DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Introduction;
Centrally acting drugs are of major therapeutic and clinical importance. They can produce diverse physiological and psychological effects such as induction of anaesthesia, relief of pain, prevention of epileptic seizures, reduction of anxiety, . . . etc. They also include drugs that are administered without medical intervention like tea, coffee, nicotine, and opiates.

STRUCTURE OF THE CNS

- The CNS comprises the "brain" and the "spinal cord".
- The brain is formed of 3 main parts (figure 1)
  - I. Forebrain, which includes:
    - The cerebrum
    - The thalamus
    - The hypothalamus
  - II. The midbrain
  - III. The hindbrain, which includes:
    - The cerebellum
    - The pons
    - The medulla oblongata
Different "PARTS" of the CNS. & their functions:

- **The cerebrum (cerebral hemispheres):**
  - It constitutes the largest division of the brain.
  - The outer part is known as cerebral cortex,
    - Motor areas which govern voluntary movements,
    - Sensory areas which control sensations, and the
    - Association areas which control consciousness, memory, and behavior.
  - The deep part is basal ganglia which control the motor activities and include
    - Corpus striatum
    - Substantia nigra

- **The thalamus**
  - It functions as a sensory integrating center for well-being and malaise.

- **The hypothalamus:**
  - It serves as a control autonomic nervous system. In addition, it regulates blood pressure, body temperature, water balance, metabolism, and secretions of the anterior pituitary gland.
The midbrain
- It serves as a "bridge" area which connects the cerebrum to the cerebellum and pons. It is concerned with motor coordination.

The cerebellum:
- It plays an important role in maintaining the appropriate body posture and equilibrium.

The pons
- It bridges the cerebellum to the medulla oblongata. The "locus ceruleus" is one of the important areas of the pons.

The medulla oblongata:
- It serves as an organ of conduction for the passage of impulses between the brain and spinal cord. It contains many important centers like: the cardioinhibitory, the vasomotor, the respiratory, and the vomiting center (chemoreceptor trigger zone).

The spinal cord
- It is a cylindrical mass of nerve cells extending from the end of the medulla oblongata to the lower lumbar vertebrae. Impulses flow from and to the brain through ascending and descending tracts of the spinal cord.
Different "SYSTEMS" of the CNS & their functions:

I. The Pyramidal system (corticospinal tract).
- It originates from the cerebral cortex and passes through the spinal cord.
- It regulates fine voluntary movements.

II. The extrapyramidal system:
- It controls motor function and gross voluntary movements.
- It consists of basal ganglia, substantia nigra and corpus striatum, dysfunction may cause Parkinson's disease.

III. The limbic system:
- It includes hypothalamus, basal ganglia, hippocampus (responsible for short term memory).
- It controls "behavior" & "emotions".

IV. The reticular formation:
- It is an upper part of the spinal cord and extending upwards.
- It is important in the control of "consciousness" & "wakefulness".

V. The tuberohypophyseal system:
- It is a group of short neurons running from the hypothalamus to the hypophysis regulating pituitary secretions.
CHEMICAL TRANSMISSION IN THE CNS

I. Biogenic amines:
   - Acetylcholine
   - Noradrenaline
   - Dopamine
   - 5-Hydroxytryptamine (5-HT)
   - Histamine

II. Amino acids
   - 1. Excitatory amino acids (glutamate & aspartate)
   - 2. Inhibitory amino acids (GABA & glycine).

III. Others
   - 1. Adenosine
   - 2. Melatonin
Acetylcholine
- Acetylcholine is widely distributed in major parts of the CNS.
- Cholinergic receptors (nicotinic & muscarinic) (predominantly M1)
- Cholinergic pathways play an important role in "arousal", "learning", "motor control", and "short term memory".
- Hyperactivity of cholinergic neurons in the corpus striatum leads to "Parkinson's disease".
- Loss of cholinergic neurons in the hippocampus is associated Alzheimer's disease.

Noradrenaline
- Noradrenergic neurons arise mainly from the "locus ceruleus" (in the pons) and the reticular formation.
- Adrenergic receptors are described in the CNS as in the periphery.
- It plays an important role in the regulation of both "arousal" and "mood".
- Increase; is responsible for wakefulness and alertness,
- Deficiency; cause of “depression".
Dopamine

It is precursor for noradrenaline by "dopamine β-hydroxylase"

Neurotransmitter in dopaminergic neurons which lack this enzyme.

Dopamine receptors are G-protein coupled D1 (Gs) (D1 & D5) and D2 (Gi) (D2, D3, & D4).

It is the major neurotransmitter of the 3 following systems:

- Nigrostriatal system,
  - Control of motor function
  - Deficiency of dopamine in this system causes Parkinson's disease".
- The limbic system
  - Control behavior and emotion.
  - Increased dopaminergic activity in this system cause "schizophrenia".
- The tuberohypophyseal system,
  - Inhibits the secretion of prolactin but stimulates that of growth hormone from the pituitary gland.
- In addition dopamine has a role in the production of "nausea & vomiting" by stimulating dopamine receptors in the chemoreceptor trigger zone in the medulla oblongata.
5-Hydroxytryptamine (5-HT):
- 5-HT-containing neurons arise from nuclei in the pons and medulla known as the "raphe nuclei"
- 5-HT receptors in the CNS include 5-HT1, 5-HT2, and 5-HT3 receptors.
- It involved in behavioral changes, mood, hallucinations, sleep, wakefulness, and control of sensory transmission.

Histamine:
- Histamine is present in the brain in much smaller amounts than in other tissues (skin & lung).
- Histaminergic neurons arise from a small region in the hypothalamus and extend to the forebrain and midbrain.
- Histamine are G-protein coupled receptors include H1-, H2-, and H3.
- It involved in the regulation of arousal, body temperature, and vascular dynamics.
- Blocking central H1 induce sedative and antiemetic effects.
- **Excitatory amino acids (EAAs):**
  - They include glutamate & aspartate.

- **Glutamate receptors**
  - **I. Ionotropic (ion channel coupled)**
    - 1. *NMDA* (N-methyl D-aspartate) receptors
    - 2. *AMPA* (amino methyl propionic acid derivative) receptors
    - 3. *Kainate* receptors.
  - **II. Metabotropic (G-protein coupled)**

- **Glutamate antagonists;** involved in the treatment of "epilepsy" & "schizophrenia" as well as reduction of "brain cell death" caused by excessive *NMDA* receptor activation.

- **Inhibitory amino acids (IAAs)**
  - **GABA** (γ-amino butyric acid) and glycine
    - GABA is synthesized by decarboxylation glutamate.
    - It is mainly in the nigrostriatal system.
    - *GABA* acts on 2 types of receptors:
      - **GABA receptors:** They are **GABAA** (chloride channel-linked) and **GABAB** (G-protein-coupled)
Glycine
- Present in high concentrations in the spinal cord.
- Strychnine" produces convulsions by competitive antagonism of glycine.
- Tetanus toxin inhibit glycine release from inhibitory neurons causing excessive muscle spasms.

Adenosine
- Receptors; A1, A2 (A2A and A2B), and A3 receptors (G-protein coupled).
- Adenosine is mainly inhibitory producing drowsiness, analgesia, and anticonvulsant actions.
- Xanthines, such as caffeine, produce arousal and alertness by acting as antagonists at the A2-receptors.

Melatonin
- Melatonin receptors are G-protein coupled, and are mainly found in the brain and retina.
- Melatonin secretion is high at night and low by day.
Antipsychotic Drugs
(Anti-schizophrenic, Neuroleptics, Major Tranquillizers)

- These drugs acts mainly by antagonizing dopamine and 5 – HT receptors.

**Schizophrenia**

- There is strong hereditary factor in its etiology of schizophrenia. Schizophrenia occurs equally in men and women. It is very rare in children.

**Symptoms**

**Positive symptoms**
- Delusions (false personal beliefs)
- Hallucinations (auditory & visual)
- Thought disorders: Thoughts may come and go rapidly that is not possible to catch them.
- Abnormal behaviors: such as aggressive behaviors.

