UNIT-V

Psychopharmacological agents

Points to be covered in this topic

- ❖ Antipsychotics

- ❖ Antidepressants

- ❖ Anti-anxiety agents

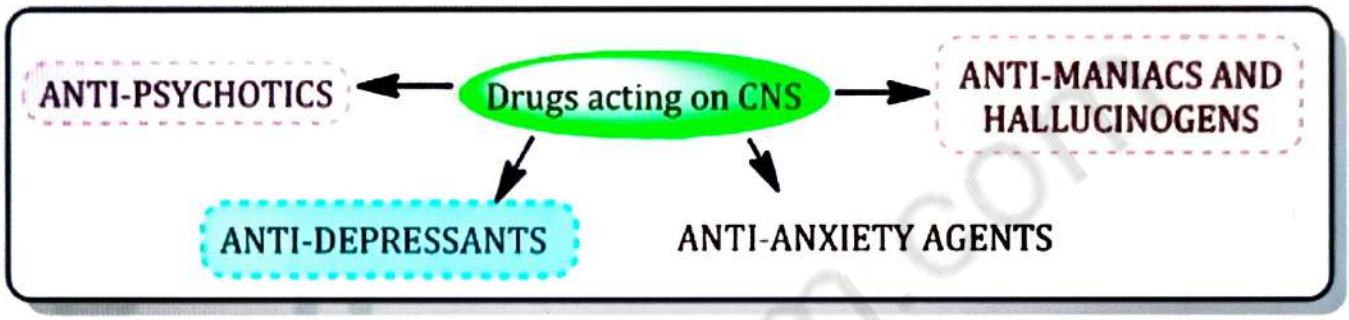
- ❖ Antimanic

- ❖ Hallucinogens

PSYCHOPHARMACOLOGICAL AGENTS

❑ Introduction

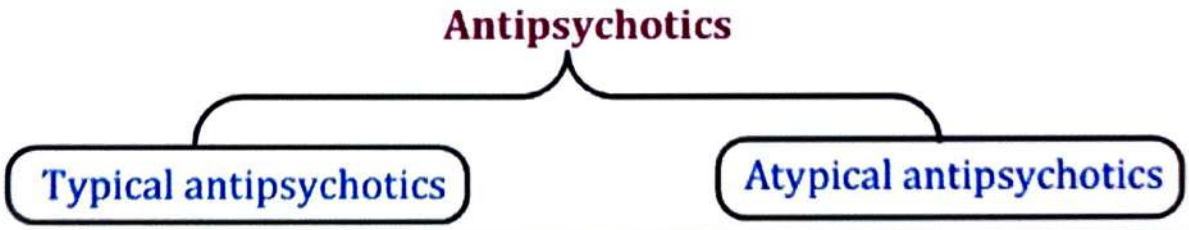
- Psychopharmacological agents are the drugs used to treat **CNS – conditions** related to behavior of a person. They are further sub-classified as **antipsychotics, antidepressants, antianxiety agents, antimanic and hallucinogens.**
- Drugs acting on CNS are classified in different categories:



❑ Antipsychotics

- Antipsychotics are used to treat **schizophrenia.**
- **Genetic predisposition** is considered to be one of the causes of schizophrenia, there are three hypotheses, based on neurotransmitters used to explain pathogenesis of schizophrenia.

❖ Classification of Antipsychotics



I. TYPICAL ANTIPSYCHOTICS	
a) Phenothiazines	
✓ **Aliphatic side chain**	Chlorpromazine
✓ **Piperidine side chain**	Thioridazine
✓ **Piperazine as side chain**	Trifluoperazine, Perfenazine, Fluphenazine

