analgesic:*** Morphine is used in the following conditions:
   - In the treatment of any severe, constant pain.
   - Visceral pain e.g. myocardial infraction, renal and biliary colic.
   - Traumatic pain e.g. long bone fractures and burns.
   - Pain of terminal illness e.g. in cancer patients.
   - Postoperative pain.
2. In suppression of cough and dyspnea (due to left ventricular failure and pulmonary edema).
3. For sedation.
4. As preanaesthetic medication.

Codeine

It is less potent analgesic than morphine. It is widely used as antitussive agent. Pholcodeine is also used as antitussive agent and causes less constipation (Details are given in chapter ‘Drugs acting on respiratory system’).

Pethidine

In equianalgesic doses, pethidine produces as much sedation, respiratory depression and euphoria as does morphine. A few patients may experience dysphoria. It is mainly indicated for analgesia, as preanaesthetic medication, for epidural and intrathecal analgesia.

Fentanyl

It is a potent opioid analgesic. It is 80-100 times more potent than morphine, both in analgesia and respiratory depression. It is **indicated** as a narcotic analgesic supplement in general or regional anaesthesia, as an anaesthetic agent with oxygen and skeletal muscle relaxant in selected high risk patients (e.g. open heart surgery).

Methadone

It is synthetic compound having same or more analgesic activity than morphine. Its pharmacology and side effects are similar to that of morphine. It is **used** in the treatment of visceral pain and as an antitussive. It is also used as substitution therapy of opioid dependence.

Tramadol

It is centrally acting synthetic analgesic compound that is not derived from natural sources nor is chemically related to opiates. It is indicated in moderate to severe, acute or chronic pain and in painful diagnostic procedures and surgery; arthralgia, musculoskeletal pain, pain associated with fractures, dislocation and other related type of pain.

9.3.2 Agonists-Antagonists

These are the agents which are used as antidote of opioid poisoning and addiction.

Pentazocine

It is **agonist-antagonist** of morphine and is used as an analgesic. It exerts morphine like action. It is effective in mild to moderate type of pain associated with surgery, trauma, burns, colics, cancer, in labour and as preanaesthetic medication.

Nalorphine

It is a congener of morphine. It is **used** mainly in the treatment of acute morphine poisoning.

Nalbuphine

Its agonistic property is approximately three to four times more than pentazocine and its antagonistic property is approximately 10 times more than pentazocine. It has less abuse liability in comparison to pentazocine. It is **useful** in postoperative pain, myocardial infarction and labour.

Naloxone

It is an analogue of oxymorphone. It is inactive orally because of high first pass metabolism in liver. The main **use** of naloxone is in the treatment of acute opioid overdose (acute morphine poisoning).

Naltrexone

It is a pure antagonist and chemically related to naloxone. It is more potent than naloxone and because of its longer duration of action, it can be used as maintenance drug for morphine addicts.

SAQ 2

a) Morphine depresses respiration by acting on the ___________________.

b) Morphine is contraindicated in asthmatics because it can cause bronchoconstriction by ________________ release.

c) The main use of naloxone is in the treatment of ___________________.

9.4 NON-NARCOTIC ANALGESICS (NSAID's)

Non-steroidal anti-inflammatory drugs (NSAIDs) are also known as non-opioid or non-narcotic analgesics. They relieve pain without interacting with opioid receptors and do not depress CNS and have no drug dependence or drug abuse property and possess antipyretic activity also. They act primarily on peripheral pain mechanisms and also in CNS to raise pain threshold.

NSAIDs exert analgesic, antipyretic, anti-inflammatory and related effects. During pain, fever and inflammation the arachidonic acid is liberated from the phospholipid fraction of the cell membrane which is then converted to prostaglandins (PGs) via cyclooxygenase pathway.

9.4.1 Individual Agents

These can be put into following categories.

Salicylates

Salicylates relieve pain by both central and peripheral action. The site of action of central analgesia seems to be the hypothalamus. They are useful in relieving all dull itching, throbbing pain of muscles and joints, dysmenorrhoea, toothache, headache etc. Salicylates lower the elevated body temperature. The antipyretic action of salicylates is probably due to the inhibition of PG synthesis. Salicylates stimulate respiration by increasing the consumption of oxygen primarily by skeletal muscles. Salicylates suppress the clinical signs and symptoms of rheumatoid arthritis and other related inflammatory disorders by inhibiting prostaglandin synthesis. The main therapeutic uses of salicylates as given below:

1. As analgesic-antipyretic: Salicylates are effective in the treatment of mild to moderate types of pain. They are used in the treatment of headache, toothache, bodyache, arthralgias, neuralgias and dysmenorrhoea. They are also effective in fever of any origin.
2. As an anti-inflammatory, anti-rheumatic, anti-gout and as a anti-platelet agent.