**The negative symptoms**
- Social withdrawal and disturbed personal relations
- Blunted emotions inconsistent with the person's speech or thoughts
- Poverty of speech
- Loss of drive
Theories of schizophrenia

The cause of schizophrenia remains unclear, but involves a combination of genetic and environmental factors

1. Dopamine theory
   - This theory states that excessive amounts of the neurotransmitter dopamine may play a profound and unique role in inducing psychotic/schizophrenic symptoms.
   - Pharmacologic evidence supporting this theory includes reports that drugs that increase dopamine (i.e., Levodopa, amphetamine) may exacerbate psychotic symptoms. Most evidence suggests that the abnormality in schizophrenia is related to D2 rather than D1 receptors.

2. Glutamate theory
   - The glutamate and NMDA receptor antagonists, such as phencyclidine, ketamine and dizocilpine produce psychotic symptoms (e.g. hallucinations, thought disorder) in humans.
Antipsychotic drugs

1. Classification

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<th>Typical (Classical) Antipsychotics</th>
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<td>Phenothiazines</td>
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Atypical compound characterized by:
- No unwanted motor side effects
- Other pharmacological more than classical compounds
- Improve the negative as well as the positive symptoms.

2. **Mechanism of action of antipsychotics**
   - **Dopamine antagonists**
     - Selective D2 receptor antagonists (e.g. **Haloperidol** and **sulpiride**)
     - Non selective D receptor (D1 & D2) antagonists.
     - **Clozapine** is relatively non-selective between D1 & D2 but has higher affinity for D4
   - **Serotonin receptor blocking activity in brain:**
     - **Clozapine**: blocks D1, D2, D4, S2, muscarinic and α-adrenoceptors.
     - **Risperidone**: blocks S2 receptor to greater extent than it does D2 receptors.
     - Both of these drugs exhibit a low incidence of extrapyramidal side effects.

   - *Anti psychotic drugs take several weeks to take effect, even though their receptor – blocking action is immediate*
3. Pharmacological effects
   I- Action related to dopaminergic receptors
      a. Behavioral effects

- Experimental animals
  - They reduce spontaneous motor activity and in larger doses cause *Catalepsy*. CPZ reduces social interactions (grooming, mating, fighting)

- In man
  - Induce calming, reduce spontaneous physical movement and inhibit aggressive.
  - Inhibit hallucinations and agitation. Delusions and disorganized or thinking tend to disappear.
  - Subjects are slow in respond to external stimuli and tend to be drowse off
b. Other effects related to dopamine antagonism:

- **Antiemetic activity**
  - This action is due to dopamine receptor blockade (D2) centrally in the chemoreceptor trigger zone of the medulla.

- **Endocrine system**
  - Galactorrhea, due to blocking of D2 results in increased serum prolactin.
  - Sodium water retention (increase of aldosterone secretion).

- **Hypothermic action**
  - Chlorpromazine may lower the normal body temperature through increasing heat loss via cutaneous vasodilatation through depression of VMČ and HRC.

II- Actions unrelated to dopamine antagonism

- Phenothiazines and other antipsychotic drugs block the action of:
  - Acetylcholine
  - Histamine (H1)
  - Norepinephrine (α)
  - Serotonin (5-HT)

- Blocking muscarinic receptors
- Blocking α - adrenoceptor: results in orthostatic hypotension
- Antihistaminic (H1) activity: is a property of many phenothiazines.
4- Pharmacokinetics:
- They show variable absorption after oral administration readily distributed all over the body
- Highly bound to plasma protein 90%, t1/2 15 – 30 hs and long duration (months)
- Metabolized in the liver

5- Adverse effects
I. Hypotension (α- adrenergic blocking and direct VD).
II. Sedation (H1-blocking) activity is a property of phenothiazines.
III. Weight gain (5 – HT antagonism).
IV. Autonomic effects: Atropine-like side effects
V. Extrapyramidal side effects (EPS): (D2 – receptor blockade).

Extrapyramidal Side Effects consist of:
A. Parkinson’s like syndrome: characterized by muscle rigidity, resting tremors, and akinesia or bradykinesia

Treatment:
- Decreasing the dose
- Changing to a more anticholinergic antipsychotic
- Adding an anticholinergic agent (benztropine or trihexphenidyl)
B. **Dystonia**; mainly in children treated with phenothiazine
   - It is characterized by an exaggerated posture of the head, neck, or jaw & spastic contraction of the muscles of the lips, tongue, face, or throat, which makes drinking, eating, swallowing, and speech difficult.

Treatment:
- Anticholinergic agent such as **benztropine & trihexphenidyl**.
- Diazepam has also been used

C. **Akathisia**
   - Akathisia is characterized by an inability to sit or stand still, by shifting of the legs and tapping of feet while sitting, and by shifting of the whole weight while standing.

D. **Tardive dyskinesia**
   - Tardive dyskinesia is characterized by abnormal involuntary movements frequently involving the facial, buccal, and masticatory muscles and often extending to the upper and lower extremities, including the neck, trunk, fingers, and toes. For example, the typical abnormal facial movements include opening the mouth, protrusion, and retrieval of the tongue then closing of the mouth, chewing, licking, sucking and smacking.
   - **Clozapine** and **risperidone** exhibit a low incidence of these symptoms may be due to their marked antimuscarinic effect.
   - Sulpiride has much less tendency to produce this effect
VI. Endocrine disturbances:
- Hyperprolactinemia; libido in both (males & females), Gynecomastia and galactorrhea

VII. Idiosyncratic and hypersensitivity reactions
- Jaundice occurs with CPZ and other phenothiazines used in large doses
- Leukopenia and agranulocytosis (clozapine)
- Skin reactions: urticaria
- Antipsychotic malignant syndrome (similar to malignant hyperthermia syndrome)
5- Clinical uses:

1. Treatment of Schizophrenia
2. Antiemetics except thioridazine
3. Treatment of Huntington’s Chorea (mainly haloperidol)
4. Sulpiride have claimed to have specific antidepressant actions
Classification of drugs used in treatment of Parkinson’s disease:

- Drugs that replace dopamine: Levodopa, usually used concomitantly with peripherally acting dopa decarboxylase inhibitors, e.g. Carbidopa, Benserazide.

- Drugs that mimic the action of dopamine: bromocriptine, pergolide, lisuride, Pramipexole and Ropinirole

- Drugs that release dopamine: Amantadine

- MAO – B inhibitors: Selegiline (Deprenyl)

- Selective and reversible inhibitors of COMT: Tolcapone given with levodopa & carbidopa to treat symptoms of Parkinson’s disease.

- Acetylcholine antagonists: Benztropine, trihexphenidyl & biperiden
Parkinson’s Disease
(Shaking Palsy)

- It is a progressive disorder of muscle movement, which occurs most commonly in the elderly. Due to imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

- The main symptoms are
  - Tremors at rest
  - Muscle rigidity
  - Bradykinesia (decrease in the frequency of voluntary movements)
  - Postural and gait abnormalities
  - Dementia

- Etiology
  - Cerebral ischemia (progressive arteriosclerosis or stroke)
  - Virus encephalitis (secondary Parkinson’s disease)
  - Drug-induced, (reserpine, CPZ and haloperidol)
1. Levodopa: (levodopa + Carbidopa) (Sinemet®)

- It is the first – line treatment for Parkinson’s disease

- Dopamine does not cross the blood brain barrier and therefore, has no therapeutic effect in Parkinson’s disease. However, Levodopa, the immediate metabolic precursor of dopamine, does penetrate the brain, where it is decarboxylated to dopamine. Large doses of Levodopa are required because much of the drug is decarboxylated to Dopamine in the periphery resulting in peripheral side effects (nausea, vomiting, cardiac arrhythmia). About 95% of orally administered Levodopa is rapidly decarboxylated in the periphery to dopamine (resulting in the peripheral side effects) which does not penetrate the blood – brain barrier, large doses must be taken to allow sufficient accumulation of Levodopa in the brain (less than 1% enters the brain).