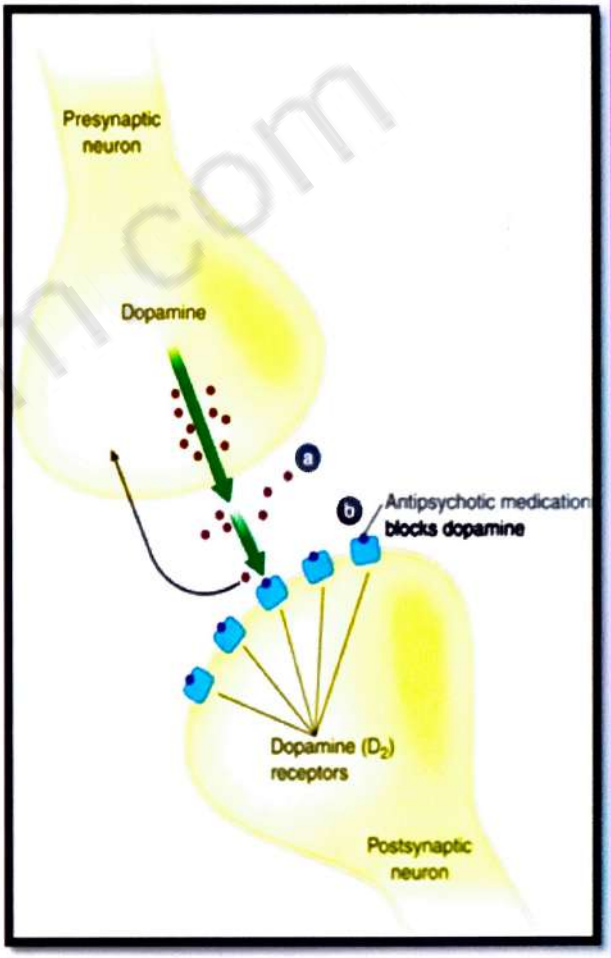
b) Thioxanthenes	**Flupenthixol, Thiothixene, Zuclopenthixol**
c) Butyrophenones	Haloperidol, Benperidol, Droperidol.
d) Miscellaneous	Pimozide, Penfluridol, Molindone, Loxapine, Sulpiride, Amisulpride, Remoxipride.

II. ATYPICAL ANTIPSYCHOTICS

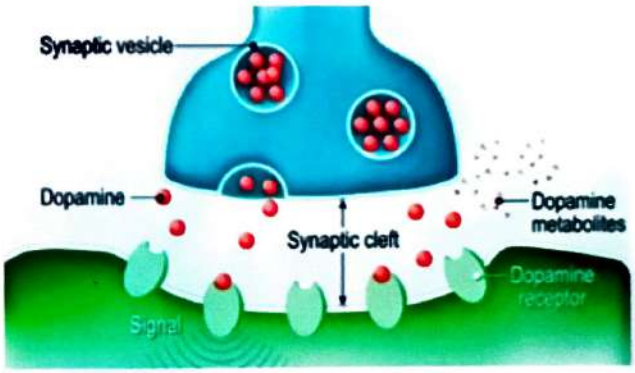
✓ Clozapine, Olanzapine, Quetiapine, Zotepine, Risperidone, Ziprasidone, Paliperidone, Aripiprazole, Sertindole, Asenapine

❖ Mechanism of Action

- All typical antipsychotic drugs act as antagonists at **D_2 and/or D_3/D_4 dopamine receptors.**
- Atypical antipsychotics block other **monoamine receptors**, especially 5-HT_{2A} receptors.
- Typical antipsychotics produce **competitive blockade** of post-synaptic D_2 receptors in mesolimbic system.
- Atypical antipsychotics have a high affinity for **5-HT_{2A} receptors**, but they have antagonistic action on α1, ACh M_1, Histamine H_1 and Dopamine D_2 receptors.