Phenylbutazone

It is a potent antiinflammatory agent. It has poor analgesic and antipyretic action. Mechanism of action is similar to other NSAIDs. It is indicated in ankylosing spondylitis, rheumatoid arthritis, rheumatic fever, osteoarthritis, after blunt injuries, fractures, tooth extraction, vasectomy and acute gout.

Indomethacin

It possesses potent antiinflammatory property and has good analgesic and antipyretic action also. It is **used** in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout.

Propionic Acid Derivatives

The drugs like ibuprofen, flurbiprofen, ketoprofen, naproxen etc. possess antiinflammatory property similar to aspirin but toxicity and adverse effects are fewer and of lesser intensity. They are **indicated** in rheumatoid and osteoarthritis, ankylosing spondylitis, mild to moderate pain including dysmenorrhoea, soft tissue injuries, fractures and postoperative analgesia.

Anthranilic Acid Derivatives

The drugs like mefenamic acid and enfenamic acid are inhibitors of cyclooxygenase with analgesic, antiinflammatory and antipyretic properties. They are **indicated** in muscle, joint and soft tissue pain, dysmenorrhoea, rheumatoid and osteoarthritis, as antipyretic, in dental pain, postoperative or postpartum pain.

Piroxicam

Piroxicam is a new NSAID and has anti-inflammatory, analgesic and antipyretic activity. It provides effective and long-lasting relief of pain and stiffness. It is **indicated** in acute or long term use in acute and chronic rheumatoid arthritis and other rheumatic disorders like osteoarthritis, ankylosing spondylitis, cervical spondylosis, acute gouty arthritis and acute musculoskeletal disorders.

Diclofenac

It is a NSAID with pronounced antirheumatic, antiinflammatory, analgesic and antipyretic properties. It also exerts a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin. It is **used** in the treatment of inflammatory and degenerative forms of rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondyloarthritis, painful syndromes of the vertebral column, nonarticular rheumatism and acute attacks of gout.

Paracetamol

It acts on CNS to produce analgesia and antipyretic effect. It has negligible anti-inflammatory action peripherally in therapeutic uses. It is poor inhibitor of PG synthesis in peripheral tissues. It also raises the pain threshold. Paracetamol is **used** for the rapid relief of fever, pains and aches such as headache, earache, toothache, fibrositis, myalgia, neuralgia, arthralgia, osteoarthritis and postoperative pain.

Ketorolac

Ketorolac has anti-inflammatory, antipyretic and analgesic actions. It is **indicated** in short term management of acute pain, pain associated with surgical procedures.

Celecoxib

It is a NSAID which has COX-2 selectivity. It exhibits anti-inflammatory, analgesic and antipyretic activities which are believed to be due to inhibition of

COX-2. At therapeutic concentrations in humans, celecoxib does not inhibit COX-1 enzyme. It is **used** in rheumatoid arthritis, osteoarthritis and other conditions including rheumatic pain, neuralgia, gout and ankylosing spondylitis etc.

9.4.2 Drugs Used in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory joint disease. It is a progressive symmetrical, destructive and deforming polyarthritis affecting proximal small joints of hand (usually) and large joints as well. Initial treatment consists of NSAIDs, low dose corticosteroids. If the symptoms are not controlled then second line/disease modifying drugs (DMDs) are added. Since it is a progressive disease, spontaneous remissions are rare and joint damage occurs early, DMDs are started early and continued indefinitely with regular monitoring.

The disease modifying drugs (DMDs/DMARDs) used are gold, d-penicillamine, hydroxychloroquine, sulfasalazine and immunosuppressants like methotrexate, azathioprine, cyclosporin etc.

9.4.3 Drugs for Gout

Gout results from hyperuricemia i.e. increased serum uric acid levels. Normal serum uric acid level is 1-5 mg/dl. Uric acid is formed in the metabolism of purine. When the blood levels of uric acid are high, it precipitates in joints, cartilage, kidney and subcutaneous tissues and leads to various signs and symptoms. Drugs used for gout can be divided into two groups:

a) Drugs for acute attack of gout: NSAIDs, colchicine, corticosteroids.

b) Drugs for chronic gout/hyperuricemia: Can be uric acid synthesis inhibitors (allopurinol) and uricosurics (increase renal excretion of uric acids) e.g. probenecid and sulfinpyrazone.

