Drugs Acting On Central Nervous System

I. Narcotic Analgesics and Antiparkinsonian Drugs

[1] ANALGESICS

Analgesics are drugs that relieve pain due to multiple causes. Drugs that relieve pain due to a single cause, e.g. ergotamine (migraine), glyceryl trinitrate (angina pectoris) are not classed as analgesics.

- Analgesics are classified into 2 main groups:

<table>
<thead>
<tr>
<th>Opioid (Narcotic) Analgesics</th>
<th>Non-opioid Analgesics (analgesics- antipyretics)</th>
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<tbody>
<tr>
<td>Are the <em>most powerful</em> analgesics that can relieve <em>any type</em> of pain except itching.</td>
<td>Are mild analgesics and effective in certain types of pain as headache, toothache …</td>
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<tr>
<td>Act <em>mainly</em> at the level of the cortex.</td>
<td>Act on the level of the thalamus and hypothalamus.</td>
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<tr>
<td>Can produce <em>addiction</em>.</td>
<td>No addiction.</td>
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<td><strong>Example:</strong> Morphine and codeine.</td>
<td>Used to lower the elevated body temperature.</td>
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<td>Example: NSAIDs e.g. salicylates, and paracetamol</td>
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NARCOTIC ANALGESICS
They are derived from opium alkaloids. Many alkaloids are isolated from opium, but few of them are used clinically (Morphine, Codeine and Papaverine).

**OPIUM ALKALOIDS**

I. Morphine

**Absorption and Fate:**
- It can be absorbed after oral, subcutaneous or intramuscular injection as well as after being smoked. It cannot be absorbed from the intact skin.
- Subcutaneously, the action starts after 10-20 minutes, reaches its maximum after 1-1.5 hour and disappears after 2-2.5 hours.
- Morphine is detoxicated in the liver (conjugated and broken down).
- Excreted in the urine in the free and bound forms.
- A certain portion is excreted in the stomach (gastric lavage should be performed in morphine poisoning even if it has been taken parenterally).
- Morphine can cross blood placental barrier so it can cause respiratory depression in the newly born child.

Dose: 8-15mg by injection (subcutaneously or IM) as morphine hydrochloride or morphine sulfate.

**Pharmacological Actions of Morphine:**

(I) On C.N.S: Morphine is mainly a central depressant but certain centers are stimulated by morphine:

A. Centers Depressed by Morphine:

1. Cortical pain center:
   - Morphine has analgesic effect through:
     - *(a)* Elevation of the threshold of pain perception in the sensory area.
     - *(b)* Alteration of the response to pain i.e. pain is still present but its effect on the behavior e.g. anxiety, restlessness are greatly reduced.
   - It produces euphoric action; this can pass to central excitement or even convulsions i.e. idiosyncrasy to morphine. In this case, morphine is contraindicated.

2. Respiratory center:
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• Respiration is depressed and the sensitivity of the respiratory center to CO₂ is reduced leading to decrease in the rate and depth of respiration.

• Respiratory failure is the cause of death in morphine poisoning.

3. Cough center:
• It is made less sensitive by morphine so morphine can suppress cough.
• Codeine is used more because:
  ▪ It is not addicting.
  ▪ Has side effects less than morphine (No respiratory depression).

4. Inhibition of the polysynaptic spinal reflexes.

5. Inhibition of the vasomotor center in large doses.

B. Centers stimulated by Morphine:
1. Vomiting center: Emetic chemoreceptor trigger zone (CTZ) in the medulla is stimulated by morphine leading to nausea and vomiting.

2. Occulomotor center:
   ▪ Morphine causes severe miosis (Pin Point Pupil – PPP) due to stimulation of the Edinger-Westphal nucleus of the oculomotor; 3rd cranial nerve [as a result of inhibiting the cortical inhibitory effect on the nucleus].
   ▪ This effect is central so it occurs only if the drug is given systemically not when applied locally in the eye.

3. Stimulation of monosynaptic spinal reflexes (stretch reflex).

4. Release of antidiuretic hormone (ADH) form the posterior pituitary.

5. Stimulation of cardiovagal center: leading to slow and full pulse.

(II) On Plain Muscles (A, B, C, D, E)
Morphine increases the tone of the smooth muscles and causes spasm of the sphincters:

A. On the Gastro Intestinal Tract:
1. Decreases G.I.T secretions (gastric, biliary, pancreatic and intestinal).
2. Increase tone of the intestinal smooth muscles.
3. Spasm of the sphincters.
4. Decreases the peristaltic activity (propulsive contraction) and increase segmentation movement (increase absorption).

5. Decreases the perception (unawareness) of the defecation reflex.
   - All this will lead to constipation, which is considered as a side effect (but of value in treatment of severe diarrhea).

B. Spasm of the Biliary Passages:
   - Marked increase in biliary tract pressure due to:
     (a) Spasm of sphincter of Oddi.
     (b) Spasm of biliary muscles.
   - Atropine partially antagonizes this effect while nalorphine completely abolishes it.

C. Bronchi:
   - Therapeutic doses of morphine do not cause bronchoconstriction in normal individuals.
   - But it may precipitate bronchoconstriction in asthmatic patients due to histamine release.
   - So, morphine is contraindicated in bronchial asthma due to:
     (a) Bronchoconstriction.
     (b) Release of histamine.
     (c) Respiratory center depression.

D. Urinary Bladder:

Urine retention due to:
   (1) ↑ Tone of urinary bladder sphincter.
   (2) Depression of the micturition reflex.
   (3) Urine formation is decreased due to central effect of the drug that causes the release of ADH.

(E) Increase the Tone of the Ureter.

(III) On Metabolism:
Morphine decreases the basal metabolic rate.

(IV) On Histamine:
*Morphine is a histamine releaser.*
(V) On the Skin:
Morphine causes: (as a result of histamine release)
(a) Sweating (wet skin).
(b) Vasodilation (flushed skin).
(c) Itching.
(d) Allergic skin reactions can occur.

(VI) On Cardiovascular System
- Therapeutic dose has no effect.
- High dose can cause hypotension due to:
  (a) Peripheral vasodilation (histamine release).
  (b) Inhibition of vasomotor center (VMC).

Opioid Receptors:
- Several types of opioid receptors have been identified at various sites in the nervous system and other tissues.
  - **Mu (μ) receptors are responsible for:**
    1. Supraspinal analgesia
    2. Euphoria, sedation.
    3. Respiratory depression,
    4. Physical dependence.
    5. Constipation.
  - **Kappa (κ) receptors are responsible for:**
    1. Spinal analgesia.
    2. Miosis and sedation.
  - **Sigma (σ) receptors mediate:**
    1. Dysphoric,
    2. Hallucination,
    3. Respiratory and vasomotor stimulation.
  - **Delta (δ) receptors:**
    Supraspinal analgesia

Tolerance: (failure of responsiveness to the usual dose of the drug)
- Tolerance develops to the analgesic and respiratory depressant actions of morphine after 10-14 days.
- But no tolerance to the constipating and miotic actions of morphine. Morphine addict always has constipation and PPP.
- Cross-tolerance occurs between morphine and various other narcotic analgesics.

**Therapeutic Uses of Morphine:**

1. As a powerful analgesic in the treatment of **severe pain**:
   i. Coronary thrombosis.
   ii. Renal colic (with *atropine*).
   iii. Post-operative pain (*except after cholecystectomy*).  
   iv. Terminal stages of painful malignant disease.

2. Pre-anaesthetic medication: 10-15 mg subcutaneously or IM one hour before the general anaesthesia.

3. In paroxysmal nocturnal dyspnoea (cardiac asthma = left ventricular failure leading to pulmonary congestion and dyspnoea) to alleviate dyspnoea.

4. Certain cases of **severe cough** e.g. cancer of the bronchial tree.

5. Certain cases of **severe diarrhea** (loperamide) given orally after removing the poison causing the diarrhea from the intestine by a purgative.

**Side Effects:**

(A) **Minor side effects:**
   1. Nausea and vomiting.
   2. Constipation.
   3. Itching, bronchoconstriction and hypotension due to histamine release.
   4. Urine retention.
   5. Increased intracranial tension.

(B) **Major side effects:**
   1. Respiratory depression.

**Contra-Indications:**

1. *Bronchial asthma* due to:
   - Bronchoconstriction.
   - Release of histamine.
   - Respiratory depression.
2. Chronic pulmonary disease e.g. emphysema.
3. Cases of idiosyncrasy to morphine.
4. Advanced liver disease.
5. Extremes of age (very young or very old patients).
6. Head injuries (Respiratory depression increases CO₂ which causes cerebral vasodilatation and so elevates C.S.F pressure).
7. During delivery (morphine crosses the placenta leading to respiratory center depression and neonatal asphyxia).
8. Biliary colic (increase biliary pressure). N.B. may be used with nalorphine or atropine.
9. Acute abdomen (relieves the pain but interferes with the diagnosis of the condition).
10. Myxedema (low basal metabolic rate).
11. In prostate hypertrophy (morphine may cause urine retention).
12. Hypotension
13. Constipation.

Opium or Morphine Addiction:

- Repeated administration of morphine leads to psychological as well as physiological dependence.
- If morphine is suddenly withdrawn, withdrawal symptoms will occur. The withdrawal symptoms are characterized by:
  - Yawning.
  - Rhinorrhea (watery discharge from the nose).
  - Lacrimation.
  - Restless sleep and insomnia.
  - Dilated pupils.
  - Vomiting.
  - Diarrhea.
  - Severe muscle cramps.
  - Severe headache.
  - Excitement.
  - Patient refuses food leading to dehydration and acidosis.
Cause of these withdrawal symptoms:

- There are endogenous morphine-like compounds present in the body.
- They are present in the brain and G.I.T and are called enkephalins and those present in the pituitary gland are called endorphins.
- If morphine is given externally, the opiate receptors become saturated (or overloaded) leading to inhibition of the synthesis of the endogenous morphine-like compounds.
- If the exogenous opiate administration is stopped, withdrawal symptoms will occur, because the endogenous opioid is deficient and the receptor is deprived from both the endogenous and the exogenous opioids.

Treatment of Morphine Addiction:

1. Hospitalization and psychotherapy (attention to nursing and feeding).
2. Gradual withdrawal of morphine till we reach a stabilizing dose which is just sufficient to prevent withdrawal symptoms from occurring.
3. Substitution therapy with methadone:
   - In the ratio of 1mg methadone to 4 mg morphine for 1 week.
   - Then, methadone is withdrawn gradually over a period of 3 days.
   - It is an addicting drug but the withdrawal symptoms of methadone are less than those of morphine.
4. Hypnotics to help sleeping.