- Therefore, carbidopa (a peripheral dopa decarboxylase inhibitor) is combined with levodopa. This greatly helps to reduce the dose of levodopa and consequently the adverse effects.

- Mechanism of action

- The beneficial effects of Levodopa and other dopaminergic agonists in Parkinson’s disease are mediated via D2 receptors.
Pharmacological effects:
- Continued therapy results in significant reductions in bradykinesia, rigidity and tremors. This may produce fluctuations in motor response (on – off phenomenon).

Pharmacokinetics:
- It is rapidly absorbed from the small intestine (when empty of food).
  - Ingestion of meals particularly if high in protein content interferes with the transport of levodopa into the CNS. Large neutral amino acids (leucine) compete with levodopa for absorption from the gut and for transport across the BBB.
  - It should be taken on empty stomach (45 min before meal).

- It has a short half – life: 1 – 2 h

- It is inactivated by MAO in the wall of intestine (enzyme present in liver, kidney & GIT).
Adverse effects:

I. Two phenomena appear to be the result of prolonged Levodopa treatment

a. Involuntary Writhing movements (Dyskinesia):
   - As a result of excessive activation of dopamine receptors
   - It usually affect the limbs, hands, trunk, tongue and face
   - It happens in the majority of patients within 2 years of starting Levodopa therapy
   - It disappears if the dose of Levodopa is reduced

b. Rapid fluctuation in clinical state:
   - Hypokinesia and rigidity may suddenly worsen for a few minutes (30 min) to a few hours (3 – 4 h) and then improve again. This is called on – off phenomenon. It is not seen in untreated PD patients or with other antiparkinsonism (Suddenly stops while walking or unable to rise from a chair, the patient suddenly lose normal mobility and experience tremors, cramps and immobility).
II. Acute Unwanted effects:

- Nausea, anorexia & vomiting (dopamine stimulates the vomiting center). *Domperidone, peripherally acting dopamine antagonist may be useful in preventing this effect*  
- Hypotension, it may cause postural hypotension in patients on antihypertensive drugs.  
- Psychological effects: increase dopamine in the brain produce schizophrenia like syndrome with delusions, hallucinations, confusion, insomnia or nightmares.

**Optimization of Levodopa treatment:**

1. Inhibition of dopa decarboxylase in the periphery using Carbidopa or Benserazide

2. Inhibition of dopamine degradation in the CNS by the MAOI, Selegiline (Deprenyl) which is highly selective MAO – B inhibitor  
   - MAOB which catalyzes the metabolism of dopamine in brain,t  
   - MAOA metabolizes NE & 5 – HT  
   - Selegiline may be used alone in early cases of Parkinson’s

3. Use of selective and reversible inhibitors of COMT: e.g. Tolcapone
2. Drugs that mimic the action of dopamine

a. Bromocriptine
   - Potent agonist at dopamine D2 receptor in the CNS
   - An ergotamine (an alkaloid with vasoconstrictor action) derivative
   - It inhibits prolactin secretion
   - Similar effects to levodopa and very similar disadvantages (hallucinations, confusion delirium, nausea & orthostatic hypotension are very common)
   - On – Off effect less common
   - Duration of action is longer (6 – 8 h)

b. Pramipexole & Ropinirole
   - They are non – ergot agonists at dopamine receptors
   - They alleviate the motor deficits in both patients that have never been treated with levodopa, and patients with advanced Parkinson’s disease taking levodopa.
   - Nausea, hallucinations, insomnia, dizziness constipation and orthostatic hypotension are among the more distressing side – effects of these drugs
3. Amantadine (Antiviral drug)
- Mechanism of action may be due to increased dopamine release or inhibition of amine uptake. This drug is less effective than Levodopa

4. Acetylcholine antagonists
- **Atropine and related drugs**
  - Benztpoline
  - Trihexphenidyl
  - Biperiden
  - They have less peripheral effect than atropine
  - They diminish the tremors.

- **Side effects**
  - Dry mouth
  - Impaired vision
  - Constipation
  - Urine retention
  - They are less efficacious than levodopa
The Nature of Affective Disorders:

- Affective disorders are characterized primarily by changes of mood (depression or mania) rather than by thought disturbances.

- Depression is the most prevalent psychiatric illness, occurring more often in women (16%) than among men (8%). It may range from a very mild condition, bordering on normality, to severe depression accompanied by hallucinations and delusions.

- Depression causes significant problems in the functioning of those who are affected more than arthritis, hypertension, diabetes and chronic artery disease. In addition, depression can increase risk for developing asthma, HIV and some other medical illness.
Symptoms of depression include emotional and biological components:

**Emotional symptoms:**
- Persistantly sad mood
- Restlessness and irritability
- Feeling of hopelessness and pessimism
- Low self-esteem: feelings of guilt, worthlessness and helplessness
- Difficulty concentrating and remembering
- Indecisiveness, loss of motivation
- Thoughts of death or suicide attempts

**Biological symptoms:**
- Fatigue, decreased energy
- Loss of libido
- Sleep disturbances
- Disturbed appetite

There are two distinct types of depressive syndrome, namely:
- **Unipolar depression,** in which the mood swings are always in the same direction.
- **Bipolar affective disorder,** in which depression alternates with mania.
Mania is in most respects exactly the opposite, with excessive, enthusiasm and self-confidence, these signs include
- Inappropriate elation (pride and joy)
- Irritability
- Severe insomnia
- Impatience and aggression.
- Markedly increased energy
- Increased talking speed
- Disconnected and racing thoughts
- Inappropriate social behaviour

The monoamine theory of depression:
- It states that depression is caused by a functional deficit of monoamine transmitters (NE and/or 5-HT) at certain sites in the brain, while mania results from functional excess.
ANTIDEPRESSANT DRUGS

Antidepressant Drugs fall into the following categories

I. Tricyclic/Polycyclic antidepressants (TCA)
   - They include imipramine, desipramine, amitriptyline, nortroptiline, amoxapine, doxipin.

II. Selective 5-HT(serotonin) reuptake inhibitors (SSRIs):
   - They include fluoxetine, fluvoxamine, paroxetine, sertraline, trazodone, venlafaxine

III. Monoamine oxidase inhibitors (MAOI)
   - Phenelzine, tranylcypromine, which are non-selective with respect to the MAO-A and B subtypes,
   - clorgyline, moclobemide, which are MAO-A-selective
I- Tricyclic Antidepressant Drugs (TCA)

Mechanism of action
- The main effect of TCA is to block the uptake of amines by nerve terminals, by competition for the binding site of the transport protein.
- Most TCA inhibit nor-adrenaline and 5-HT uptake by brain to a similar degree, but much less effect on dopamine uptake.

Pharmacokinetics
- Rapidly absorbed when given orally and bind strongly to plasma albumin, most being 90-95% bound at therapeutic plasma concentrations.
- Metabolized in the liver by two main routes,
  - N-demethylation, whereby tertiary amines are converted to secondary amines (e.g. imipramine to desmethylinimipramine, amitriptyline to nortriptyline)
  - Ring hydroxylation.
- Both the desmethyl and the hydroxylated metabolites commonly retain biological activity. Inactivation of the drugs occurs by glucuronide conjugation of the hydroxylated metabolites, the glucuronides being excreted in the urine.

Actions
- In non-depressed human subjects, TCA cause sedation, confusion and motor incoordination. These effects occur also in depressed patients in the first few days of treatment, but tend to wear off in 1-2 weeks as the antidepressant effect develops.
Adverse effects

- **Atropine-like effects**: dry mouth, blurred vision, constipation, and urinary retention. These effects are strong with amitriptyline, and much weaker with desipramine.

- **Postural hypotension**: It possibly results from an effect on adrenergic transmission in the medullary vasomotor center.

- **Sedation**: and the long duration of action means that daytime performance is often affected by drowsiness and difficulty in concentrating.

Drug Interactions:

- They are strongly bound to plasma protein, so their effects tend to be enhanced by competing drugs (e.g. aspirin and phenylbutazone).