Colchicine

It is effective for treatment of acute attacks of gout. In gout, the useful of colchicine is due to the inhibition of the release of glycoproteins from granulocytes in inflamed joint thus preventing precipitation of uric acid crystals and release of lysosomal enzymes.

Allopurinol

It is **indicated** in primary hyperuricaemia of gout, secondary hyperuricaemia due to myeloid metaplasia, radiation, cancer chemotherapy, thiazide diuretics.

Probenecid

It increases the excretion of uric acid (by inhibiting its reabsorption from kidney tubules) and hence causes reduced serum levels of uric acid. It is **used** in chronic gout and secondary hyperuricaemia.

Sulfinpyrazone

Pyrazolone derivative related to phenylbutazone. It has uricosuric action. It also inhibits platelet aggregation.

SAQ 3

a) ________________ is indicated in short term management of acute pain, pain associated with surgical procedures.

b) The site of action of colchicines is the ______________ protein.

c) ___________________ inhibits the terminal steps in uric acid biosynthesis by inhibiting enzyme xanthine oxidase.

9.5 GENERAL ANAESTHETICS

General anaesthetics are the group of drugs which bring about a reversible loss of pain sensation and consciousness. The depth of anaesthesia appropriate for the conduct of surgical procedures can be achieved by a wide variety of drugs, either alone or by a combination of drugs, each drug for a specific purpose. General anaesthetics can be administered by a variety of routes, but intravenous or inhalation administration is preferred, because the effective dose and the time course of action are more predictable when these techniques are used.

The general anaesthetics are divided into two main groups, inhalational and intravenous anaesthetics.

9.5.1 Inhalational Anaesthetics

i) Nitrous Oxide (N_2O)

Nitrous oxide is used for induction and maintenance of anaesthesia. It is widely used as carrier gas for other volatile agents in general anaesthesia. Nitrous oxide, if administered along with air, produces a stage of excitement and delirium and also produce amnesia. Hence, the name 'laughing gas.'

Nitrous oxide, due to its analgesic action in subanaesthetic concentration, is employed for minor operation like tooth extraction, for obstetrical analysis, painful procedures such as changing dressing of burns. It is cheap and very commonly used.

ii) Volatile Liquids

Ether (Diethyl Ether)

It was one of the first substances to be employed for general anaesthesia. Because of its slow induction and recovery, irritant property and other disadvantages ether is rarely used these days and may be occasionally used as a supplement to nitrous oxide-oxygen mixture in children.

Halothane

It is most widely used volatile anaesthetic due to its smooth and rapid induction. It inhibits laryngeal and pharyngeal reflexes. Recovery is smooth and reasonably quick. It is currently one of the most popular anaesthetic used due to its non-irritant, non-inflammable, pleasant and rapid action.

9.5.2 Intravenous Anaesthetics

Intravenous anaesthetics are mainly used for rapid induction of anaesthesia, which is then maintained by an inhalational agent. They also serve to reduce the amount of maintenance anaesthetics.

i) Barbiturates

Thiopentone Sodium

It is an ultra short acting thiobarbiturate. Induction is generally smooth and takes approximately 10 to 15 seconds. Because of its poor analgesic property, painful procedures should not be carried out under its influence unless an opioid or nitrous oxide has been given. Thiopentone is sometimes used for rapid control of convulsions. Methohexitone sodium is preferred to thiopentone sodium for short procedures and out patients due to its rapid recovery. It is approximately three times more potent than thiopentone sodium with quicker and briefer action.

i) Non-Barbiturate Intravenous Anaesthetics

Propanidid

It is an oily liquid less potent than thiopentone. It is a very short acting intravenous anaesthetic and specially used for very short outpatient operations and dental procedures.

Ketamine

It is a new non-barbiturate anaesthetic agent and pharmacologically related to phencyclidine, a hallucinogen. Intravenous ketamine produces unconsciousness and analgesia within 30 seconds.

Diazepam

It may be used to produce light sedation and amnesia for unpleasant procedures by intravenous injection. It has also been used for induction and to supplement nitrous oxide anaesthesia. The benzodiazepines are further discussed in chapter 'Sedatives and Hypnotics' in detail.