Acute Morphine Poisoning:

Clinical picture:

1. The patient is in coma.
2. Respiration is slow and depressed.
3. Cyanosis and the skin is cold and wet (sweating).
4. Pinpoint pupil (however, the pupil may dilate due to medullary depression, when it is terminal).

Treatment:
1. Gastric lavage with potassium permanganate 0.2% to oxidize the alkaloid (even if morphine was given by injection) + saline purgative, Mg SO\(_4\) to evacuate the intestine.
2. Artificial respiration with O\(_2\) – CO\(_2\) mixture.
3. Mild respiratory stimulant may be used
4. Specific antidotes:
   - Naloxone.
   - Naltrexone

**II. Codeine (Methyl Morphine)**

1. It is less potent.
2. It produces constipation.
3. Nausea and vomiting are less.
4. Less addiction.

**Uses:**
1. As cough depressant (for dry cough).
2. As analgesic with aspirin and paracetamol.

**SEMISYNTHETIC MORPHINE DERIVATIVES**

**Heroin (Diacetyl Morphine)**

- Extremely powerful analgesic.
- More addicting than morphine.
- Causes respiratory depression more than with morphine.

**Uses:**
Not used clinically except in severe pain of terminal stages of malignancy.

**SYNTHETIC MORPHINE DERIVATIVES**

**I. Meperidine (Pethidine)**

It has:
1. Atropine-like action (parasympatholytic).
3. Papaverine-like action (smooth muscle relaxant effect).

- **Difference from morphine:**
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1. Its analgesic action is \(\frac{1}{10}\) that of morphine.
2. It does not depress cough.
3. It does not depress respiration in therapeutic doses.
4. It does not cause constipation.
5. Has atropine-like action.
6. Pupil is dilated (does not cause PPP).
7. Tolerance and addiction are less than with morphine.

**Dose:** 50-100 mg orally or parenterally (S.C. or I.M).

- **Similar to morphine in:**
  1. Stimulation of CTZ.
  2. Release of ADH.

**Therapeutic Uses:**
1. As analgesic instead of morphine.
2. In obstetrics to relieve labour pain.
3. As preanesthetic medication instead of morphine.
4. Better than morphine in renal and biliary colics (It has atropine and papaverine-like actions).

**II. Fentanyl**
- Analgesic potency is 80 times that of morphine.
- Duration of action shorter than morphine and pethidine.
- **Uses:**
  1. As analgesic alone.
  2. With a tranquillizer to produce Neuroleptanalgesia (a state of sedation and analgesia) which is used in minor procedures e.g. bronchoscopy or in obstetrics.

**III. Methadone**
- A potent analgesic.
- With long duration of action.
- Depresses respiratory and cough centers.
- Causes addiction but the withdrawal symptoms are milder than morphine.
- **Uses:**
1. Analgesic.
2. Treatment of opium (morphine) addiction.

**IV. Loperamide (Imodium) and diphenoxylate:** are non-analgesic opioids, used for antimotility effect on the gut. They are constipating agents. (refer to pharmacology of GIT)

**MIXED AGONIST-ANTAGONIST OPIOID ANALGESICS**

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. This group is characterized by:

1. The effect of these drugs depends on previous exposure to opioids
   a) In individuals who have not recently received opioids, mixed agonist-antagonist shows agonistic effect and are used to relieve pain.
   b) In patients with opioid dependence the agonist-antagonist drug produce withdrawal symptoms.

2. These drugs induce respiratory depression which reaches a ceiling effect at relatively low doses. This property may represent an advantage over morphine-like analgesics as it is possible to increase the analgesic activity by increasing the dose without the hazard of increasing the respiratory depression.

**Example:**

Pentazocine is agonist on kappa receptors and is a weak antagonist at Mu receptors.

**OPIOID ANTAGONISTS**

**Nalorphine**

It has antagonist action on Mu receptors, with a partial agonist action on delta and Kappa receptors so it is considered as a partial antagonist.

**Naloxone (Narcan)**
It is a pure narcotic antagonist at all opioid receptor sites with no morphine like properties i.e. it is a pure antagonist. Therapeutic uses of naloxone are the same of that of nalorphine. Naloxone is preferred since it lacks any agonistic activity.

**Naltrexone:** has a longer duration of action than naloxone and a single oral dose of naltrexone blocks the effects of injected heroin up to 24 hours.

**Therapeutic Uses:**
1. Treatment of acute morphine poisoning (it stimulates respiration, improves miosis, vomiting and G.I spasm).
2. Diagnosis of opium addiction (precipitate withdrawal symptoms).
3. Decreases the neonatal respiratory depression secondary to administration of morphine, because it can traverse the placental barrier. It is given to the mother before delivery or to the infant through the umblical vein after delivery.

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**[2] DRUGS USED IN TREATMENT OF PARKINSONISM**

*In parkinsonism, there are:*
1. Slowing of movement.
2. Rigidity of skeletal muscles.
3. Resting tremors.
4. Abnormality of posture and gait.
5. Mood changes.
7. Masked face.

**Causes of Parkinsonism:**
1. Idiopathic.
2. Arteriosclerotic.
3. Post encephalitic (after viral encephalitis).
4. Iatrogenic (caused by drugs) i.e. long use of large doses of chlorpromazine or reserpine.
   - Parkinsonism is due to an imbalance between the levels of acetylcholine and dopamine in the basal ganglia (substantia nigra, corpus striatum that are responsible for motor control).
   - In parkinsonism, the dopamine content is low so that the cholinergic system is dominant.

**Treatment of parkinsonism**
1. Anticholinergic drugs to reduce cholinergic activity.
2. Dopaminergic drugs to enhance dopaminergic activity.

(A) Anti-cholinergic drugs

1. Atropine or hyoscine
   - Reduce tremors, rigidity, and excessive salivation.
   - Tolerance occurs after prolonged use, increasing the dose will increase the side effects.

2. Synthetic atropine substitutes
   - Reduce tremors, and rigidity.
   - Less side effects.
   - Examples:
     - Benztropine (*Cogentin*).
     - Trihexphenidyl (*Artane*).

3. Drugs with anticholinergic and antihistaminic effect: (e.g. Diphenhydramine)
   i. Reduce tremors and rigidity (atropine-like action).
   ii. Anti-histaminic effect producing a sedative effect.

Contraindications of anticholinergic drugs:
1. Glaucoma.
2. Prostate enlargement.

(B) Dopaminergic drugs

Amantadine:
- This is an anti-viral drug.
- Decreases tremors and rigidity of parkinsonism.
- It acts by:
  - Stimulating the release of dopamine from dopaminergic nerve terminals in the basal ganglia.
  - Inhibiting dopamine re-uptake.

Bromocryptine (*Parlodel*):
- It is an ergot derivative.
- It is a dopamine receptor agonist.
- Stimulates dopaminergic receptors in the basal ganglia.
- Inhibits prolactin release (suppresses lactation).

**Selegiline**

- Selectively inhibits monoamine oxidase B (MAO_B) which metabolizes dopamine, but doesn’t inhibit MAO_A (which metabolizes norepinephrine and serotonin). Thus, by decreasing the metabolism of dopamine, selegiline has been found to increase dopamine levels in the brain. Therefore, it enhances the actions of L-Dopa and when these drugs are administered together, selegiline substantially reduces the required dose of L-Dopa.

**L-Dopa:**

- It is the precursor of dopamine.

\[
\text{L-Dopa} \xrightarrow{\text{Dopa decarboxylase enzyme}} \text{Dopamine}
\]

- Dopamine is not used in the treatment of parkinsonism because it cannot cross the blood brain barrier (BBB).
- L-Dopa can cross the BBB and increase the dopamine content of basal ganglia.
- 95% of given L-Dopa is transformed to dopamine in the peripheral tissues by decarboxylation (dopamine can not cross BBB).
- So only 5% of the given dose of L-Dopa will be converted to dopamine in the basal ganglia (by decarboxylation) and improves parkinsonism.
- Carbidopa is given with L-dopa.
- Carbidopa is a Dopa decarboxylase inhibitor only in the periphery because it can not cross the BBB so all the given L-Dopa will reach the basal ganglia.
- Dopamine accumulation in the periphery leads to nausea and vomiting.
- So, give Carbidopa + L-Dopa (Sinemet) 1:10

**To:**

1. Decrease the dose of L-Dopa.
2. Decrease the side effects of L-Dopa.
3. Increase the efficiency in treatment of parkinsonism.

**Drug interactions with L-dopa:**

1. L-Dopa + Vit. B₆ reduces its anti-parkinsonian effect because it elevates dopa decarboxylase activity (if used alone without carbidopa).
2. **Anti-cholinergic drugs** + L-Dopa cause **synergism** (the effect is greater than the sum of their individual effects).
3. **Phenothiazines** e.g. chlorpromazine (block dopamine receptors), antagonize its antiparkinsonian effect.

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II. Sedative- Hypnotics, Antipsychotic, Antidepressant Drugs and CNS Stimulants
[1] Sedative–Hypnotic Drugs

The major therapeutic use of sedative-hypnotic drugs is to cause sedation (with concomitant relief of anxiety) or to encourage sleep. Disorders involving anxiety and sleep disorders are common problems, which are effectively treated by the sedative-hypnotic agents.

An effective sedative (sometimes called anxiolytic, or minor tranquilizer) should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions.

A hypnotic drug should produce drowsiness and encourage the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep from which patient can be easily aroused. Hypnotic effects involve more pronounced depression of the CNS than sedation, and this can be achieved with most sedative drugs simply by increasing the dose.

Examples of Sedative-Hypnotic drugs:

1. Benzodiazepines
2. Buspirone
3. Zolpidem
4. Barbiturates
5- Choral hydrate, paraldehyde
6- Ethyl alcohol (Ethanol)

I. BENZODIAZEPINES

Benzodiazepines (BZs) are the most widely used anxiolytic drugs. They have largely replaced barbiturates in the treatment of anxiety, since BZs are more effective and safer. BZs induce sleep when given in high doses at night, provide sedation, and reduce anxiety when given in low, divided doses during the day.

Mechanism of Action:

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. BZs potentiate GABA-ergic inhibition at all levels of the CNS.

BZs bind to specific, high affinity BZ receptors present in various parts of the CNS. These receptors are separate but adjacent to the receptor for GABA. The binding of BZ enhances the affinity of the GABA receptors for GABA neurotransmitter, resulting in a more frequent opening of adjacent chloride channels. The increased influx of Cl\(^-\) into the neuron results in enhanced hyperpolarization and inhibition of neuronal firing.