- They rely on hepatic microsomal metabolism for elimination from the body, and this may be inhibited by competing drugs (e.g. antipsychotics and some steroids).

- TCA cause a strong potentiation of the effects of alcohol, and deaths have occurred as a result of this.
II- Selective 5-HT Uptake Inhibitors (SSRIs)

- This group includes fluoxetine, fluvoxamine, paroxetine and sertraline. Fluoxetine is currently the most prescribed antidepressant.
- As well as showing selectivity with respect to 5-HT over noradrenaline uptake, they are less likely than TCA to cause anticholinergic side effects, and are less dangerous in overdose.
- In contrast to MAOI, they do not cause 'cheese reactions'.
- SSRIs are used in a variety of psychiatric disorders as well as in depression, including anxiety disorders, panic attacks, and obsessive-compulsive disorder.

Pharmacokinetics

- SSRIs are well absorbed orally, fluoxetine being longer-acting (24 - 96 hours).
- The delay of 2-4 weeks before the therapeutic effect develops is similar to that seen with other antidepressants.

Adverse effects

- Nausea, anorexia, insomnia, and loss of libido
- In combination with MAOI, SSRIs can result in ‘serotonin syndrome’ associated with tremors, hyperthermia and cardiovascular collapse, from which deaths have occurred.
III- Monoamine Oxidase Inhibitors (MAOI)

- The main examples are phenelzine, tranylcypromine and iproniazid.
- **Mechanism:** These drugs cause irreversible inhibition of the enzyme, and do not distinguish between the two main isozymes.
- **MAO** is found in nearly all tissues, and exists in two similar molecular forms:
  - **MAO-A** has a substrate preference for 5-HT, and is the main target for the antidepressant MAOI.
  - **MAO-B** has a substrate preference for phenylethylamine
  - *Both enzymes act on* noradrenaline *and dopamine.*
  - Type B is selectively inhibited by selegiline, which is used in the treatment of parkinsonism
- *Moclobemide* acts as a reversible competitive inhibitor
- MAO is important in the inactivation of endogenous and ingested amines, which would otherwise produce, unwanted effects.

**Pharmacological actions**

- MAOI cause a rapid and sustained increase in the 5-HT, noradrenaline and dopamine content of the brain, 5-HT being affected most and dopamine least. Similar changes occur in peripheral tissues such as heart, liver, and intestine, and increases in the plasma concentrations of these amines are also detectable
- In normal human subjects, MAOI cause an immediate increase in motor activity, and euphoria and excitement develop over the course of a few days.
Adverse effects

- **Excessive central stimulation:** may cause tremors excitement, insomnia, and in overdose, convulsions.
- **Weight gain:** associated with increased appetite,
- **Hypotension:** is a common side effect
- **Atropine-like side effects:** dry mouth, blurred vision urinary retention, etc. are common with MAOI, though they are less than with TCA

Interaction with other drugs and foods

- Interaction with other drugs and foods is the most serious problem with MAOI, and is the main factor that caused their clinical use to decline. The ‘Cheese reaction’ is a direct consequence and occurs when normally innocuous amines produced during fermentation (mainly tyramine) are ingested. Tyramine is normally metabolized by MAO in the gut wall and liver. MAO inhibition allows tyramine to be absorbed, and also enhances its sympathomimetic effect. The result is acute hypertension, and occasionally intracranial hemorrhage. Foods contain some tyramine include, aged cheese, chicken liver, beer and red wine.
- Administration of indirectly acting sympathomimetic amines (e.g. ephedrine, amphetamine) is also likely to cause severe hypertension in patients receiving MAOI.
- MAOI interacts with some drugs to cause an abnormal syndrome. An important example is the opioid analgesic pethidine, *which* may cause severe hyperpyrexia, with restlessness, coma and hypotension when given in combination with MAOI.
IV- Electroconvulsive Therapy (ECT)

ECT in humans involves stimulation through electrodes placed on either side of the head, with the patient lightly anesthetized, paralyzed with a neuromuscular-blocking drug so as to avoid physical injury, and artificially ventilated. The main disadvantage of ECT is that it often causes confusion and memory loss lasting for days or weeks.
Indications of antidepressants

- **Depression**
- **Panic disorder** (imipramine, MAOI, SSRIs)
- **Obsessive –compulsive Disorders:** The SSRIs have shown to be uniquely effective for treating these disorders
- **Enuresis** is an indication for tricyclics
- **Chronic pain:** Tricyclics found to be especially useful for treating a variety of chronically painful states that often cannot be definitively diagnosed.
Mood Stabilizers

Lithium

Lithium is different in its effects from the antidepressant drugs in that it controls the manic phase of manic-depressive (bipolar) illness and is also effective in unipolar depression. Used prophylactically in bipolar depression, lithium is able to prevent the swings of mood and thus to reduce both the depressive and the manic phases of the illness. Given in an acute attack, lithium is effective only in reducing mania and has no effect during the depressive phase.

Pharmacological Effects and Mechanism of Action

- Lithium is clinically effective at a plasma concentration of 0.5-1 mmol/L, and above 1.5 mmol/L it produces a variety of toxic effects, so the therapeutic window is narrow.
- Lithium is a monovalent cation, which can mimic the role of sodium in excitable tissues, being able to permeate the fast voltage-sensitive channels that are responsible for action potential generation. It is, however, not pumped out by the Na+ / K+-ATPase and therefore tends to accumulate inside excitable cells, leading to a partial loss of intracellular potassium, and depolarization of the cell.
- Lithium inhibits several important enzymes in the normal recycling of membrane phosphoinositides, including conversion of IP2 to IP1 (IP, inositol monophosphate) and the conversion of IP to inositol. This block leads to a depletion of phosphatidylinositol-4,5-biphosphate (PIP2), the membrane precursor of IP3 and DAG. Over time, the effects of transmitters on the cell will diminish in proportion to the amount of activity in the PIP2-dependent pathways.
Pharmacokinetics
- Lithium is given by mouth as the carbonate salt, and is excreted by the kidney.
- The narrow therapeutic limit for the plasma concentration (approximately 0.5-1.5 mmol/L) means that monitoring is essential.

The main toxic effects that may occur during treatment are
- Nausea, vomiting and diarrhea
- Tremors, confusion
- Renal effects: polyuria with resulting thirst
- Thyroid enlargement, sometimes associated with hypothyroidism
- Weight gain

Other Mood-Stabilizing Drugs
- The toxicity of lithium and need for regular monitoring have led to alternatives being sought for the treatment of bipolar disorder.
- Drugs currently investigation include certain antiepileptic drugs-notably carbamazepine and valproate.
ANTIEPILEPTIC DRUGS

- Epilepsy, a physical condition caused by sudden, brief changes in how the brain works.
- **Causes:** In about half of all cases no cause can be found, but head injuries, brain tumors, lead poisoning, problems in brain development before birth, and certain genetic and infectious illnesses can all cause epilepsy.
- Epilepsy occurs when nerve cells in the brain fire electrical impulses at a rate of up to four times higher than normal. This causes a sort of electrical storm in the brain, known as a seizure.
- The particular symptoms produced depend on the function of the region of the brain that is affected. Thus,
- Motor cortex causes convulsion; hypothalamus causes peripheral autonomic discharge; reticular formation in the upper brain stem leads to loss of consciousness.

**Etiology:**

**Primary Epilepsy: (Idiopathic)**
- When no specific anatomic cause for the seizure such as trauma or neoplasm. These seizures may be produced by an inherited abnormality in the CNS. Patients are treated chronically with antiepileptic drugs often for life.

**Secondary Epilepsy:**
- A number of reversible disturbances such as tumors, head injury, hypoglycemia, and meningeal infection can precipitate seizures.
- Antiepileptic drugs are given until the primary cause of seizures can be corrected.
Types of Epilepsy:

I. Partial seizures: Those are seizures in which the discharge begins locally and often remains localized. These may produce relatively simple symptoms without loss of consciousness. The symptoms depend on the brain region or regions involved, and include involuntary muscle contractions, abnormal sensory experiences, abnormal autonomic discharge, or effects on mood and behavior.