9.5.3 Preanaesthetic Medication

Preanaesthetic medication refers to the use of drugs before the administration of an anaesthetic agent, which makes it more pleasant and safe to the patient. To achieve all the objectives, a combination of 2 or 3 drugs is used depending on the need. The commonly employed drugs are opioids, sedative-hypnotics, antianxiety agents, anti-cholinergics, neuroleptics and antiemetics.

Opioids

These are the most commonly used drugs. Morphine and pethidine are frequently used drugs for their sedative and analgesic property. They reduce the anxiety and apprehension, produce pre and postoperative analgesia, and help in smooth induction.

Sedative-Hypnotics

The barbiturates like pentobarbitone, secobarbitone or butobarbitone have been used to provide sedation and to relieve apprehension before operation. Promethazine an antihistaminic with sedative, antiemetic and anticholinergic properties is generally used in children as it causes little respiratory depression.

Antianxiety Drugs

The tranquillizers like benzodiazepines are now preferred for preanaesthetic medication because they produce tranquility, have better muscle relaxant property and smoothen induction. Other tranquillizer compounds include phenothiazines which possess sedative, antiemetic and antihistaminic properties. They can be given orally as well as parenterally.

Anticholinergics

Atropine or scopolamine is generally given in combination with morphine to block the vagal action so as to reduce the salivary and bronchial secretions. Hyoscine produces amnesia and antiemetic effect also.

Neuroleptics

Chlorpromazine, triflupromazine or haloperidol is used as preanaesthetic medication. They reduce anxiety, emesis and help in smooth induction. However, these compounds potentiate respiratory depression.

Antiemetics

Droperidol and hydroxyzine is sometime used for their antiemetic activity. Hydroxyzine has antianxiety, antihistaminic and anticholinergic properties also.

SAQ 4

a) Fill in the blank spaces in the following:

   i) ______________ produces analgesia in subanaesthetic concentration.
   ii) Thiopentone sodium produces anesthesia within ____________ min.

b) What do you mean by preanesthetic medication?

9.6 ANTIEPILEPTIC DRUGS

Epilepsy is a neurological disorder characterised by short, recurrent and periodic attacks of motor, sensory or psychological malfunction. It is associated with paroxysmal abnormal electrical discharge in the brain. Epilepsy is due to sudden, excessive and rapid discharge in the grey matter of the brain. Anti-epileptic drugs inhibit the spread of abnormal electrical discharge in the brain with minimal general depressant action on the central nervous system.

The individual antiepileptic drugs are discussed below.

9.6.1 Individual Agents

Phenobarbitone

Phenobarbitone raises the threshold of seizures and abolishes the tonic phase thus useful in the treatment of grandmal epilepsy. Phenobarbitone is useful in grandmal, focal and temporal lobe epilepsy and sometimes petitmal also. It is also useful in the treatment of febrile convulsions.

Primidone

It is twice as active as phenobarbitone. It is effective against all type of seizures e.g. grandmal epilepsy, psychomotor epilepsy, focal and myoclonic epilepsy. It is not effective in petitmal epilepsy.

Diphenylhydantoin (Phenytoin)

Phenytoin prevents repetitive detonation of these normal brain cells as it has a stabilising influence on the neuronal membrane. It is used in prophylactic treatment of all varieties of partial epilepsy whether or not seizure becomes secondarily generalized. It is also used in prophylactic treatment of generalised convulsive seizures and treatment of status epilepticus.

Carbamazepine

It is effective in grandmal and psychomotor epilepsy.

Ethosuximide

Ethosuximide was the most commonly used antiepileptic agent in the treatment of petitmal epilepsy.

Methsuximide

It is similar to ethosuximide and used along with the other drugs in the treatment of temporal lobe epilepsy.

Sodium Valproate (Valproic Acid)

Valproate is a *broad range antiepileptic drug*. It is commonly employed in the treatment of absence seizures.

Clonazepam

It is used in the treatment of petitmal epilepsy not responding to ethosuximide and sodium valproate.

Topiramate

It is used as adjunctive treatment of seizures including refractory seizures, simple and complex partial seizures.

Gabapentin

It is a new anticonvulsant drug **used** as adjunctive therapy in the treatment of partial seizures with or without secondary generalisation in adults.

Vigabatrin

It is used in partial seizure with or without generalisation.

Lamotrigine

It is phenyltriazine compound, chemically unrelated to existing antiepileptic drugs. It is mainly used as adjunctive therapy in patients for simple partial seizures, complex partial seizures, secondary generalised tonic and clonic seizures.