Pharmacological Actions:

BZs have neither antipsychotic activity nor any analgesic action and do not affect the autonomic nervous system. BZs exhibit the following actions:

1. **Reduction of anxiety**: At low doses, BZs are anxiolytic.
2. **Sedation and induction of sleep**: At higher doses, all BZs which are used to treat anxiety can produce hypnosis.
3. **Muscle relaxation**: BZs relax the spasticity of skeletal muscles, probably by increasing presynaptic inhibition in the spinal cord. Diazepam in particular, has a very pronounced depressant activity on skeletal muscles.
4. **Anticonvulsant effect**.

Pharmacokinetic Aspects:

_BZs are lipophilic and are rapidly and completely absorbed after oral administration. BZs as well as most other sedative-hypnotics bind extensively to plasma proteins._
BZs are metabolized by the hepatic microsomal metabolizing system and are excreted in urine as glucuronides or oxidized metabolites.

**Classification of Benzodiazepines**

BZs can be roughly divided into short, intermediate and long-acting groups. The longer acting agents form active metabolites with long half-lives.

- **Short-acting**: triazolam (3-8 hours).
- **Intermediate-acting**: alprazolam (10-20 hours).
- **Long-acting**: diazepam (1-3 days).

**Therapeutic Uses:**

1. **Anxiety state**: BZs should only be used for short periods of time because of addiction potentials e.g. alprazolam.
2. **Insomnia**: The most commonly prescribed BZs for sleep disorders are long-acting flurazepam, intermediate-acting temazepam, and short-acting triazolam.
3. **As anticonvulsants**:
   - Diazepam i.v. in status epilepticus.
   - Clonazepam in chronic treatment of epilepsy.
4. **Muscular disorders**: Diazepam is useful in the treatment of skeletal muscle spasms and spasticity from degenerative disorders such as multiple sclerosis and cerebral palsy.
5. **For sedative effects** during medical or surgical procedures such as endoscopy and bronchoscopy as well as for premedication prior to anaesthesia.
6. **Induction of general anaesthesia**.
7. **Treatment of alcohol withdrawal symptoms**: Diazepam can be useful in controlling the tremors, acute agitation and the impending acute delirium tremors.

**Advantages of BZs over barbiturates**:

1. less rapid eye movement (REM) suppression.
2. less tolerance and enzyme induction.
3. limited capacity to produce profound and fatal CNS depression (i.e. BZs are relatively safe in overdose in contrast to many sedative hypnotics e.g. barbiturates).

The Most Common Side Effects of the BZs are:
1. Drowsiness and confusion.
2. Hypotension in old patients.
3. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving a car.
4. If high doses of BZs are given over a prolonged period, weight gain as well as psychological and physical dependence may develop. Abrupt discontinuation of BZs results in withdrawal symptoms, including confusion, anxiety, restlessness and insomnia.

Contraindications:
1. Pregnant and lactating women: due to
   a) The ability of BZs to cross fetal placental barrier. If these drugs are given in the pre-delivery period, they may contribute to the depression of neonatal vital functions.
   b) Sedative-hypnotics are detectable in breast milk during lactation and may exert depressant effects on CNS function in the nursing infant.
2. In patients with myasthenia gravis: due to the muscle relaxing effect of BZs.
3. In acute depression or psychosis: due to their additive CNS depression.

Drug Interactions:
BZs have additive or synergistic effects with other CNS depressants such as alcohol, barbiturates and antihistaminics. Although BZs are safer than other sedative-hypnotic drugs even in acute overdosage, they are used cautiously in treating patients with liver disease.
**BZ antagonist “Flumazenil”**

**Mechanism of action**

Flumazenil carries similar structure to BZs, and competitively antagonize the binding of BZs to their receptors. It blocks many of the actions of BZs but does not antagonize the CNS effects of other sedative-hypnotics, ethanol, opioids or general anesthetics.

**Therapeutic uses**

1. To reverse the sedative effect of BZs used during anaesthesia
2. In the treatment of acute BZs overdose.
3. Hepatic coma

**II. BUSPIRONE**

Buspirone is a non-sedating alternative to BZs but it may take up to four weeks to act. (Useful in chronic anxiety states)

**Mechanism of action:** Buspirone is a partial agonist at presynaptic 5HT\textsubscript{1A} receptors, producing negative feedback inhibition of 5HT release. Also, it displays some affinity for dopamine receptors.

**Advantages of buspirone:**

1. Unlike BZs, buspirone has no hypnotic, anticonvulsant, or muscle relaxant properties.
2. It has minimal abuse liability.
3. Buspirone causes less psychomotor impairment than BZs and does not affect driving skills.
4. The drug does not potentiate the CNS depressant effects of other sedative-hypnotics, ethanol or tricyclic antidepressants.

**Side effects of buspirone:** Tachycardia, palpitations, nervousness, gastrointestinal distress may occur more frequently than with BZs. These side effects are possibly caused by postsynaptic 5HT\textsubscript{1A} receptor stimulation.
III. ZOLPIDEM

**Mechanism of action:**
Zolpidem is a hypnotic that binds selectively to a subset of the BZs receptor family and facilitates GABA-mediated neuronal inhibition. Zolpidem has a rapid onset and a short duration of action (about 4 hours), its actions are antagonized by flumazenil. It has minimal muscle relaxing and anticonvulsant effects. Respiratory depression may occur if large doses of zolpidem are ingested together with other central depressants.

**Advantages of zolpidem** include:
1. Rapid onset
2. No withdrawal effects.
3. Minimal rebound insomnia.
4. Little or no tolerance with prolonged use.
5. Minimal muscle relaxing effect.
6. Respiratory depression occurs only if large doses of zolpidem are ingested together with other central depressants.
7. Antagonized by flumazenil

**Disadvantages of zolpidem** include:
1. Short duration of action (about 4 hours),
2. Nightmares, headache and daytime drowsiness.
3. Gastrointestinal upset

IV. BARBITURATES

Non-selective CNS depressants, which produce effects ranging from sedation and reduction of anxiety to hypnosis and unconsciousness. Barbiturates were in the past the mainstay of treatment used to sedate or to induce and maintain sleep.

Today, they have been largely replaced by BZs, because barbiturates induce drug-metabolizing enzymes, produce tolerance and physical dependence and severe withdrawal symptoms.
Classification:

- **Ultra-short acting:** Thiopental Na is highly lipid soluble; it is an IV anaesthetic that acts within seconds with duration of action of 20 minutes. (refer to pharmacokinetics of anaesthesia).
- **Short-acting:** Pentobarbital and secobarbital act for 3-8 hours.
- **Long-acting:** Phenobarbital (more than 24 hours).

Mechanism of Action:

Barbiturates facilitate the actions of GABA at multiple sites in the CNS but they do not bind to the same site of BZs on the GABA-receptor/chloride channel. They cause activation of GABA\(_A\) receptors. This increases the duration of opening of the Cl\(^-\) channel associated with the receptor, and the neuronal membrane is therefore hyperpolarized and less likely to fire.

Actions:

At low doses, barbiturates produce sedation, at higher doses, they cause hypnosis followed by anaesthesia. Overdosage may cause respiratory depression and death.

Pharmacokinetics:

Lipid solubility and ionization influence the onset and duration of action. The ultra-short acting drug; thiopental is very lipid soluble, and a high rate of entry into the CNS contributes to the rapid onset of its central effects. Also the drug is rapidly redistributed from the brain, first to highly perfused tissues such as skeletal muscle and subsequently to poorly perfused adipose tissue. These processes contribute to the termination of its major central nervous system effects.

Long-acting agents (less lipid soluble) have slower onset and longer duration of action. They are slowly metabolized by the liver microsomal enzymes. Barbiturates cross the placental barrier and their concentrations in the fetal blood approach that in maternal blood.

Barbiturates and their metabolites are excreted by the kidney and their rate of excretion is increased by alkalinization of urine.

Therapeutic Uses:

1. **Anaesthesia:** Thiopental Na is used intravenously to induce anaesthesia.
2. **As sedative-hypnotic agents:** Barbiturates have been replaced by BZs. However, pentobarbital may still be used as sleeping pills.
3. **Anticonvulsants:** Emergency treatment of convulsions in status epilepticus by thiopental as the last approach. Phenobarbital is used in long-term management of tonic-clonic seizures and eclampsia.
4. To lower serum bilirubin in:
   a) Patients with chronic cholestasis
   b) Neonatal jaundice (kernicterus) which can cause brain damage because unconjugated bilirubin can penetrate the blood brain barrier. Barbiturates such as phenobarbital can increase the conjugation of bilirubin and reduces this risk by inducing the activity of glucuronyl transferase enzyme.

**Side effects**

1. **CNS effects**: drowsiness that can interfere with motor and mental performance; hangover. In large doses, barbiturates cause marked depression of CNS and are likely to be fatal.
2. **GIT disturbance**.
3. **Folate deficiency**.
4. **Induction of P450** thus the rate at which they are metabolized increases over the first few days of administration. Also, it leads to increased metabolism of other drugs e.g. warfarin and oestrogen (reducing the effectiveness of oral contraception and oral anticoagulants).
5. **Tolerance**.
6. **Physical dependence with prolonged use**.
7. **Teratogenicity**.

**Treatment of Barbiturates Overdosage:**

1- Controlled ventilation and O₂ inhalation.
2- Gastric lavage in comatose patients who have open airway.
3- Osmotic diuresis and alkalinization of urine for phenobarbital.
4- Hemodialysis in severe cases.

**Contraindications:**

- Liver and kidney diseases.
- During labour.
- Old age.
- Shock.
- In patients with acute intermittent porphyria.
N.B. Hepatic porphyria is an inherited disorder in which the enzymes required for haem synthesis are lacking; this will lead to acute attacks of GIT, neurological, and behavioral disturbances due to accumulation of porphyrin–containing haem precursors. Barbiturates induce amino laevulinic acid (ALA) synthetase, which stimulates the hepatic formation of porphyrins from these precursors.

**Drug Interactions:**

- As barbiturates are potent inducers of hepatic metabolizing enzymes, they are liable to cause drug interactions. They increase the rate of metabolic degradation of many other drugs i.e. dicumarol, phenytoin, digitalis, and griseofulvin.
- Additive effects to other CNS depressants.

**V. SOME OLDER AND LESS COMMONLY USED SEDATIVE–HYPNOTICS**

- **Chloral hydrate** is an effective sedative and hypnotic that induces sleep in about 30 minutes and lasts about 6 hours. It causes GIT irritation and epigastric distress and an unpleasant taste sensation. Chloral hydrate is metabolized into two major metabolites; trichloroethanol (active and relatively non-toxic) and the other is trichloroacetic acid, which is toxic and tends to accumulate in the body.
- **Paraldehyde** produces hypnosis in about 15 minutes and its effect lasts for 4-8 hours. It has a strong odour, bad taste and may irritate the GIT. Paraldehyde was used in patients with hepatic or renal failure as it is mainly eliminated through the lung.