<table>
<thead>
<tr>
<th>Partial Seizures</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Produced by a small area of the brain)</td>
<td></td>
</tr>
<tr>
<td>1. Simple (awareness is retained)</td>
<td></td>
</tr>
<tr>
<td>a. Simple Motor</td>
<td>a. Jerking, muscle rigidity, spasms, head-turning</td>
</tr>
<tr>
<td>b. Simple Sensory</td>
<td>b. Unusual sensations affecting either the vision, hearing, smell, taste or touch</td>
</tr>
<tr>
<td>c. Autonomic</td>
<td>c. Tachycardia, stomach upset, diarrhea, loss of bladder control</td>
</tr>
<tr>
<td>d. Simple Psychological</td>
<td>d. Memory or emotional disturbances</td>
</tr>
<tr>
<td>2. Complex</td>
<td>Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements</td>
</tr>
<tr>
<td>(Impairment of awareness)</td>
<td></td>
</tr>
<tr>
<td>3. Partial seizure with secondary generalization</td>
<td>Symptoms that are initially associated with a preservation of consciousness that then evolves into a loss of consciousness and convulsions.</td>
</tr>
</tbody>
</table>
II. Generalized Seizures: Generalized seizures involve whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. It may be convulsive or non-convulsive with immediate loss of consciousness.

<table>
<thead>
<tr>
<th>Generalized Seizures</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Produced by the entire brain)</td>
<td></td>
</tr>
<tr>
<td>1. &quot;Grand Mal&quot; or Generalized tonic-clonic</td>
<td>Unconsciousness, convulsions, muscle rigidity</td>
</tr>
<tr>
<td>2. Absence</td>
<td>Brief loss of consciousness</td>
</tr>
<tr>
<td>3. Myoclonic</td>
<td>Sporadic (isolated), jerking movements, loss of consciousness</td>
</tr>
<tr>
<td>d. Status epilepticus</td>
<td>Seizures are rapidly recurrent.</td>
</tr>
<tr>
<td>e. Febrile Seizures</td>
<td>When in high fever, children may develop tonic-clonic seizures.</td>
</tr>
<tr>
<td>6. Atonic</td>
<td>Loss of muscle tone</td>
</tr>
</tbody>
</table>
Drugs used in Partial Seizures & Generalized Tonic – Clonic Seizures

1. Phenytoin

Mechanism of action
- The major action of phenytoin is to block sodium channels and inhibit the generation of repetitive firing of neurons.
- Actions:
  - Phenytoin reduces the propagation of abnormal impulses in the brain.

Clinical Use
- It is one of the most effective drugs against partial seizures (simple or complex) and generalized tonic – clonic seizures, but not against absence seizures.

Pharmacokinetics
- Phenytoin is well absorbed when given orally
- It is highly bound to plasma proteins (80 – 90 %)
- It is metabolized by hydroxylation system followed by conjugated with glucuronic acid.
- The metabolites are clinically inactive and are excreted in the urine
- Plasma half – life varies from 12 – 36 hr.
Drug interactions & interference with laboratory tests

- Interactions with highly plasma bound drugs: Phenylbutazone or sulfonamides, can displace phenytoin from its binding sites
- Phenytoin has been shown to induce microsomal enzymes responsible for the metabolism of a number of drugs, it increases the rate of metabolism of other drugs e.g., oral anticoagulants, quinidine, doxycycline, and levodopa
- Phenobarbitone and carbamazepine cause decrease in phenytoin steady state concentration through induction of hepatic microsomal enzymes
- On the other hand,
- Isoniazid inhibits the metabolism of phenytoin resulting in increased steady state concentrations when the two drugs are given concomitantly

Unwanted Effects

- Nystagmus
- Diplopia & ataxia
- Sedation usually occurs only at higher levels
- Gingival hyperplasia (gums grow over the teeth specially in children)
- Coarsening of facial features occurs in children
- Hirsutism
- Osteomalacia (due to abnormalities of vitamin D metabolism)
- Megaloblastic anemia (i.e. low folate levels due to interference with vitamin B12 metabolism)
2. Carbamazepine

Mechanism of action
- It appears to be similar to that of phenytoin
- It blocks sodium channels at therapeutic concentrations

Clinical Use:
- Carbamazepine is considered the drug of choice for partial seizures
- It appears to be particularly effective in treating complex partial seizure
- It is also used for generalized tonic – clonic seizure
- It is very effective in some patients with trigeminal neuralgia (a condition that is characterized by intermittent, shooting pain in the face).

Drug interactions
- The increased metabolic capacity of the hepatic enzymes may cause a reduction in steady state carbamazepine concentration, and an increased rate of metabolism of phenytoin, ethosuximide, valproic acid, and clonazepam.
- No clinically significant protein – binding interactions have been reported.

Adverse effects
- Diplopia and ataxia and mild gastrointestinal upsets
- Drowsiness and hyponatremia
- Idiosyncratic blood dyscrasias including fatal aplastic anemia and agranulocytosis
3. Phenobarbital

- It has long been considered one of the safest of the antiepileptic agent.
- Phenobarbital
- Primidone (Metabolized to phenobarbitone)

**Mechanism of action**

- It potentiates the inhibitory effects of GABA via activation of GABAA – receptors, i.e. facilitates the GABA – mediated opening of the Cl- channels.

**Adverse Effects**

- Sedation, ataxia, nystagmus, vertigo, and acute psychotic reactions may occur with chronic use.

**Clinical use**

- It is useful in treatment of: Partial seizures, Generalized tonic – clonic seizures
4. Vigabatrin

Mechanism of action

- It is an irreversible inhibitor of GABA - transaminase (GABA – T)
- It apparently acts by increasing the amount of GABA released at synaptic sites, thereby enhancing inhibitory effects.

Clinical use

- It is useful in the treatment of partial seizures and West’s syndrome

Adverse effects

- Drowsiness, dizziness, weight gain, agitation, and confusion

5. Lamotrigine

Mechanism of Action

- It blocks Na channels (as phenytoin) and inhibits repetitive firing.

Clinical Use

- It is effective as monotherapy for partial seizures.
- The drug is also active against absence and myoclonic seizures in children.

Adverse Effects

- Dizziness, headache, diplopia, nausea, and skin rash.
6. Felbamate

**Mechanism of Action**
- NMDA receptor blockade

**Clinical Uses**
- It is effective in patients with partial seizures
- Its recommended use is to a form of resistant epilepsy in children (Lennox – Gastaut syndrome)

**Side Effects**
- Its acute side effects are mild, mainly nausea, irritability, and insomnia, but it occasionally causes severe reactions, resulting in aplastic anemia or hepatitis.

7. Gabapentin

- It is an analogue of GABA.
- It is effective against partial seizures & generalized tonic – clonic seizures.
- It is effective in the treatment of neuropathic pain and postherpetic neuralgia.

**Side effect:** somnolence, dizziness, ataxia, headache, and tremors
8. Topiramate
- It is a substituted monosaccharide that is structurally different from all other antiseizure drugs.
- Mechanism of action:
  - Blocking of sodium channels, enhancing the action of GABA, acting at a site different from the benzodiazepine or barbiturate sites
  - Blocking AMPA receptors
  - Its spectrum of action resembles that of phenytoin
- Side effects:
  - Somnolence, fatigue, dizziness, nervousness, and confusion

9. Tiagabine
- It is an inhibitor of GABA uptake.
- Clinical Use:
  - It is indicated for the adjunctive treatment of partial seizures.
- Adverse effects:
  - Nervousness, dizziness, tremors, and depression.
Drugs Used in Generalized Seizures

1. Ethosuximide

**Mechanism of action**
- The mechanism of action probably involves inhibition of a particular calcium channel subtype (the T – channel)

**Clinical use**
- Drug of choice for absence seizure

**Pharmacokinetics**
- Completely absorbed orally
- It is not protein bound
- Completely metabolized principally by hydroxylation
- Half – life is about 40 hrs

**Adverse effects**
- Gastric distress (pain, nausea & vomiting, anorexia)
- *Transient lethargy or fatigue, headache, dizziness, hiccup*
2. Valproic acid & Sodium Valproate

**Mechanism of action:**
- Blocking voltage-dependent sodium channels.
- It may facilitate the action of GAD (glutamic acid decarboxylase), a GABA-synthesizing enzyme.
- At high levels, it restricts GABA transaminase, an enzyme that speeds the degradation of GABA.