SAQ 5

a) __________is the most commonly used drug in the treatment of absence seizures.

b) ___________ is the most commonly used drug in the treatment of absence petit mal epilepsy.

9.7 PSYCHOPHARMACOLOGICAL AGENTS

Psychopharmacological agents may be classified into three broad groups used in various states of psychic disorders.

1. **Antipsychotic drugs** used in all types of psychosis mainly schizophrenia.
2. **Antianxiety drugs** used in anxiety.
3. **Antidepressants** for minor and major depressive disorders and mood stabilizers (antimanic drugs) for mania.

9.7.1 Antipsychotic Drugs

They are mainly divided into two main groups and certain newer compounds.

i) Phenothiazines

These agents produce sedation which does not progress to anaesthesia. They decrease the agitation, anxiety and aggressiveness in psychotic patient without affecting wakefulness. In schizophrenic patients, they improve thought disorders, blunted affect, withdrawal and self centered behaviour. They also improve the hallucinations and delusions. Chlorpromazine depresses the chemoreceptor trigger zone (CTZ) and acts as a powerful antiemetic agent. It is used in the following conditions:

1. Treatment of psychosis (schizophrenia): Schizophrenia is a split mind or splitting of perception from reality. The patient of schizophrenia is dissociated from the world around him and lives in their own world which is characterised by aggression, anxiety, restlessness, hallucinations and delusions. Phenothiazines reduce the hallucinations, aggression, anxiety and make them acceptable and cooperative.
2. In treatment of manic depressive psychosis (mania).
3. In alcoholic hallucinosis and Huntington's disease.
4. As an antiemetic in drug and disease induced vomiting. Also useful in morning sickness but are ineffective in motion sickness.
5. In the treatment of intractable hiccough.
6. In the treatment of behavioural disorders in children.
7. As preanaesthetic medication.
8. To produce hypothermia.

ii) Butyrophenones

Haloperidol

It is a potent antipsychotic drug. It does not cause weight gain. Its pharmacological effects are similar to phenothiazines. It is **indicated** in acute and chronic schizophrenia, anxiety disorders, acute mania, and behavioural disorders in children; antiemetic neuroleptanalgesia and Huntington's disease.

iii) Other Newer Compounds

Loxapine

It is the antipsychotic agent resembling chlorpromazine in pharmacological actions. It is **used** in manifestation of psychotic disorders, acute and chronic paranoid schizophrenia.

Clozapine

It is an atypical neuroleptic drug. It produces few extrapyramidal symptoms. It is **indicated** in all types of schizophrenia including resistant cases not responding to conventional antipsychotics and chronic schizophrenia.

9.7.2 Antianxiety Drugs

Anxiety is an emotional feeling of fear along with discomfort and uneasiness. Antianxiety drugs are used to control the symptoms of anxiety without affecting the other mental and physical functions of the body. They are mainly divided into two main groups.

i) Benzodiazepines

The detailed pharmacology of all the benzodiazepines used in anxiety disorders is discussed in chapter 'Sedative and hypnotics'. They have selective action on limbic system and have little effect on other body systems. They help in improving the anxiety and stress related symptoms. They are widely used because of lower dependence producing liability and wide margin of safety.

ii) Azapirones

Buspirone belongs to azapirones which is chemically and pharmacologically distinct class. It acts as a partial agonist at serotonin and dopamine receptors. It is **used** in short-term management of anxiety disorders and relief of symptoms of anxiety with or without accompanying depression.

iii) Others

Hydroxyzine is an antihistaminic agent having antiemetic, sedative, anticholinergic and local anaesthetic property. It is used in anxiety, as an adjunct therapy in acute/chronic alcoholism.

Beta blockers provide symptomatic relief by decreasing the symptoms due to sympathetic overactivity e.g. palpitation, tremors, rise in blood pressure, etc. They are **used** as adjuvant to benzodiazepines.

9.7.3 Antidepressants

Antidepressants are agents that are used to alleviate depression. These agents are classified into two main groups.

i) MAO inhibitors

MAO inhibitors increase the catecholamine content of various organs so that more catecholamine is to be released by indirectly acting sympathomimetic amines.

ii) Tricyclic and Related Compounds

Tricyclic antidepressants (TCAs) are the most commonly used drugs in the treatment of depression. **Imipramine** is an efficacious drug in alleviating depression. When the drug is given to depressed patients, elevation of mood occurs in about three weeks. It is indicated in all types of depression, nocturnal enuresis, intractable chronic pain, narcolepsy, mood disturbances and sleep apnoea syndrome. **Amitryptaline** is **indicated** in depression, illness accompanied by anxiety, agitation, restlessness and disturbances of sleep; masked depression; dysphoria and depression in alcoholics; childhood bed wetting. It is also useful for prophylaxis of migraine.