**VI. ETHYL ALCOHOL (Ethanol)**

Ethyl alcohol (ethanol) is the most commonly abused drug in the world. Like other sedative-hypnotic drugs, ethyl alcohol in low to moderate amounts relieves anxiety and fosters a feeling of well being or even euphoria.

**Pharmacokinetic Aspects:**

Ethanol is absorbed rapidly from the GIT. Distribution is rapid, with tissue levels approximating the concentration in blood. In the CNS, the concentration of ethanol rises quickly since the brain receives a large proportion of blood flow and ethanol readily crosses biologic membranes.

Ethanol is metabolized in a two-step process. As the drug passes through the liver, it is first dehydrated by alcohol dehydrogenase, forming acetaldehyde, which is then metabolized by aldehyde dehydrogenase into acetone that enters the citric acid cycle.

Over 90% of alcohol consumed is oxidized in the liver; much of the remainder is excreted through the lungs and in the urine.
**Treatment of Acute Alcohol Intoxication:**
1. The most important goals are to prevent severe respiratory depression and aspiration of the vomitus.
2. Treat hypoglycemia and ketosis by administration of glucose.
3. Electrolyte solutions for dehydrated patients. If vomiting is severe, large amounts of potassium may be required as long as renal function is normal.
4. Thiamine is given to protect against the severe neurological disturbances.
5. Analeptics may be used.

**Treatment of Chronic Alcoholism:**
Hospitalization, psychotherapy and nutritional therapy may be needed.

**Drug therapy includes:**
1. **BZs** (e.g. diazepam) are used to prevent alcohol withdrawal symptoms. They are preferred over barbiturates because of their wide margin of safety. The dose must be tapered slowly over several weeks.
2. **Disulfiram**: This drug causes extreme discomfort to patients who drink alcohol. The drug given by itself to nondrinkers has little effects however, flushing, throbbing headache, nausea, vomiting, sweating, hypotension and confusion occur within a few minutes after drinking alcohol.

Disulfiram acts by inhibiting aldehyde dehydrogenase thus, alcohol is metabolized as usual but acetaldehyde accumulates. Acetaldehyde will form the toxic intermediates; methanol and formaldehyde.

**Alcohol-Drug Interactions:**

I. **Pharmacokinetic alcohol–drug interactions:**
   a) **Chronic alcohol consumption** induces activity of drug-metabolizing enzymes in liver cells. Ethanol-mediated induction of hepatic cytochrome P<sub>450</sub> enzymes is particularly important with regard to paracetamol. This will lead to increased conversion of paracetamol to reactive heptotoxic metabolites.
   b) **Acute alcohol consumption** may inhibit metabolism of other drugs e.g. phenothiazines and tricyclic antidepressants (due to decreased metabolism or decreased liver blood flow).
II. Pharmacodynamic alcohol interactions  
   a) Additive CNS depression with other sedative-hypnotics is the most important, for example alcohol and barbiturates are potentially lethal combination.
   b) Alcohol potentiates the pharmacologic effects of many non-sedative drugs, including vasodilators and oral hypoglycemic agents.

VII. OTHER CLASSES OF DRUGS THAT MAY EXERT SEDATIVE EFFECTS

These classes include:
1. **β-blocking drugs** (e.g. propranolol), which are used mainly to reduce physical symptoms of anxiety (tremors, sweating, and palpitation). Their effect depends on blockade of peripheral sympathetic responses rather than on any central effects.
2. Antipsychotic drugs.
3. Tricyclic antidepressants.
4. Some antihistaminic agents (e.g. hydroxyzine).

[2] ANTIPSYCHOTIC DRUGS

Antipsychotic drugs (also called antischizophrenic drugs, neuroleptic drugs or major tranquilizers) are used mainly to treat schizophrenia but are also effective in some psychotic states; such as manic states and delirium.

*Schizophrenia* is one of the most important forms of psychiatric illness, which often affects people during adolescence and tends to be a chronic and disabling disorder. Patients with schizophrenia have delusions (paranoid in nature), hallucinations (often in the form of voices) and abnormal thoughts. The pathogenesis of schizophrenia is unclear but the disease has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly an increased dopamine activity of the mesolimbic system.

**Examples of antipsychotic Drugs:**
1- Phenothiazine derivatives: Chlorpromazine, promethazine.
2- Butyrophenone derivatives: Haloperidol, droperidol.
3- Newer antipsychotics: Risperidone and clozapine.
**Mechanism of Action:**

All of psychotropic drugs block dopamine receptors in the brain and in the periphery specifically D₂ receptors. Some of the newer psychotropic drugs (clozapine and risperidone) exert part of their action through inhibition of serotonin receptors.

**Pharmacokinetic Aspects:**

Most antipsychotic drugs are readily but incompletely absorbed; many undergo significant first pass metabolism. These drugs have a large volume of distribution and are highly protein bound. They are highly lipid soluble, cross easily into the CNS and accumulate in fatty tissues. These drugs are almost completely metabolized and then excreted by the kidney and through bile.

**Pharmacological Actions:**

1. **Antipsychotic effects:** These are now thought to be produced -at least in part- by their ability to block dopamine D₂ receptors in the mesolimbic system. Antipsychotic drugs relieve hallucination, improve thoughts and calm the hyperactive psychotic patients.

The therapeutic effects of antipsychotic drugs take several weeks to occur.

2. **Extrapyramidal effects:** Blocking of dopamine receptors in the nigrostriatal pathway causes unwanted parkinsonian-like symptoms; rigidity and tremors and motor restlessness. Clozapine and risperidone exhibit a low incidence of these symptoms.

3. **Antiemetic effect:** Most antipsychotic drugs have strong antiemetic effects that are mediated by blocking D₂ receptors both centrally in the chemoreceptor trigger zone in the medulla and peripherally in the stomach.

4. **Autonomic effects:** Most of the antipsychotic drugs, particularly chlorpromazine cause anticholinergic effects; including blurred vision, dry mouth, constipation and urine retention. Blocking of α-adrenergic receptors causes orthostatic hypotension and light headedness.

5. **Endocrine effects:** Antipsychotic drugs produce striking adverse effects on the reproductive system. Amenorrhea-galactorrhea, false–positive pregnancy tests have been reported in women, whereas men have experienced decreased libido and gynecomastia. These effects are due to blockage of
dopamine inhibitory effect on prolactin release from the pituitary leading to an increase in prolactin release.

6. Other effects: Antipsychotic drugs can block $H_1$ histaminic receptors causing sedation and confusion. They can also alter temperature-regulating mechanisms.

**Therapeutic Uses:**

1- Treatment of schizophrenia: The traditional antipsychotic drugs are most effective in treating positive symptoms of schizophrenia (delusion, hallucinations and thought disorders). The newer agents with serotonin blocking activity are effective in many patients resistant to the traditional agents, especially in treating negative symptoms of schizophrenia (blunted emotions and reduced ability to react with people).

2- Prevention of severe nausea and vomiting like in cases of drug-induced nausea.

3- The butyrophenone (droperidol) is used in combination with opioid (fentanyl) in neuroleptanalgesia.

4- Due to its antihistaminic effects, promethazine is used in cases of pruritus and as a preoperative sedative.

5- To induce hypothermia in certain major operations.

6- Chlorpromazine is used to treat intractable hicough.

**Adverse Effects:**

Most of the unwanted effects of antipsychotics are extension of their known pharmacologic actions, but a few are allergic and some are idiosyncratic.

1. Extrapyramidal effects.

2. Autonomic effects: Orthostatic hypotension, impaired ejaculation and anticholinergic adverse effects.

3. Endocrine effects: Weight gain, hyperprolactinemia in the form of galactorrhea, amenorrhea in women and gynecomastia, changes in libido and impotence in men.

4. Tardive dyskinesia: It is the most important adverse effect of long-treatment with antipsychotic drugs and is characterized by involuntary movements, including lateral jaw movements and fly-catching motions of the tongue.
Tardive dyskinesia is postulated to result from increased number of dopamine receptors that are synthesized in response to long-term dopamine receptor blockade, which leads to neuronal supersensitivity to dopamine.

5. Allergic reactions: Agranulocytosis, cholestatic jaundice and skin eruptions.

6. Ocular complications: Chlorpromazine causes deposits in the cornea and lens.

**Advantages of the newer antipsychotic drug "clozapine":**

1. Clozapine is effective in the treatment of negative symptoms of schizophrenia.

2. Clozapine may be effective in patients resistant to treatment with other antipsychotics and may produce a better quality of response.

3. The incidence of extrapyramidal symptoms is lowest with clozapine.

4. Clozapine apparently does not cause tardive dyskinesia.

**Contraindications:**

1- During withdrawal from alcohol or other drugs, antipsychotic drugs may aggravate acute agitation.

2- Chlorpromazine is contraindicated in patients with seizure disorders, since it can lower seizure threshold.

**Drug Interactions:**

1- Antipsychotic drugs through the α-adrenoceptor blockade produce vasodilatation and lower systemic pressure. The concomitant use of antihypertensive agents must be noticed.

2- Phenothiazines in particular produce a quinidine-like depression of the myocardium. Their use with antiarrhythmic drugs such as quinidine, or digitalis glycosides could produce marked depression of the myocardium.

3- Epinephrine stimulates both adrenergic α₁ and β₂ receptors, providing a balance of vasoconstrictor and vasodilator actions. With antipsychotic drug, the α₁ receptors are blocked. Thus, the effects of epinephrine on the vasodilatory β₂ receptors would predominate, resulting in hypotension.

4- Additive effects may occur when antipsychotic drugs are combined with others that have sedative, α-adrenoceptor blocking or anticholinergic effects.
[3] ANTIDEPRESSANT DRUGS

*Depression* is one of the most common psychiatric disorders, characterized by intense feeling of sadness, hopelessness, despair and inability to experience ordinary pleasure or to cope with ordinary life events. There are two types of depression; unipolar and bipolar.

**Unipolar depression** is more common and affects old patients who are subjected to certain circumstances associated with anxiety. The patients are usually inert. **Bipolar depression** develops early in life and a hereditary factor may be involved. Bipolar depression has some features common with schizophrenia, and patients oscillate between depression and mania.

**Monoamine theory of depression** suggests that depression results from deficient monoamine (norepinephrine or/and serotonin) transmission in the CNS. Reserpine, a drug that causes depletion of NE and 5-HT can cause depression while drugs which elevate the levels of these key neurotransmitters in the CNS can be used in the treatment of depression.

**Types of Antidepressant Drugs:**

1- **Tricyclic antidepressants (TCAs):** They closely resemble the phenothiazines. Imipramine (Tofranil), and amitriptyline are the prototypical drugs of the class. TCAs block the amine (NE and 5-HT) reuptake pumps, though they have several other properties.