**Clinical use:**
- Absence seizure
- Valproate is preferred if the patient has concomitant generalized tonic – clonic attacks.
- Valproate is unique in its ability to control certain types of myoclonic seizures.

**Pharmacokinetics:**
- It is well absorbed following an oral dose.
- Food may delay absorption.
- 90% of the drug is bound to plasma proteins.
- Only 3% is excreted unchanged; the rest is converted to active metabolites by the liver, excreted mainly as glucuronide in the urine.
Drug interactions:
- Clearance of valproate is dose dependent
- Valproate inhibits its own metabolism at low doses.
- Valproate inhibits the metabolism of several drugs including: Phenobarbital, phenytoin & carbamazepine.
- It also displaces phenytoin from plasma protein binding.

Adverse Effects:
- Teratogenic
- Nausea, vomiting, gastrointestinal complaints such as abdominal pain & heartburn (The drug should be started gradually to avoid these symptoms),
- Weight gain,
- Hair loss
- Hepatotoxicity
Other Drugs Used In the Management of Epilepsy

Benzodiazepines

Diazepam:
- IV diazepam is the drug of choice for generalized tonic–clonic status epilepticus.
- Status epilepticus: Generalized tonic – clonic status epilepticus is the most common and is a life threatening emergency requiring immediate cardiovascular, respiratory and metabolic management as well as pharmacologic therapy.

Clonazepam:
- Effective against absence seizures
- Effective in some cases of myoclonic seizure
<table>
<thead>
<tr>
<th>Other Drugs</th>
<th>Generalized Seizures</th>
<th>Partial Seizures &amp; Generalized Tonic–Clonic Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diazepam</td>
<td>1. Ethosuximide</td>
<td>1. Phenytoin</td>
</tr>
<tr>
<td>2. Clonazepam</td>
<td>2. Valproic acid</td>
<td>2. Carbamazepine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Phenobarbital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Vigabatrin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Lamotrigine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. Felbamate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Gabapentin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8. Topiramate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9. Tiagabine</td>
</tr>
</tbody>
</table>
Anxiety is an unpleasant state of tension, apprehension, uneasiness or fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances.

The symptoms of severe anxiety are similar to those of fear (such as, tachycardia, sweating, trembling and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment.

Biologic Theories:
(1) Noradrenergic model.
(2) Benzodiazepine receptor model.
Anxiety disorders as recognized clinically include:

- **Generalized anxiety disorder (GAD)** Excessive worries about more than one circumstance characterize this anxiety problem. People with GAD are bothered or worried most of the time. Many times the worries are unrealistic. Symptoms include motor tension: trembling, twitching, muscle tension, restlessness, fatigability, dry mouth, dizziness, hot flushes, trouble falling asleep and difficulty in concentrating.

- **Panic disorder** (attacks of fear occurring in association with marked somatic symptoms, such as sweating, tachycardia, chest pains, trembling, choking, etc)

- **Phobias** (strong fears of specific things or situations, e.g. snakes, open spaces, as animal phobias, blood injury phobias, phobias of heights or air travel, social phobias).

- **Post – traumatic stress disorder** (anxiety triggered by insistent recall of past stressful experiences such as rape, sexual abuse, emotional abuse, living through negative natural events such as devastating earthquake or hurricane).

- **Stress Anxiety**

- **Obsessive Compulsive disorder**
Classification of Anxiolytic and Hypnotic Drugs

- I. Benzodiazepines & related compounds
- II. Barbiturates
- III. Miscellaneous
I. Benzodiazepines

A. Advantages as anxiolytics and hypnotics:
- They possess a wide safety margin.
- A benzodiazepine antagonist is available.
- They do not induce liver microsomal enzymes (less drug interactions).
- They produce less inhibition of REM sleep (less hangover).

B. Mechanism of action
- Benzodiazepines act selectively on GABAA-receptors. Benzodiazepines bind specifically to a regulatory site of the receptor, distinct from the GABA binding site, and act allosterically to increase the affinity of GABA for the receptor.

C. Actions
- 1. Reduction of anxiety & aggressiveness
- 2. Sedative and hypnotic actions
- 3. Antiepileptic; such as clonazepam and diazepam (IV)
- 4. Muscle relaxant; by central action eg clonazepam & flunitrazepam at small dose.
D. Pharmacokinetics:
- Well absorbed orally, iv, im and strongly to plasma proteins.
- Their high lipid solubility (accumulate gradually in body fat).
- Metabolized in the liver and are excreted as glucuronide conjugates in the urine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall duration of action</th>
<th>Main uses</th>
</tr>
</thead>
</table>
| Triazolam
Midazolam    | Ultra-short (< 6h)         | Hypnotic
| Zolpidem*        | Ultra-short (≈ 4h)         | Hypnotic
| Lorazepam
Oxazepam
Temazepam        | Short (12 – 18h)           | Anxiolytic, hypnotic          |
| Alprazolam
Nitrazepam     | Medium (24h)               | Anxiolytic                     |
| Diazepam
Chlordiazepoxide
Clorazepate      | Long (24 – 48h)            | Anxiolytic, muscle relaxant   |
E. Adverse Effects:

**Acute toxicity:**
- Benzodiazepines in acute overdose cause prolonged sleep.

**Treatment:** an effective antagonist: Flumazenil

**Unwanted effects during normal therapeutic use:**
- Drowsiness, amnesia, impaired motor coordination (ataxia), and confusion
- Enhancement of the depressant effect of other drugs, including alcohol
- Tolerance & dependence

F. Clinical uses:
- Both acute and chronic anxiety disorders
- Insomnia
- Epilepsy & seizures
- Treatment of skeletal muscle spasm
G. Benzodiazepine Antagonists

**Flumazenil**
- It competitively antagonizes the binding of benzodiazepines.
- It is not effective in drug overdose with barbiturates or TCAs.
- **Adverse effects**: Agitation, confusion, dizziness, nausea

**Zolpidem**
- It has hypnotic actions.
- The drug binds selectively to the BZ1 subtype of benzodiazepine receptors and facilitates GABA-mediated neuronal inhibition.
- Like the benzodiazepines, the actions of zolpidem are antagonized by flumazenil.
- Zolpidem has minimal anticonvulsant & muscle relaxing properties.

**Zaleplon**
- It binds selectively to the BZ1 receptor subtype, facilitating the inhibitory actions of GABA.
- Zaleplon is rapidly absorbed from the GIT and has an elimination half – life of about 1 hour.
- Rapid onset and short duration of action are favorable properties for those patients who have difficulty falling asleep.
- The risk of development of tolerance and of withdrawal symptoms indicative of physiologic dependence appears to be low.
II. Barbiturates

- Benzodiazepines are commonly used than barbiturates because
  - Tolerance
  - Induction drug-metabolizing enzymes,
  - Physical dependence,
  - Withdrawal symptoms
  - Cause coma in toxic doses.
  - Induce anesthesia such as thiopental.

A. Mechanism of action:
- Enhance the action of GABA, but they bind to a different site on the GABAA-receptor / chloride channel.

B. Pharmacological actions:
- 1. Depression of CNS; sedation to general anesthesia.
- 2. Sedation and Hypnosis; in hypnotic doses they induce sleep within 20 – 60 min,
- 3. Anesthesia
- Thiopental, methohexital & (IV to induce surgical anesthesia).
- 4. Anticonvulsant
- Phenobarbital (grand mal epilepsy)
C. Pharmacokinetics

- Barbiturates are absorbed orally, distributed widely throughout the body, metabolized in the liver and excreted in the urine.