Sertaline belongs to the group of selective serotonin reuptake inhibitors (SSRI), which are currently the most commonly used group of drug in the treatment of depression. It exerts its antidepressant actions by inhibiting the reuptake of serotonin in the brain. It is indicated for the treatment of symptoms of depressive illness including accompanying symptoms of anxiety. It is also indicated in preventing relapse of the initial episode of depression or recurrence of further depressive episodes including accompanying symptoms of anxiety. It is indicated in the treatment of obsessions and compulsions in patients with obsessive compulsive disorder.

9.7.4 MOOD Stabilizers (Antimanic Drugs)

Lithium carbonate is the drug of choice for treatment of bipolar disorders. It has narrow therapeutic index and treatment requires facility for therapeutic monitoring of serum lithium levels. It is indicated in acute hypomania, mania, recurrent mania, schizoaffective psychosis, mental depression, cluster headache, chemotherapy induced leukopenia and agranulocytosis.

SAQ 6

a) Sertaline acts by inhibiting ___________ reuptake.

b) __________ is the drug of choice for treatment of bipolar disorders.

c) Moclobemide is a __________________ inhibitor.

9.8 CNS STIMULANTS

These are the group of drugs which are used to stimulate the central nervous system. Some of them are also known as analeptics, but they are not much useful clinically due to non-selectivity of action. They are discussed below.

9.8.1 Analeptics

These drugs stimulate respiration in coma or fainting but because of its narrow margin of safety, they are occasionally used. Nikethamide is no longer used. Doxapram stimulates respiration and raises the blood pressure.

9.8.2 Psychostimulants

Amphetamines (dexamphetamine, methamphetamine etc.) are central sympathomimetics. These are drugs of abuse and repeated use can cause long lasting behavioural abnormalities and can precipitate psychosis. The detail is discussed in chapter 'Adrenergic Drugs'.

9.8.3 Convulsants

Strychnine (alkaloid obtained from the seeds of *Strychnos nux vomica*) was used earlier due to its convulsant properties. **Picrotoxin** (obtained from fish berries) is a potent convulsant. It is not used now-a-days. **Bicuculline** is a synthetic convulsant and possessing picrotoxin like action. **Pentylenetetrazol** is a CNS stimulant, acting by direct depolarisation of central neurons.

But none of these compounds are used therapeutically and their use is restricted to laboratories as research tools.

9.8.4 Cerebroactive Drugs

In this category, some of the compounds are used in the treatment of dementia and other related cerebral disorders. **Pyritinol** enhances cholinergic transmission and improves cerebral microcirculation in ischemic regions. It protects the neurons against hypoxia & disturbance of glucose metabolism. It is indicated in organic brain syndrome, intellectual impairment of senility, encephalitis, alcohol withdrawal state and perinatal distress and cerebrovascular accidents. **Piracitam** improves the functioning of the brain involved in cognitive processes e.g. memory, thought, learning in normal and in subnormal conditions. It is indicated in mental retardation and learning problems in children, confusional state in old age, cerebrovascular accidents, senile dementia, cerebral insufficiency and behavioural problem in elderly.

9.8.5 Drugs Used in Alzheimer's Disease

Alzheimer's disease (AD) is progressive neurodegenerative disorder and mainly affects older individuals. It is the most common cause of dementia which is an impairment of intellect, memory and personality in the absence of gross clouding of motor involvement.

The drugs used in AD are:

- **Centrally acting ChE inhibitor:** Tacrine, donepezil.
- **ChE inhibitors:** Metrifonate, rivastigmine, epastigmine, galantamine.
- **Cholinergic agonists:** Milameline, xanomeline.

SAQ 7

a) _____________ is the analeptic used to stimulate respiration in coma and fainting.

b) ___________ is indicated in mental retardation and learning problems in children.

c) _____________ has dual actions, inhibition of central ChE and agonism on central acetylcholine nicotinic receptors.

9.9 DRUGS USED IN PARKINSONISM

Parkinsonism is an extrapyramidal motor disorder, characterised by akinesia, rigidity and tremor with secondary manifestations such as excessive salivation, seborrhoea, mood changes (especially depression) and in certain patients, liver damage has been reported. It was first described by James Parkinson in 1817. The drugs used in the treatment of parkinsonism is classified into two broad groups.