2- **Heterocyclic antidepressants:** They are also known as second- and third–generation drugs that act similarly to TCAs but may exhibit slightly different pharmacokinetics e.g. maprotiline.

3- **Selective serotonin reuptake inhibitors (SSRIs):** SSRIs are new group of chemically unique antidepressant drugs that specifically inhibit serotonin reuptake e.g. fluoxetine (Prozac).

4- **Monoamine oxidase (MAO) inhibitors:** These drugs bind to and inhibit the actions of MAO, a mitochondrial enzyme responsible for the degradation of catecholamines, particularly NE and serotonin e.g. tranylcypromine.

5- **Lithium salts:** Lithium is a mood-stabilizing agent as its main action is to prevent mood swings in patients with bipolar affective (manic–depressive) disorders.
TRICYCLIC ANTIDEPRESSANTS

TCAs- so called because of the characteristic three-ring nucleus – have been used clinically for almost four decades.

Mechanism of Action:

TCAs inhibit the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals leading to an increased concentration of monoamines in the synaptic cleft. Like phenothiazines, TCAs block adrenergic, histamine and muscarinic receptors.

As the antidepressant action of TCAs develops after several weeks of continued treatment, it has been suggested that monoamine receptors in the brain may change over a 2 to 4 week period with drug use and may be important in the onset of activity.

Pharmacokinetic Aspects:

TCAs are well absorbed upon oral administration, and because of their lipophillic nature, are widely distributed and penetrate into the CNS. The initial treatment period is typically 4 to 8 weeks. These drugs are metabolized by the hepatic microsomal system and conjugated with glucuronic acid and excreted as inactive metabolites via the kidney.

Pharmacological Actions:

TCAs elevate the mood, improve mental alertness and increase physical activity. In non-depressed patients, TCAs cause sedation, confusion and motor incoordination. These effects occur in the first few weeks of treatment and disappear by the onset of the antidepressant effect. TCAs can be used for long periods without loss of effectiveness.

Therapeutic Uses:

TCAs are effective in treating severe major depression and some panic disorders.

1- Unipolar depression.
2- Bipolar depression with lithium.
3- Together with antipsychotic drugs in the treatment of depressed psychotic patients.
4- Imipramine has been used to control bed-wetting in children by causing contraction of the internal sphincter of the bladder.

**Adverse Effects:**

One of the major drawbacks of most TCAs has been their many irrelevant pharmacologic actions- a trait inherited from the phenothiazine antipsychotic agents.

1. **Anticholinergic effects:** blurred vision, dry mouth, urinary retention, constipation and aggravation of glaucoma and epilepsy.

2. **Blockade of α-adrenoceptors** leading to orthostatic hypotension. In clinical practice, orthostatic hypotension, reflex tachycardia and arrhythmias are the most serious problem in the elderly.

3. **Sedation, confusion and motor incoordination** may be prominent particularly in the first few weeks of treatment.

4. TCAs may cause **weight gain and sexual dysfunction**.

5. TCAs have **narrow therapeutic index**. Depressed patients tend to be suicidal and should be given only limited quantities of these drugs and should be monitored closely.

6. **Toxic manifestations** include severe anticholinergic effects, arrhythmia (due to cardiac overstimulation by the increased catecholamine activity), seizures, hyperpyrexia, and respiratory depression.

**Treatment of TCAs Toxicity:**

1. Gastric lavage with activated charcoal.

2. Antiarrhythmic drugs with the least depressant effect on cardiac conduction e.g. lidocaine, propranolol, and phenytoin.

3. Physostigmine i.v. to reverse the severe anticholinergic symptoms and to treat supra-ventricular arrhythmia.

4. Sodium bicarbonate and i.v. potassium chloride to restore acid-base balance and to correct hypokalemia.

**Contraindications:**

TCAs are contraindicated in:

1- Patients with prostate hypertrophy.

2- Patients with hyperthyroidism.
3- Patients with pheochromocytoma.
4- Patients suffering from seizures.

**Drug Interactions:**
1. Additive sedative effects with other CNS depressants especially alcohol. Small amount of alcohol in patients taking TCAs may cause severe respiratory depression and death.
2. Additive anticholinergic effects with anti-parkinson’s drugs and antipsychotic drugs.
3. TCAs are strongly bound to plasma proteins, their effects are enhanced by competing drugs e.g. aspirin.

**NB.**
- Antidepressants don’t cause addiction.
- They have delayed effect.
- Fluoxetine is relatively safe in pregnancy.

**SELECTIVE SEROTONIN REUPTAKE INHIBITORS**
SSRIs are new group of chemically unique antidepressant drugs that specifically inhibit serotonin reuptake. This contrasts with TCAs which nonselectively inhibit the uptake of NE and 5-HT, and block muscarinic, H₁ histamine, α₁-adrenergic receptors.

**Pharmacological Actions:**
Fluoxetine is the prototype of SSRIs. It is as effective in the treatment of major depression as TCAs. However, it inhibits various drug-metabolizing enzymes, which has led to a number of significant drug interactions.

Other antidepressants that primarily inhibit serotonin reuptake include sertraline and fluvoxamine but they differ from fluoxetine in their relative effects on the reuptake of serotonin and norepinephrine.

**Therapeutic Uses:**
1- Treatment of depression and panic disorders.
2- Obsessive-compulsive disorders.
3- Some eating disorders especially bulimia.
4- Pain associated with diabetic neuropathy.
5- Anorexia nervosa.
6- Premature ejaculation.

**Advantages of SSRIS:**
SSRIs lack many of the adverse effects of tricyclic antidepressants (anticholinergic, cardiovascular effects, weight gain) and MAO inhibitors (food and drug interactions). SSRIs are much safer in overdose.

**Adverse Effects:**
SSRIs may cause nausea, headache, insomnia, fatigue, and sexual dysfunction (delayed ejaculation).

**Drug Interactions:**
A dangerous pharmacodynamic interaction may occur when fluoxetine is used in the presence of MAO inhibitors. The combination of increased stores of the monoamine plus inhibition of reuptake after release- is thought to result in marked increase of serotonin in the synapses leading to the **serotonin syndrome** which is potentially lethal and must be avoided. This syndrome is characterized by hyperthermia, muscle rigidity, agitation, hypotension and coma.

**MONOAMINE OXIDASE (MAO) INHIBITORS**
Monoamine oxidase inhibitors (MAOIs) are either hydrazides e.g. phenelzine which, combine irreversibly with the enzyme and are no longer marketed or non-hydrazides e.g. tranylcypromine that reversibly combines with the enzyme however, it has a prolonged action.
MAO-A is the amine oxidase primarily responsible for NE, 5-HT and tyramine metabolism. MAO-B is more selective for dopamine. These drugs bind to and inhibit the action of MAO-A resulting in elevated levels of both NE and serotonin. Older MAOIs are non-selective inhibitors of both MAO-A and MAO-B.

**Therapeutic Uses:**
MAOIs are helpful in patients with atypical depression. Depressed patients with considerable anxiety and phobic features are the ones who respond best to these drugs. The therapeutic effects of MAOIs may take up to 4 weeks to be manifested.
Use of MAOIs is now limited because of the complicated dietary restrictions required of patients taking MAOIs.

**Adverse effects:**
MAOIs may cause sleep disturbances, orthostatic hypotension, sexual dysfunction, weight gain as well as dangerous and even fatal interactions with other drugs or certain food.

**Drug Interactions:**
1. Tyramine-induced hypertension: Many kinds of food and beverages (e.g. wine, beer, chicken liver, aged cheese) contain tyramine, which is normally degraded in the gut by MAO-A. Since the enzyme is inhibited by MAOIs, tyramine from ingested food is absorbed, and then taken up into adrenergic neurons, where it is converted into octopamine - a false transmitter. This results in a massive release of NE and may result in hypertensive crisis.
2. The use of MAO inhibitors with TCAs causes elevated levels of NE and hypertensive crisis.
3. Concurrent use of a MAOI and fluoxetine may lead to the serotonin syndrome.
4. With local anaesthetics (often contain a sympathomimetic drug) or cold medications (which contain pseudoephedrine or ephedrine). These drugs would have synergistic effects with the increased levels of catecholamines produced by MAOIs.
5. MAOIs with pethidine may lead to abnormal syndrome characterized by hyperpyrexia, irritability, hypotension and coma probably due to an abnormal pethidine metabolite resulting from the inhibition of the normal demethylation pathway by MAOIs.

**LITHIUM**

**Mechanism of action**
The mode of action is unknown but it is proposed that lithium acts by altering the cellular concentration of the second messenger inositol triphosphate (IP₃).

**Therapeutic uses**
Lithium salts (e.g. carbonate or citrate) are used in:
1. Manic-depressive patients.
2. Manic episodes of bipolar disorders
3. Mania and hypomania
4. Preventing relapse of depression.

Lithium at therapeutic concentrations is devoid of autonomic blocking effects and of activating or sedating effects.

NB. Lithium has a narrow therapeutic margin so plasma level monitoring is important.

**Adverse Effects:**
1. Neurological: tremors, motor hyperactivity, ataxia, confusion, and convulsions.
2. Renal: polydipsia and polyuria (nephrogenic diabetes insipidus).
3. Cardiac: the bradycardia-tachycardia syndrome.
4. Edema due to sodium retention.
5. Enlargement of thyroid gland with decreased function.

### [4] CENTRAL NERVOUS SYSTEM STIMULANTS

*Stimulation of CNS can be produced in men and animals by a large number of natural and synthetic substances. As a group, the CNS stimulants have few clinical uses, but some are important as drugs of abuse.*

**Drugs which cause CNS stimulation fall into three broad categories:**

1. **Convulsants and respiratory stimulants.**
2. **Psychomotor stimulants.**
3. **Psychotomimetic drugs (hallucinogens).**

N.B. Anatomically, CNS stimulants were divided into; spinal cord, brain stem, and cerebral cortex stimulants.

**1- CONVULSANTS and RESPIRATORY STIMULANTS**

They are also called *analeptics* and act mainly on brain stem and spinal cord. They mainly stimulate the respiratory and vasomotor centers in the brain stem but have little effect on the mental function. They are used in patients with terminal coma and in respiratory failure. Unfortunately, the margin of safety of
these drugs is narrow and unpredictable. In high doses, most of the analeptics are capable of producing generalized convulsions.

**Mechanism of Action:**
The mechanism of action of most of CNS stimulant drugs is unclear. Generally, there is a balance between excitatory and inhibitory influences, which normally maintain the CNS functions. Drugs can increase excitability either by blocking the inhibition (inhibitory transmitter) or by enhancing excitation.