<table>
<thead>
<tr>
<th>Barbiturates</th>
<th>Duration</th>
<th>Absorption from GIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>6 – 8 h</td>
<td>slow</td>
</tr>
<tr>
<td>Mephobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amobarbital</td>
<td>4 - 6 h</td>
<td>Fairly rapid</td>
</tr>
<tr>
<td>Butabarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>3 h</td>
<td>Rapid</td>
</tr>
<tr>
<td>Secobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultra short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>15 min</td>
<td>Used as iv anesthetic</td>
</tr>
</tbody>
</table>
D. Drug Interactions

- Barbiturates + other CNS depressants (e.g. alcohol, and benzodiazepines) ------ severe respiratory depression
- Barbiturates + CNS stimulants (e.g. caffeine) -------- antagonism.
- Barbiturates induce liver microsomal enzymes. Thus, they cause significant acceleration of disappearance of corticosteroids, oral anticoagulant, oral contraceptives, phenytoin, digitoxin, metoprolol, propranolol.

E. Therapeutic uses

1. Hypnosis; short acting to induce sleep and long acting to long time sleep
2. Sedation: (Phenobarbital & butabarbital)
   - Sedation dose is ½ to ¼ the hypnotic dose.
3. Anesthesia; e.g. thiopental
4. Anticonvulsants; such as in tetanus & strychnine
5. Antiepileptics; e.g phenobarbital and mephobarbital in Grand mal epilepsy
6. Narcoanalysis in psychiatry
   - The barbiturates are employed as diagnostic and therapeutic aids in psychiatry, in narcoanalysis. They are used to activate latent abnormalities in the EEG.
F. Adverse effects

1. Hangover: Drowsiness may last for a few hours after a hypnotic dose of barbiturate. Residual effects may take the form of vertigo, nausea, or vomiting.

2. Idiosyncrasy (*Paradoxical Excitement)*:

3. Pain: Barbiturates may cause restlessness, excitement and even delirium when given in the presence of pain.

4. Hypersensitivity: Allergic reactions occur especially in persons who tend to have asthma, skin rash & urticaria.
III. Miscellaneous

1. Buspirone
   - It is a partial agonist at 5-HT1A-receptors used in anxiety disorders. Buspirone takes days or weeks to produce its effects in man.
   - It is ineffective in controlling panic attacks.
   - Side effects: withdrawal effects, nausea, dizziness, headache and restlessness.

2. Chloral hydrate
   - It is converted to trichloroethanol in the body.
   - The drug is an effective sedative and hypnotic that induces sleep in about 30 minutes and lasts about 6 hours.
   - It does not depress REM sleep.
   - Side effects: irritating of GIT tract, unpleasant taste

3. Meprobamate: It is no longer used.
4. Methaqualone: It is no longer used.
5. Antihistamines (e.g. Hydroxyzine, diphenhydramine): They may be used in mild cases of anxiety.
6. β-adrenoceptor antagonists (e.g. Propranolol): These are used to treat some forms of anxiety, particularly where physical symptoms, such as sweating, and tachycardia are troublesome.
General Anesthetic Agents

Characters of General anesthetic agents
- Depress the CNS reversibly
- Produce loss of consciousness
- Produce analgesia, muscular relaxation
- Produce minimal depression of the vital functions

Theories explaining the mechanism of action of general anesthetics:
- A. Lipid solubility theory
- B. Surface tension theory
- C. Adsorption theory
- D. Biochemical theory
- E. Neurophysiological theory
- F. Physical theories (hydrate theory)
Stages of Anesthesia

Stage I: Analgesia
- Subject is conscious but drowsy; responses to painful stimuli are reduced.

Stage II: Excitement
- The subject loses consciousness & no responds to non-painful stimuli, but responds to painful stimuli. Respiration is irregular & cough reflex is present. It is a dangerous state; in modern anesthetiac this stage cannot be distinguished.

Stage III: surgical anesthesia
- Spontaneous movement ceases, respiration become regular & muscles are markedly relaxed.

Stage IV: Medullary paralysis
- Start by stopping of respiration, ends by failure of circulation (death occurs within a few minutes).
- The use of a single anesthetic agent is now uncommon. Listed stages of anesthesia are seldom observed in practice.

The anesthetic state of clinical purposes consists of three components mainly: loss of consciousness, analgesia & muscle relaxation. To produce these effects a combination of drugs rather than a single drug is used.
Classification of General Anesthetics:

I- Inhalation Anesthetics

II- Intravenous Anesthetics

I. Inhalation Anesthetics

The potency of inhaled anesthetics is indicated by the minimum alveolar concentration (MAC). MAC is small for potent gases as halothane, and large for less potent agents as nitrous oxide.

These are either volatile liquid or gases

A. Diethyl ether (volatile liquid)
B. Chloroform (volatile liquid)
C. Halothane (volatile liquid)
D. Enflurane (volatile liquid)
E. Methoxyflurane (volatile liquid)
F. Isoflurane (volatile liquid)
G. Desflurane (volatile liquid)
H. Sevoflurane (volatile liquid)
I. Nitrous oxide (volatile gas)
I. Inhalation Anesthetics

Absorption, distribution, excretion of inhalation anesthetics

Very rapidly absorbed from the lungs, the anesthetic passes through the alveolar membrane into the arterial blood from which it is transported to the various body tissues and in particular to the CNS. All inhalation anesthetics are excreted mostly unchanged through the lungs.

A. Diethyl ether (Ether) (obsolete now)

<table>
<thead>
<tr>
<th>Advantages of Ether</th>
<th>Disadvantages of Ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide safety margin</td>
<td>Inflammable &amp; explosive</td>
</tr>
<tr>
<td>Good muscle relaxation</td>
<td>Irritant to the respiratory passage</td>
</tr>
<tr>
<td>No significant action on the cardiovascular system</td>
<td>Unpleasant slow induction &amp; delayed recovery</td>
</tr>
<tr>
<td>Sufficiently potent to allow good oxygenation</td>
<td>Post anesthetic vomiting &amp; pulmonary complications</td>
</tr>
<tr>
<td>Non expensive</td>
<td>Acidosis &amp; hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>Prolonged ether anesthesia causes convulsions</td>
</tr>
<tr>
<td></td>
<td>Postoperative nausea and vomiting</td>
</tr>
</tbody>
</table>
**Advantages of Chloroform** | **Disadvantages of Chloroform**
--- | ---
Rapid pleasant induction | Narrow safety margin
No irritation of respiratory passages | Vagal bradycardia & cardiac arrest may occur
Non inflammable and non explosive | Sensitization of myocardium to catecholamines may produce ventricular fibrillation
Good skeletal muscle relaxation | Myocardial depression with progressive fall in BP

Delayed liver necrosis
## C- Halothane

<table>
<thead>
<tr>
<th>Advantages of Halothane</th>
<th>Disadvantages of Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td>It has a sweet odor</td>
<td>Inadequate muscle relaxation</td>
</tr>
<tr>
<td>It is highly potent</td>
<td>Poor analgesic (supplemented with NO&lt;sub&gt;2&lt;/sub&gt; &amp; opiates)</td>
</tr>
<tr>
<td>Non – inflammable, non explosive liquid</td>
<td>May produce respiratory failure</td>
</tr>
<tr>
<td>Non – irritant to the respiratory system</td>
<td>Marked arterial hypotension due to myocardial depression and vasodilatation</td>
</tr>
<tr>
<td>Useful in plastic surgery to produce “bloodless area” through inducing controlled hypotension</td>
<td>Hepatotoxic (life threatening hepatic necrosis)</td>
</tr>
</tbody>
</table>
D- Enflurane

Halogenated anesthetic that is similar to halothane in its potency

<table>
<thead>
<tr>
<th>Advantages of Enflurane</th>
<th>Disadvantages of Enflurane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faster induction and recovery than halothane</td>
<td>may cause seizures</td>
</tr>
<tr>
<td>Less sensitization of the heart to catecholamines</td>
<td>may induce malignant hyperthermia (similar to many other halogenated anesthetics)</td>
</tr>
<tr>
<td>It does not produce hepatic or renal toxicity (little production of fluoride)</td>
<td></td>
</tr>
<tr>
<td>Great potentiation of muscle relaxants due to more potent curare-like effect</td>
<td></td>
</tr>
</tbody>
</table>

**Malignant hyperthermia**

It results from excessive metabolic heat production in skeletal muscle, due to excessive release of Ca2+ from the sarcoplasmic reticulum. The result is a dramatic rise in body temperature, associated with muscle contractions & acidosis. It can be fatal unless treated promptly. It is treated with dantrolene a muscle relaxant drug which blocks these Ca2+ channel.
E. Methoxyflurane
- This agent is the most potent inhalation anesthetic because of its high solubility in lipid. Prolonged administration of methoxyflurane is associated with the metabolic release of fluoride, which is toxic to the kidneys. Therefore, methoxyflurane is rarely used outside of obstetric practice. It finds use in child-birth because it does not relax the uterus when briefly inhaled.