9.9.1 Drug Acting on Central Dopaminergic System

- **Levodopa**

  Levodopa is the most effective drug available for the treatment of parkinsonism and used in combination with peripheral dopa decarboxylase inhibitors.

Levodopa does not produce any significant action in normal individual. In parkinsonism patient, it improves all manifestations of parkinsonism. The drug also improves mood, memory and patients become more alert and interested in life and surroundings.

- **Peripheral Decarboxylase Inhibitors**

  Carbidopa and benserazide are peripheral decarboxylase inhibitors used in combination with levodopa. They do not penetrate blood-brain barrier and do not inhibit the conversion of levodopa to dopamine in the brain.

- **Dopaminergic Agonists and Other Drugs**

  Bromoergocriptine is an ergot preparation which has a specific dopamine receptor agonist. It is less active than levodopa and used only in late cases as a supplement to levodopa. **Amantadine** is an antiviral compound and also improves the symptoms in parkinsonism. It is more effective than atropine like drugs but it is less effective than levodopa. Its effect on tremors is less than on rigidity. **Selegiline** is a selective mao-b inhibitor that is used with levodopa in early cases of parkinsonism. It prolongs the duration of action of levodopa, attenuates motor fluctuations and decreases wearing off effect. But clinical benefits are short lived (6-24 months).

9.9.2 Drugs Acting on Central Cholinergic System

The central anticholinergic drugs having a higher central versus peripheral cholinergic action ratio are useful. The drugs like atropine are much less effective than levodopa but they are used when levodopa is not tolerated or contraindicated or the patient is not benefitted by levodopa or drug induced parkinsonism.

Atropine like drugs antagonise the symptoms of parkinsonism. They act by reducing the unbalanced cholinergic activity in Parkinsonism. **Benzhexol** is most commonly used effective drug among the atropine substitutes used in parkinsonism. Atropine like drugs cause several side effects such as dry mouth, blurred vision, urinary retention, mental confusion, hallucinations etc. Antihistaminics are better tolerated by elderly patients who do not tolerate anticholinergics.

Ropinirole is the new drug **indicated** for the treatment of signs and symptoms of idiopathic Parkinson's disease. **Pramipexole** has preferential affinity for D_3 family of receptors.

SAQ 8

a) Carbidopa and benserazide are ______________inhibitors used in the treatment of Parkinson's Disease.

b) _____________ is an antiviral agent used in the treatment of Parkinson's Disease.

9.10 SUMMARY

- Barbiturates are general CNS depressants. In higher doses, barbiturates severely depress respiration.
- Benzodiazepines exhibit good efficacy, are relatively safe and have minimum toxicity.
- Pentazocin a partial agonist at opioid receptors and is effective in mild to moderate type of pain associated with surgery, trauma, burns, colics, cancer, in labour and as preanaesthetic medication.
- Naltrexone, due to its longer duration of action can be used as maintenance drug for morphine addicts.
- NSAIDs produce analgesic action by inhibiting the synthesis of prostaglandins (PGs). The common side effects of non-selective NSAIDs are gastric irritation and gastric ulceration due to inhibition of prostaglandin mediated gastric mucous production.
- Drugs used in the treatment of rheumatoid arthritis are NSAIDs, low dose corticosteroids and disease modifying antirheumatic drugs (DMARDs).
- Colchicine, corticosteroids and NSAIDs like indomethacin are used to terminate an acute attack of gout.
- General anaesthetics are the group of drugs which bring about a reversible loss of all sensation and consciousness.
- Preanaesthetic medication refers to the use of drugs before the administration of an anaesthetic agent, which makes it more pleasant and safe to the patient. Drugs mostly employed are anticholinergics, antiemetics, sedatives, opioid analgesics, proton pump inhibitors, etc.
- Tricyclic antidepressants are one of the most commonly used drugs. They produce antidepressant effect by blocking the neuronal uptake of noradrenaline.
- Lithium has narrow therapeutic index and treatment with lithium carbonate requires facility for therapeutic monitoring of serum lithium levels.
- Donepezil and rivastigmine are the most commonly used anti-ChE drugs used in the treatment of Alzheimer's Disease.
- Levodopa is the most effective drug available for the treatment of Parkinsonism and used in combination with peripheral dopa decarboxylase inhibitors.