**Examples of analeptics:**
1. **Nikethamide** (Couramine): It is available in aqueous solution for oral use or parenteral administration to stimulate the VMC and RC. Nikethamide is of short-term duration and large doses may cause convulsions.
2. **Doxapram**: A safe analeptic that can be used to stimulate respiration in post-anesthetic period. Doxapram is of short duration of action and therefore, it is administered by i.v. infusion in patients with acute respiratory failure.
3. **Strychnine**: Strychnine is an alkaloid found in the seeds of an Indian tree, and was used as a poison. It is of no important therapeutic value but is used as a pharmacological tool in laboratories.

**Mechanism of Action:**
Strychnine blocks the receptors for glycine which is the main inhibitory transmitter acting on motor neurons this will lead to increased reflex excitability of the spinal cord.

Any sensory stimulus, will initiate asymmetrical, uncoordinated tonic convulsions of all limbs that affect the most powerful muscles acting at a given joint. The back is arched, the neck is thrown backwards and the face shows a bitter smile. Death occurs due to involvement of the respiratory muscles, respiration ceases and medullary paralysis occurs due to the hypoxia.

**Treatment of Strychnine Poisoning:**
1. Transfer the patient to quiet dark room under the supervision of well-trained staff. Any external stimulus must be avoided.
2. Thiopental i.v. in small repeated doses to stop convulsions. Mephensin (a central muscle relaxant) may be used.

3. Gastric lavage with 0.5% potassium permanganate or 2% tannic acid solution to remove the alkaloid from the stomach.

4. Artificial respiration and O₂ inhalation.

2- PSYCHOMOTOR STIMULANTS
These drugs have marked effect on the mental function and behavior; they produce excitement, euphoria, reduced fatigue, and increased motor activity. Some are drugs of abuse.

Examples: methylxanthines, amphetamines, and cocaine.

A. Methylxanthines
These include theophylline found in tea, theobromine found in cocoa, and caffeine. Caffeine, the most widely consumed stimulant in the world, is found in highest concentrations in coffee but is also present in tea, cola drinks, chocolate candy and cocoa.

Mechanism of Action:
Methylxanthines act by several mechanisms including:
1. Translocation of extracellular calcium.
2. Inhibition of phosphodiesterase leading to increases in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).

Pharmacological Effects:
1. Central nervous system: One or two cups of coffee (100-200 mg) cause; diminished fatigue, insomnia, improved concentration and a clear flow of thoughts. Higher doses cause anxiety and tremors.
2. Cardiovascular system: Therapeutic doses of caffeine have no effect on the heart but a high dose has inotropic and chronotropic effects.
3. Gastrointestinal tract: All methylxanthines stimulate secretion of HCl from the gastric mucosa.
4. Smooth muscles: Relaxation of smooth muscles especially the bronchial muscle (theophylline).
5. **Kidney:** Caffeine has a mild diuretic action and it increases urinary output of sodium, chloride, and potassium

**Pharmacokinetics:**
Methylxanthines are well absorbed orally; caffeine distributes throughout the body, including the brain, crosses the placenta to the fetus and is secreted into the mother's milk. All methylxanthines are metabolized in the liver and the metabolites are excreted in the urine.

**Therapeutic Uses:**

1. **Caffeine:** In combination with salicylates to relieve simple headache and in combination with ergotamine to relieve migraine. To stimulate the depressed CNS in case of alcohol ingestion.

2. **Theophylline:** In cases of bronchial asthma, biliary colics, congestive heart failure and cardiac edema.

**Adverse Effects:**
Moderate doses of caffeine cause insomnia and agitation. Xanthines cause tolerance and habituation. Irritability and headache occur in users who have routinely consumed more than 600 mg of caffeine per day and then suddenly stop it.

**Contraindications:** Cardiac arrhythmia, peptic ulcer, and angina pectoris.

**B. Amphetamine**

It is a sympathomimetic acting by releasing intracellular stores of catecholamines (mainly NE and dopamine) into synaptic spaces. (refer to pharmacology of autonomic nervous system)

**C. Cocaine**

Cocaine is an inexpensive, widely available and highly addictive drug. Cocaine acts by blocking NE, 5-HT and dopamine reuptake by nerve terminals. This block potentiates and prolongs the CNS and peripheral actions of these catecholamines.

**Central effects** of cocaine are similar to amphetamine but of short duration, it causes both strong psychological and physical dependence. Cocaine has local anaesthetic effect and is occasionally used in ophthalmic anaesthesia.
Peripheral effects of cocaine include tachycardia, hypertension, pupillary dilatation, and peripheral vasoconstriction. Cocaine is the only local anesthetic that causes vasoconstriction, which causes necrosis and perforation of the nasal septum seen in association with chronic inhalation of cocaine powder.

3- PSYCHOTOMIMETIC DRUGS:
Psychotomimetic drugs or hallucinogens produce profound changes in thought patterns and mood, with little effect on the brain stem and spinal cord. They cause sensory changes, hallucination, and dissociation from the surrounding. Examples of hallucinogens; lysergic acid diethylamide (LSD), cannabis, and phencyclidine. LSD may precipitate schizophrenia in susceptible people.
III. Anti-Epileptic Drugs And Drugs Used In Anaesthesia

Learning objectives:
By the end of these topics, the student will be able to:
1. Recognize the drug(s) of choice in grand-mal and petit-mal epilepsy
2. State the mechanism of action, indications and side effects of major anti-epileptic drugs.
3. Outline the management of status epilepticus.
4. Describe preanaesthetic medication.
5. Recognize the differences among inhalational anaesthetic agents in rate of induction and rate of recovery.
6. List intravenous anaesthetic agents
7. Discuss the therapeutic advantages and disadvantages and toxicity of some inhalational and intravenous anaesthetic agents.
8. List the main side effects of local anaesthetic agents.

[1] Anti-epileptic drugs

Introduction

Epilepsy is a recurrent, sudden, transient, excessive discharge of cerebral neurons without any immediate provoking cause resulting in abnormal movements and/or sensory perceptions (seizure).

The clinical manifestations depend on the site of the discharge. In partial (localized) epilepsy, the discharge starts in a localized area of the brain and may remain localized or spread to affect the whole brain (secondary generalization). In generalized epilepsy, the abnormal discharge affects the whole of the brain from the onset (Table 10.1). Identification of the type of seizure is a useful guide to therapy.
Table 1: Types of epilepsy and characteristics of seizures

<table>
<thead>
<tr>
<th>Type of epilepsy</th>
<th>Characteristics of Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized</strong></td>
<td></td>
</tr>
<tr>
<td>Grand mal</td>
<td>Unconsciousness, convulsions, muscle rigidity</td>
</tr>
<tr>
<td>Absence</td>
<td>Brief loss of consciousness</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Sporadic (isolated) jerking movements</td>
</tr>
<tr>
<td>Clonic</td>
<td>Repetitive, rhythmic jerking movements</td>
</tr>
<tr>
<td>Tonic</td>
<td>Muscle stiffness, rigidity</td>
</tr>
<tr>
<td>Atonic</td>
<td>Loss of muscle tone</td>
</tr>
<tr>
<td><strong>Partial</strong></td>
<td></td>
</tr>
<tr>
<td>[1] Simple (awareness is retained)</td>
<td></td>
</tr>
<tr>
<td>Motor symptoms</td>
<td>Jerking, muscle rigidity, spasms, head-turning</td>
</tr>
<tr>
<td>Sensory symptoms</td>
<td>Unusual sensations affecting vision, hearing, smell, taste or touch</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>Stomach sensation</td>
</tr>
<tr>
<td>Psychologic symptoms</td>
<td>Memory or emotional disturbances</td>
</tr>
<tr>
<td>[2] Complex (impairment of awareness)</td>
<td></td>
</tr>
<tr>
<td>[3] Partial seizure that becomes generalized seizure</td>
<td>Begins as partial (simple or complex) and progress into grand mal seizure</td>
</tr>
</tbody>
</table>

The epileptic seizure probably arises from a local imbalance between excitatory neurotransmission, principally glutamate, and inhibitory neurotransmission, mediated by gamma-aminobutyric acid (GABA), which leads to a focus of neuronal instability.

Most antiepileptic drugs act either by blockade of depolarizing ion channels, or by enhancing the inhibitory actions of GABA.

**Carbamazepine**

Carbamazepine is structurally related to the tricyclic anti-depressants.

**Mechanism of action**

1. Use-dependent blockade of Na⁺ channels, which reduces cell excitability, is the main mechanism of action.
2. Suppresses repetitive neuronal firing.
4. Attenuates action and release of glutamate (excitatory neurotransmitter).

**Pharmacokinetics**

Absorption of carbamazepine is slow and incomplete after oral administration.
Therapeutic uses:

1. Carbamazepine is useful in most types of epilepsy, except myoclonic epilepsy or absence seizures. These types of epileptic fit can be exacerbated by carbamazepine. It is particularly effective for treatment of partial and secondarily generalized tonic-clonic seizures (Drug of choice).

2. Neuropathic pain (e.g. trigeminal neuralgia ....)

3. Mood stabilizer in manic-depressive patients.

Side effects

- GIT upset.
- Skin rashes.
- CNS toxicity leads to double vision, drowsiness or confusion. Ataxia can occur at high doses.
- Transient leucopenia is common, especially early in treatment.
- Hyponatremia may occur by potentiating the action of antidiuretic hormone.
- Teratogenicity is common.
- Induction of hepatic P450 with carbamazepine. The most common interaction is with the oral contraceptive pill, and the dose of oestrogen should be increased to avoid failure of contraception. The metabolism of warfarin and cyclosporin are also accelerated.

Phenytoin (diphenylhydantoin)

Mechanism of action

- Use-dependent blockade of Na⁺ channels, which reduces cell excitability, is the main mechanism of action
- Blockade of L-type Ca²⁺ channels
- Potentiation of GABA action at GABA_A receptors.

Therapeutic uses:

1. Phenytoin is effective against all forms of epilepsy, except absences.
2. Phenytoin is sometimes used in the management of neuropathic pain and for cardiac arrhythmias (Class IB).

**Pharmacokinetics**

1. Phenytoin is well, but slowly, absorbed from the gut. Slow intravenous injection can be used if a rapid onset of action is needed. Intramuscular injection of phenytoin should be avoided since absorption by this route is poor and muscle damage can occur.

2. Phenytoin is highly protein bound (about 90%). The concentration of phenytoin in saliva reflects the free drug concentration in plasma and can be useful to adjust the clinical effect.

3. Phenytoin is eliminated by hepatic metabolism. At low plasma concentrations, elimination is first order which means that rate of metabolism is proportional to plasma concentration.

4. At high blood concentration, maximal capacity of liver metabolism is reached (saturation of enzymes) and elimination becomes zero order. As a result:
   1. $t_{1/2}$ becomes $\uparrow$
   2. further $\uparrow$ in dose $\rightarrow$ marked $\uparrow$ blood level.
   3. Drug toxicity may occur.