F. Isoflurane (Isomer of enflurane)
- This is a newer halogenated anesthetic that has low biotransformation and low organ toxicity. Unlike the other halogenated anesthetic gases, does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. Isoflurane is a very stable molecule that undergoes little metabolism, as a result of which, less fluoride is produced. Isoflurane is not currently believed to be tissue toxic.

G. Desflurane
- Chemically similar to isoflurane
- Induction & recovery are faster
- Its potency is lower than the above mentioned halogenated anesthetics
- At the concentration used for induction (10%), desflurane causes some respiratory tract irritation which can lead to coughing & bronchospasm

H. Sevoflurane
- It resembles desflurane but it is more potent and less likely to cause respiratory irritation.
I- Nitrous oxide

<table>
<thead>
<tr>
<th>Advantages of Nitrous Oxide</th>
<th>Disadvantages of Nitrous Oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non - inflammable, non – explosive</td>
<td>Weak general anesthetic</td>
</tr>
<tr>
<td>Non – irritant to the respiratory tract</td>
<td>Inadequate muscle relaxation</td>
</tr>
<tr>
<td>Rapid induction and recovery</td>
<td>Prolonged exposure (&gt; 6h ) causes inactivation of methionine synthase, an enzyme required for DNA and protein synthesis, resulting in bone marrow depression which leads to anemia and leukopenia (It should be avoided in patients with anemia)</td>
</tr>
<tr>
<td>Good analgesia, useful for production of analgesia during child birth (during delivery)</td>
<td></td>
</tr>
<tr>
<td>No serious effect on circulation and respiration</td>
<td></td>
</tr>
</tbody>
</table>
II. Intravenous Anesthetics

<table>
<thead>
<tr>
<th>Advantages of IV Anesthetics</th>
<th>Disadvantages of IV Anesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of administration</td>
<td>The dose once injected can not be withdrawn</td>
</tr>
<tr>
<td>No irritation to the respiratory tract</td>
<td>Rate of their elimination is slower</td>
</tr>
<tr>
<td>No explosion hazards</td>
<td>An overdose is difficult to be antagonized</td>
</tr>
<tr>
<td>Rapid induction, no excitement and rapid recovery</td>
<td></td>
</tr>
<tr>
<td>No postoperative nausea or vomiting</td>
<td></td>
</tr>
</tbody>
</table>

- **Anesthetic Agents;** Produce unconsciousness in about 20 sec.
  - A. Ultrashort Acting Barbiturates
  - B. Etomidate
  - C. Propofol
- **Basal anesthetics;** Act less rapidly to produce sedation prior to anesthesia; thus reducing the amount of inhalation anesthesia.
  - D. Ketamine
  - E. Diazepam
A. Ultrashort Acting Barbiturates

Examples
- Thiopental Sodium
- Methohexital Sodium
- Thiamylal Sodium
  - Onset time 10 – 20sec. And 5 – 10 min duration
  - Pass through the placenta (thiopental) and produce respiratory depression to the fetus
  - They have no analgesic effect

Therapeutic uses
- General anesthesia for minor operations
- Inductions of anesthesia, then completed by another anesthetic agent e.g. N2O
- Anticonvulsant
- For basal anesthesia, the drug is given rectally in doses less than those required to produce full anesthesia.

B. Etomidate
- It is a potent ultra short acting non – barbiturates hypnotic agent lacking analgesic properties.
- Narrow safety margin (produce respiratory & cardiovascular depression).
- Its pharmacological properties are similar to those of barbiturates.
- It is used for induction and supplement to maintain anesthesia.
C. Propofol

- Used in induction or maintenance of anesthesia.
- Anesthesia may be maintained by continuous infusion of propofol combined with opioids & N2O
- The drug does not impair liver or kidney function

D. Benzodiazepines

- They are useful as preanesthetic medication and for induction and maintenance of anesthesia.
- Examples:
  - Diazepam
  - Lorazepam
  - Midazolam
Neuroleptanalgesia

- Combination of neuroleptic drugs and analgesics to produce a state of deep sedation and analgesia e.g. droperidol (neuroleptic) and fentanyl (potent opioid analgesic).

- The combination used in a variety of diagnostic or minor surgical procedures (e.g. endoscopy, bronchoscopy, radiological studies, burns dressing). Neuroleptanalgesia can be converted to Neuroleptanesthesia by the concurrent administration of 65% N2O in O2
Dissociative anesthesia

- It means that the patient may appear awake and reactive but does not respond to sensory stimuli (this condition is similar to Neuroleptanalgesia but results from the administration of a single drug) Example: Ketamine

- It produces analgesia, amnesia, and paralysis of movement without actual loss of consciousness.

- Ketamine is believed to act by blocking NMDA – receptor.

- It is used IM & IV (the most important advantage of ketamine is its potential for administration by IM route).

- Following a single dose, unconsciousness is lost for 10 – 15 min & analgesia persists for 40 min. The patient feels dissociated from his environment, the eyes remain open but the patient does not respond to external stimuli. There is no muscle relaxation (a state of catalepsy).

- Side effect; hallucination, delirium, irrational behavior (scream and cry) during recovery. These effects are much less marked in children, thus ketamine is often used in conjunction with benzodiazepines for minor procedures in pediatrics.
III. Preanesthetic Medication

This refers to the use of drugs prior to the administration of an anesthetic agent in order to:

- Decrease anxiety & fear
- Produce sedation
- Relieve preoperative pain if it is present
- Reduce the amount of general anesthetic required
- Minimize the undesirable side effects of anesthetic agent such as salivation, bradycardia, postoperative vomiting

1. Sedative – hypnotics and antianxiety agents:
   A. Benzodizepines: to cause amnesia e.g. Diazepam, Lorazepam and Midazolam
   B. Barbiturates: orally or IM 1 hour before operation to produce sedation and relief anxiety e.g. Pentobarbital, Secobarbital
   C. Antihistamines: in induce sedation and anticholinergic properties e.g. Hydroxyzine, Diphenhydramine
   D. Phenothiazines: to induce tranquilizing and antiemetic effect. They e.g. Promethazine, Propiomazine
2. Analgesics
   - **Opioids:** are thus frequently used IM 1 hour before anesthesia for preanesthetic medication. e. g. Morphine, Meperidine, Fentanyl

3. Antiemetics
   - Droperidol, Hydroxyzine, Ondansetron

4. Anticholinergic drugs:
   - **Atropine** or **scopolamine** is used IM 1 hour before anesthesia in order to:
     - Reduce salivary and bronchial secretion.
     - Block the reflex vagal effect on the heart produced by the anesthetic.
     - Counteract the respiratory depressant actions of morphine.
       - **Scopolamine** has the following advantages over atropine as a preanaesthetic drug:
         - It is predominantly a central depressant producing *sedation, amnesia.*
         - It is more potent as **antiemetic, antisecretory,** and to counteracts the respiratory depression of morphine.

5. Skeletal muscle relaxants: to facilitate intubation and suppress muscle tone to the required degree for surgery. e. g. Succinylcholine, Atracurium, Vecuronium