9.11 TERMINAL QUESTIONS

1. Define sedatives and hypnotics. What are the clinical uses of these drug groups?

2. What is the action of opioid analgesics? What are the important opioid analgesics used clinically?
3. What are general anaesthetics? Write a note on inducing agents.
4. What are the drugs used in the treatment of schizophrenia?
5. What are the drugs used in the treatment of clinical depression?
6. What are the drugs used in the treatment of Alzheimer's disease?
7. Discuss the drugs used in the treatment of Parkinson's Disease? Explain their mechanisms of action?

9.12 ANSWERS

Self Assessment Questions

1. a) Sedation, hypnosis and general anaesthesia
   b) Short tem insomnia
2. a) p-8 (higher centres and spinal cord)
   b) Histamine
   c) Acute morphine poisoning
3. a) Ketorolac
   b) Tubulin
   c) Allopurinol
4. a) i) Nitrous oxide
   ii) 10-15
   b) Preanaesthetic medication refers to the use of drugs before the administration of an anaesthetic agent, which makes it more pleasant and safe to the patient.
5. a) Sodium valproate
   b) Carbamazepine
6. a) Serotonin
   b) Lithium carbonate
   c) MAO-A
7. a) Doxapram
   b) Piracetam
   c) Galantamine
8. a) Peripheral decarboxylase
   b) Amantadine

Terminal Questions

1. Sedative (anxiolytic) are the agents which reduce anxiety and exert a calming effect with little or no effect on motor or mental functions.

Hypnotics are the drugs which produce drowsiness and encourage the onset and maintenance of sleep. They are classified into different categories as follows:

I. **Barbiturates:** Phenobarbitone, Butobarbitone, Pentobarbitone, Secobarbitone

II. **Benzodiazepines**

i) *Used as hypnotics:* Diazepam, Nitrazepam, Midazolam,

ii) *Used as antianxiety agents:* Diazepam, Chlordiazepoxide, Lorazepam, Alprazolam, Oxazepam

iii) *Used as antiepileptic agents:* Diazepam, Clonazepam

III. **Newer nonbenzodiazepine compounds:** Zopiclone, Zolpidem, Zaleplon

Sedatives/hypnotics are mainly used in the treatment of insomnia, derilium, anxiety conditions and as preanesthetic medication.

2. The main action of opioids is CNS depression which further results in analgesia, depression of respiratory centre, cough centre and sleep. In addition they produce euphoria or dysphoria and dependence. Opioids produces analgesia by elevation of pain threshold, thereby reducing the perception of pain. They also alter the psychic reaction to pain which may be associated with feeling of well being e.g. euphoria. The important opioids used clinically are morphine, codeine, pethidine, fentanyl, etc.

3. General anaesthetics are the group of drugs which bring about a reversible loss of pain sensation and consciousness. Inducing agents are those drugs that are administered by the intravenous route for rapid induction of anesthesia (e.g., thiopentone sodium, propofol, etomidate, methohexitone, etc). They get accumulated in the brain and produce unconsciousness rapidly (within 15 seconds). The unconsciousness is then maintained with the help of an inhalational agent like halothane.

4. Psychosis or Schizophrenia is a condition characterised by split mind or splitting of perception from reality. The patient of schizophrenia is dissociated from the world around him and lives in their own world which is characterised by aggression, anxiety, restlessness, hallucinations and delusions. The main drugs used in the treatment of schizophrenia are chlorpromazine, haloperidol, clozapine, olanzepine, etc.

5. Clinical depression is a condition associated with withdrawal from the surroundings, escapism, loss of interest in day to day affairs, etc. It develops due to a decrease in the monoamine levels in the brain. The drugs used in the treatment of clinical depressions are as follows:

MAO inhibitors and Tricyclic antidepressants

6. Alzheimer's disease is a progressive neurodegenerative disorder that mainly affects older individuals. It is the most common cause of dementia which is a impairment of intellect, memory and personality in the absence of gross clouding of motor involvement. The pathological lesion associated with the disease is a decrease in cholinergic activity in the cortex due to loss of cholinergic neurons. The drugs used in the treatment of this condition act by increasing the cholinergic activity in the cortex.

7 Parkinsonism is an extrapyramidal motor disorder, characterized by akinesia, rigidity and tremor with secondary manifestations such as excessive salivation, seborrhea and mood changes (especially depression). The drugs used in this condition are levodopa, carbidopa and benserazide, bromocriptine, amantadine and anticholinergics.