**Side effects**

Most unwanted effects of these drugs are dose-related:

1. **Nausea or vomiting.**
2. **Impaired brainstem and cerebellar function**, producing confusion, nystagmus, blurred vision, ataxia, and dysarthria (signs of overdosage).
3. **Chronic connective tissue effects**: gum hyperplasia, coarsening of facial features, hirsutism and acne (for this reason, it is usual to avoid phenytoin in young women or adolescents)
4. **Skin rashes.**
5. **Folic acid deficiency**: folic acid metabolism is increased by phenytoin producing megaloblastic haemopoiesis, although anaemia is rare.

6. **Vitamin D deficiency** as a result of increased vitamin D metabolism; in rare cases, this can produce osteomalacia

7. **Teratogenic effects**, including facial and digital malformations; these occur in up to 10% of pregnancies

8. **Induction of P_450** predisposes to several drug interactions; in particular, the metabolism of warfarin and cyclosporin is increased.

**Lamotrigine**

**Mechanism of action**

1. Use-dependent inhibition of neuronal Na\(^+\) channels (like carbamazepine and phenytoin)
2. It interferes with synthesis of glutamate and aspartate.
3. Reduces glutamate release, possibly through inhibition of voltage-sensitive Ca\(^{2+}\) channels.

**Pharmacokinetics**

Lamotrigine is well absorbed orally and half-life is long

**Therapeutic Use**

It is effective for partial and generalized seizures. In patients with newly diagnosed partial or generalized seizures, lamotrigine alone was as effective as carbamazepine or phenytoin, and better tolerated. However, it can make myoclonic epilepsy worse (similar to carbamazepine), particularly severe myoclonic epilepsy in infancy.

**Side effects**

1. Influenza-like symptoms.
2. Skin rashes particularly with rapid dose escalation. It is recommended to stop the drug.
3. Gastrointestinal disturbances, including vomiting.
4. CNS effects: drowsiness, headache and ataxia can be troublesome at high dosages.
Sodium valproate

Mechanism of action
1. Use-dependent blockade of Na\(^+\) channels.
2. Potentiation of GABA by enhanced synthesis and release as well as reduced degradation.
3. Attenuation of the excitatory action of glutamate.
4. Inhibition of T-type Ca\(^{2+}\) channels

Pharmacokinetics
Sodium valproate is well absorbed from the gut. To reduce gastric upset, tablets should be taken with food. The half-life is long. Also, there is an intravenous preparation for rapid seizure control.

Therapeutic Uses
[I] Epilepsy:
It is effective for all forms of epilepsy e.g.
1. Primary and secondary generalized tonic-clonic seizures.
2. Absence seizures
3. Complex partial seizures
4. Myoclonic
5. Atonic
6. It is highly effective in treating photosensitive epilepsy (photosensitive epilepsy precipitated by viewing a television from too close a distance)

[II] Other uses:
1. Bipolar disorder and mania
2. Prophylaxis of migraine
3. Neuropathic pain

NB: The full benefit of treatment may be delayed by several weeks.

Side effects:
1. **Pancreatitis:** serum amylase should be measured if symptoms such as abdominal pain or nausea and vomiting arise.
2. **Weight gain** caused by appetite stimulation.
3. Transient **hair** loss, with re-growth of curly hair.
4. CNS disturbances: ataxia, tremors and confusion. Rarely, encephalopathy and coma.

5. Thrombocytopenia or impaired platelet activity.

6. Severe hepatotoxicity can develop in children under 3 years of age or those who are receiving multiple drug therapy for seizures.

7. Teratogenicity.

8. Inhibition of $P_{450}$ leading to interactions with other antiepileptic drugs.

**Ethosuximide**

**Mechanism of action**

In absence seizures, T-type Ca$^{2+}$ channels are believed to generate excessive activity in thalamo-cortical relay neurons. Ethosuximide inhibits these channels and prevents neuronal firing.

**Therapeutic Uses**

Ethosuximide is a drug of choice in absence seizures. It is ineffective in other types of epilepsy.

**Side effects**

1. Anorexia, nausea and vomiting (less frequent if the drug is taken with food and if the dose is gradually increased)
2. CNS disturbances
3. Skin rashes
4. Agranulocytosis and aplastic anaemia are rare complications
5. Teratogenicity.

**Phenobarbital and Primidone**

These drugs are effective in most forms of epilepsy, but side effects limit their use. The antiepileptic activity of primidone is partly due to its metabolite phenobarbital. (refer to barbiturates)

**Benzodiazepines**

**Clonazepam and diazepam**

These drugs enhance the inhibitory action of GABA. Clonazepam is used orally for prophylaxis, usually with other drugs. Diazepam or clonazepam can be used intravenously to treat fits.
Chapter 10. Drugs Acting On The Central Nervous System

Side effects
1. Partial or complete tolerance to the antiepileptic action of benzodiazepines often occurs after about 4-6 months of continuous use.
2. Withdrawal symptoms can occur after abrupt discontinuation.

Antiepileptic drugs for adjunctive treatment:
- Gabapentin, vigabatrin and others

Prophylaxis from seizures
Treatment should begin with a single drug, the choice depending on the type of epilepsy (see table below). If the type of epilepsy is uncertain, then sodium valproate is often recommended, since it has the broadest spectrum of activity. If seizures are not controlled with the first-choice drug, a second single drug should then be tried while the first is gradually withdrawn.

<table>
<thead>
<tr>
<th>Type of seizure</th>
<th>Choice among drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial seizures:</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>or phenytoin or valproate or lamotrigine.</td>
</tr>
<tr>
<td><strong>Generalised seizures:</strong></td>
<td></td>
</tr>
<tr>
<td>Tonic-clonic (grand mal)</td>
<td>Valproate or carbamazepine or phenytoin or lamotrigine</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Valproate</td>
</tr>
<tr>
<td>Absence</td>
<td>Ethosuximide or valproate</td>
</tr>
<tr>
<td>Atonic</td>
<td>Valproate</td>
</tr>
</tbody>
</table>

Once started, treatment should usually be continued for at least 2-3 years after the last seizure. If there is a continuing predisposing condition or the person wishes to drive, treatment should probably be life-long. If withdrawal is undertaken, then it should be gradual, in order to minimise the risk of rebound seizures; when several drugs are used, one should be withdrawn at a time.
Treatment of epileptic fit

1. Maintaining the airways and ensuring adequate oxygenation
2. Prolonged or repetitive seizures (status epilepticus) usually require urgent parenteral drug treatment. *Intravenous lorazepam is the drug of choice*; diazepam can be used but has a shorter duration of action. Close observation for signs of drug-induced respiratory depression should be maintained after giving a benzodiazepine.
3. If there is no response after 30 min, or seizures recur, then a slow IV injection of phenytoin or a more rapid injection of fosphenytoin or phenobarbital should be given.
4. If seizures are still not controlled with these measures, then full anaesthesia using thiopental or propofol with assisted respiration in an intensive care unit will be necessary.

Febrile seizures in children:

Children who have experienced convulsions associated with a febrile illness have an increased risk of becoming epileptic. If anti-convulsant therapy is indicated, the drug of choice is phenobarbital. If needed carbamazepine could be added.

Antiepileptic drugs in pregnancy

1. No anticonvulsant is safe in pregnancy.
2. Neural tube defects occur with carbamazepine and sodium valproate (1-2% of pregnancies), and other developmental abnormalities occur with phenytoin.
3. It is important to advise a potential mother with epilepsy that the risks of uncontrolled seizures during pregnancy, both to her and to the fetus, may be greater than the risk associated with drug therapy.

**NB.** Women taking antiepileptic drugs who wish to become pregnant should be informed about the risk and offered antenatal screening during pregnancy, with α-fetoprotein measurement (to detect neural tube defects) and second-trimester ultrasound scanning.
[2] General anesthetics

General anaesthesia is a state of:

1. loss of sensation,
2. controllable reversible loss of consciousness and,
3. skeletal muscle relaxation.

Four stages of anaesthesia are known:

- **Stage I (analgesia):** loss of sensation but patient is still alert and speaking.
- **Stage II (Excitement):** CNS excitation\( \uparrow \) BP (irregular) + \( \uparrow \) respiratory rate + release of subconscious emotions.
- **Stage III (surgical anaesthesia):** regular respiration + relaxed skeletal muscles + progressive decrease in eye reflexes till eye movement stops and pupil is fixed
- **Stage IV (Medullary paralysis):** fatal depression of RC and VMC.

Classification of general anesthetic agents:

1. **Inhaled volatile agents:** They are hydrocarbons. They are suitable for maintaining the anesthetic state as long as the surgical procedure is going on. In the past, anaesthesia was induced and maintained by inhalation of a volatile agent alone. If this method is used, the patient passes through the previously mentioned stages (I-II) during induction and recovery of which the excitation stage (stage II) is undesirable. Nowadays, this is overcome by using a bolus of intravenous anesthetic for induction (see below), followed by an inhalational anaesthetic for maintenance. In children, this is less problematic and anaesthesia is often both induced and maintained with an inhalational anaesthetic agent.

2. **IV anesthetic drugs:** General intravenous anaesthesia can be used for short surgical procedures. For longer procedures, an IV anesthetic agent is used for rapid induction followed by an inhalational agent.
Pre-anaesthetic medications.

These are drugs used to facilitate smooth induction of anaesthesia and help to lower the dose and side effects of anesthetic drugs. According to circumstances, pre-medication may involve any combination of the following drugs (i.e. balanced general anaesthesia):

1. Benzodiazepines or barbiturates to induce sedation and to relieve anxiety.
2. H₁ blockers (anti-allergic) and H₂ blockers (to reduce gastric acidity).
3. Anti-emetic e.g. metoclopramide.
4. Opioid analgesics e.g. morphine or pethidine
5. An anticholinergic e.g. scopolamine for prevention of bradycardia and to decrease airway secretions.

Mechanism of action of general anaesthetic agents

1. It is suggested that incorporation of the anaesthetic into cell membrane phospholipids alters cell membrane fluidity.
2. Anaesthetic agents may also enhance action of GABAₐ and glycine receptors and inhibit central actions of acetylcholine, serotonin, and glutamate.

NB. Resumption of consciousness (reversal of anaesthesia) occurs when the intravenous anesthetic is redistributed out of CNS or metabolized, or when an inhalational anesthetic is redistributed out of CNS or exhaled. Residual neuromuscular blockade may need reversal with neostigmine (refer to pharmacology of ANS; Ch. 2).

Intravenous anaesthetics

Examples:

1. Thiopental
2. Ketamine
3. Propofol
# Properties of IV Anaesthetics

<table>
<thead>
<tr>
<th></th>
<th>Thiopental</th>
<th>Ketamine</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological properties</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>IV barbiturate.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Short duration of anaesthesia (about 2-5 min).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Rapid induction but slow recovery (sedation up to 24 hrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Potent anesthetic but no analgesic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Slower onset &amp; recovery than other IV anesthetics.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>It produces <em>dissociative anaesthesia</em> (i.e. patient appears awake but unconscious and doesn't feel pain. In addition, there is sedation, amnesia and immobility.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td><strong>Good analgesia.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Associated with a <em>bronchodilator</em> effect due to ↑ sympathetic outflow.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Rapid induction.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Rapid &amp; more pleasant recovery with propofol than with other IV anesthetics.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Postoperative nausea and vomiting are less than with other agents. Propofol has an anti-emetic action.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>It can be used by IV infusion for total intravenous anaesthesia or for up to 3 days in conscious patients requiring controlled ventilation (for sedation) in intensive care unit.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>No analgesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Little Sk.m. relaxation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>↓↓ BP &amp; bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Laryngospasm, apnea, cough, bronchospasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>↑ sympathetic outflow → cardiac stimulation &amp; ↑BP. (contraindicated in hypertensives or those with stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>↑ cerebral blood flow → post-operative hallucinations &amp; nightmares.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>No analgesic action &amp; causes pain at injection site that may be minimized by injection into large veins or by first injecting lidocaine.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose-related respiratory depression, bradycardia, and hypotension may occur.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Inhalational anesthetics**

Inhaled anesthetics are given with oxygen to avoid hypoxia during anaesthesia. Following induction with an intravenous anesthetic, an inhalational agent can be used to maintain anaesthesia.

**Properties of some inhalational anesthetics**

<table>
<thead>
<tr>
<th></th>
<th>Halothane</th>
<th>Isoflurane</th>
<th>Nitrous oxide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volatile hydrocarbons</td>
<td>Gaseous anesthetic</td>
<td></td>
</tr>
<tr>
<td>Potency</td>
<td>High</td>
<td>High</td>
<td>weak</td>
</tr>
<tr>
<td>Induction &amp; recovery</td>
<td>Slow</td>
<td>rapid</td>
<td>Very rapid</td>
</tr>
<tr>
<td>CVS</td>
<td>↓ BP &amp; ↓ COP</td>
<td></td>
<td>Minimal</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1. ↑ risk 2. ↑ sensitivity to catecholamines</td>
<td>No risk</td>
<td>No risk</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>↑ risk (but not in children)</td>
<td>No risk</td>
<td>No risk</td>
</tr>
</tbody>
</table>

**N.B.**

**Halothane** (Fluothane): an **old but still used** inhalational agent for mask induction in children, because it is the least irritant volatile agent.

**Enflurane**: **old and not recommended** because of its powerful cardiac and respiratory depressant actions.

**Isoflurane** has largely replaced **halothane and enflurane** because it offers the most rapid induction and recovery and has little post-anesthetic organ toxicity.
Desflurane has partly replaced isoflurane because it permits more rapid induction and recovery from anaesthesia and more rapid adjustment of anesthetic depth during the procedure. It can cause laryngospasm (i.e. irritant) in children and was not approved for pediatric induction.

Sevoflurane is widely used for children as it has a pleasant odor, an advantage when using it for induction by mask.

Nitrous oxide is not sufficiently potent to be used alone, but it has the advantage of producing analgesia and is often used in combination with other anesthetics, thus reducing the required dose of the other agent.

Intravenous opioids e.g. fentanyl is given for induction of anaesthesia, for intra-operative analgesia and to reduce the dose of anaesthetic agents. (see opioid analgesics)

Side effects of inhalational anaesthetics

A number of unwanted effects are common to most clinically useful inhaled anaesthetics; however, each agent also has additional unwanted effects.

- **Cardiovascular system.** Most agents, particularly halothane, depress myocardial contractility and produce bradycardia by interfering with transmembrane calcium flux. This decreases cardiac output and blood pressure. Halothane also sensitizes the heart to catecholamines, which can lead to arrhythmias. Inhaled anaesthetics often increase cerebral blood flow, which can exacerbate an elevated intracranial pressure.

- **Respiratory system.** All agents depress the response of the respiratory centre in the medulla to carbon dioxide and hypoxia. Some agents, e.g. isoflurane, are irritant and can cause coughing and laryngospasm if used for induction.

- **Liver.** Most agents decrease liver blood flow. Mild hepatic dysfunction because of specific hepatic toxicity is common after treatment with halothane. However, about 1 in 30000 people will develop severe hepatic necrosis following the use of halothane, especially after repeated exposure within 3-months. This is because of interaction of reactive metabolites with
cellular proteins, which initiate an autoimmune reaction. Hepatotoxicity has resulted in the decreased use of halothane, and avoidance of repeat use within 3 months.

- **Kidney.** Both renal blood flow and renal vascular resistance decrease, resulting in a reduced glomerular filtration rate.

- **Uterus.** There is relaxation of the uterus, which may increase the risk of haemorrhage if anaesthesia is used in labour. Nitrous oxide has less effect on uterine muscle compared with the other agents.

- **Skeletal muscle.** Most agents produce some muscle relaxation, which enhances the activity of neuromuscular blocking drugs.

- **Chemoreceptor trigger zone.** Inhalational anaesthetics trigger postoperative nausea and vomiting. This may be most pronounced with nitrous oxide.

- **Postoperative shivering.** This occurs in up to 65% of those recovering from general anaesthesia. The aetiology is unclear.

- **Malignant hyperthermia.** (refer to pharmacology of ANS)

## Local anesthetics

### Definition:
A local anesthetic is an agent that interrupts pain impulses in a specific region of the body without loss of patient consciousness.
Mechanism of action

Local anesthetics block nerve conduction:

1. By interacting directly with specific receptors on neuronal Na⁺ channels, inhibiting Na+ ion influx.
2. By impairing propagation of the action potential in the axons.

Factors affecting onset, intensity, and duration of neural blockade

1. **Lipid solubility**: a lipophilic local anesthetic is more potent because it is easier to cross nerve membranes. This property is determined by the aromatic portion of the molecule.

2. **Protein binding**: local anesthetics with a higher degree of protein binding have a prolonged duration of action.

3. **The pKa**: The pKa is the pH at which 50% of the local anesthetic is in the ionized form and 50% is in the unionized form. All local anesthetics are weak bases with pKa = 8-9:
   - **Local anesthetics with pKa close to physiologic pH** are associated with a greater fraction of the molecules existing in the unionized form = more penetration across nerve membranes = faster onset. (Small gap between pH and pKa)
   - **Local infection (acidosis)** increases the ionized drug fraction which means less drug will be available to penetrate across membranes and bind to intracellular local anesthetic receptors on Na⁺ channels = slower onset. (Increased gap between pH and pKa)

4. **Dose**: Increasing dose of the anaesthetic will increase the duration of the block.
### Classification and main differences between local anesthetics:

<table>
<thead>
<tr>
<th></th>
<th>Esters</th>
<th>Amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Have an ester (-COO-) link between the aromatic group and the amino terminal.</td>
<td>Has an amide (-NHCO-) link between the aromatic group and the amino terminal.</td>
</tr>
<tr>
<td>Examples</td>
<td>• <strong>Procaine:</strong> short acting</td>
<td>• <strong>Lidocaine:</strong> has fast onset (topical, injection &amp; spray).</td>
</tr>
<tr>
<td></td>
<td>• <strong>Tetracaine:</strong> long acting</td>
<td>• <strong>Mepivacaine &amp; Prilocaine:</strong> moderate duration, not active topically</td>
</tr>
<tr>
<td></td>
<td>• <strong>Benzocaine:</strong> Topical gel or ointment.</td>
<td>• <strong>Etidocaine:</strong> fast onset, long duration, muscle relaxation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Bupivacaine:</strong> dissociate slowly from cardiac Na^+ Channels →↑risk of cardiotoxicity.</td>
</tr>
<tr>
<td>NB. Amides have two (i)s in their names.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>Few minutes</td>
<td>Few hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>By <em>plasma pseudocholinesterase</em>. P-aminobenzoic acid is a metabolite &amp; a common cause allergy.</td>
<td>By the <em>liver</em>.</td>
</tr>
<tr>
<td>Incidence of allergic reactions</td>
<td><strong>High</strong> (cross allergy between esters is also high).</td>
<td><strong>Rare</strong></td>
</tr>
</tbody>
</table>

### Side effects

[1] Local:
- Irritation and inflammation at the site of administration.
• Local anesthetics produce vasodilatation but local ischaemia may arise from a co-administered vasoconstrictor, therefore this should be avoided in the extremities such as the digits.

• Cocaine, which blocks noradrenaline reuptake by noradrenergic neurons (uptake 1), produces intense vasoconstriction and has a longer duration of action. Cocaine is restricted to topical use in otolaryngeal procedures, to produce vasoconstriction and reduce mucosal bleeding. (never used by injection)

[2] Systemic:

• Cardiovascular collapse owing to systemic vasodilatation and a negative inotropic effect. Cardiotoxicity with serious arrhythmias is a particular problem with bupivacaine.

• In the central nervous system (CNS), local anaesthetics can produce dizziness, then sedation and loss of consciousness. Severe reactions can be accompanied by convulsions. Metabolites of lidocaine can cause generalised excitation and convulsions.

• True allergy is rare, but can occur with procaine and tetracaine, related to their metabolism to para-amino-benzoic acid.

**Techniques of administration**

1. **Surface administration:** High concentrations (up to 10%) of drug in an oily vehicle can slowly penetrate the skin or mucous membranes to give a small localised area of anaesthesia.

2. **Infiltration anaesthesia:** A local injection of local anesthetic solution, sometimes with a vasoconstrictor, produces a local field of anaesthesia. The anesthetic effect produced is more efficient than surface anaesthesia. This technique is extensively used in dentistry.

3. **Peripheral nerve block anaesthesia:** Injection of solution around a nerve trunk.

4. **Epidural anaesthesia:** Injection or slow infusion via a cannula adjacent to, but outside the dura mater. This technique is used extensively in obstetrics.

5. **Spinal anaesthesia:** Injection into lumbar subarachnoid space, usually between the third and fourth lumbar vertebrae. Spinal and epidural anaesthesia can be used together, often using an opioid (fentanyl) alone or in combination with a local anesthetic.

6. **Intravenous regional anaesthesia (Bier block):** Local anaesthetic injected into a vein of a limb after application of a tourniquet. The resultant anaesthesia is produced by direct diffusion of the local anesthetic from the vessels into the nearby nerves. It is used for manipulation of fractures or surgery on wrist, hand and fingers.