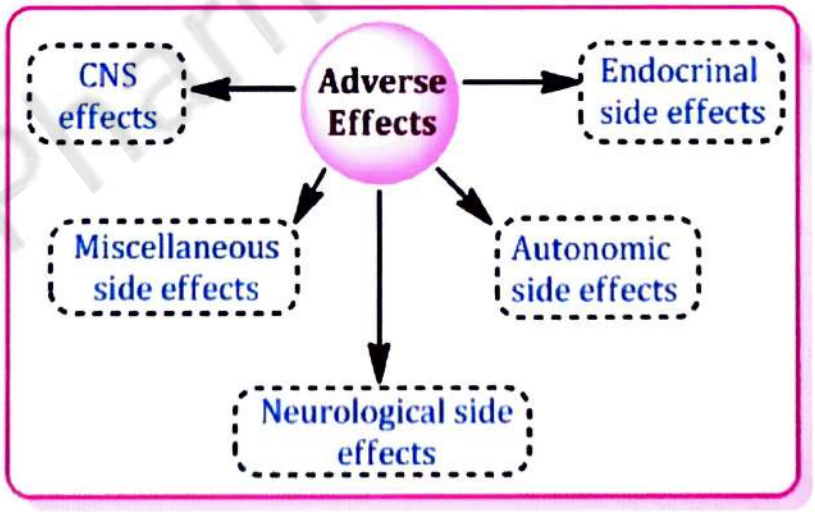
- All antipsychotic drugs exhibit a latent period of 2-3 weeks for attaining therapeutic effects.
- **Majority of them are given orally**; however their bioavailability increases ten fold when given by **IM route.**



❖ Therapeutic Uses

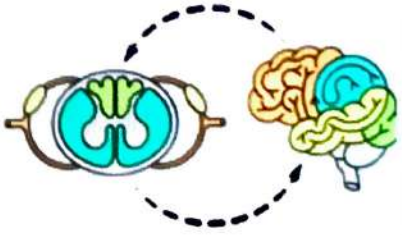
1.	**Psychiatric indications**	• They are primarily used to treat **schizophrenia.** • In drug-induced psychoses like **delusions** associated with **LSD,** Amphetamine-induced **psychoses** and **delirium** following infectious psychoses.
2.	**Neuro-psychiatric indications**	• It involves use in **Tourette's syndrome** which is marked by tics, grunts and vocalizations which are frequently obscene. • **Huntington's disease.**
3.	**Non-psychiatric indications**	• Antipsychotic like Promethazine is used as **pre-operative sedative** • Droperidol is a short acting antipsychotic with antiemetic, sedative and anticonvulsant effects. • Prochlorpromazine is preferred for antiemetic effects

❖ Adverse Effects



1. CNS Effects

- It involves **behavioral effects, tolerance** and **dependence.**
- Toxic confusional states may occur with **higher doses of drugs** having anticholinergic effects.

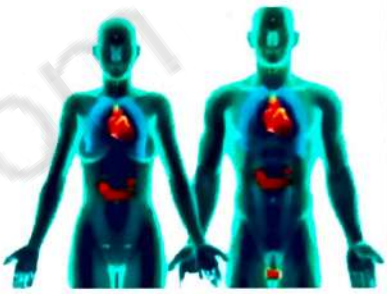


- Tolerance develops to **sedative** and **autonomic effects** but not to antipsychotic action.
- Withdrawal symptoms are manifested as **dyskinesias**. Physical dependence is not observed.

2. Neurological side effects

- **Dystonias, akathisia, parkinsoniasm** and a rare neurolept-malignant syndrome appear during treatment.
- **Parkinsoniasm, Tardive dyskinesia.**

3. Endocrinal side effects



- It results in **hyperprolactinamia** which is manifested as galactorrhea in females and **gynaecomastia** in males.
- These drugs also inhibit release of FSH and LH leading to **amenorrhoea** and **inhibition of ovulation.**

4. Miscellaneous side effects

- Drugs belonging to **Phenothiazine groups** are also known to cause jaundice, photosensitivity, corneal opacity, epileptogenic effects and poikilothermic effects.

❖ Drug Interactions

Drug interactions with antipsychotic drugs	
Drug	**Effects**
✓ **Antacids**	Decreased absorption of antipsychotic drugs
✓ **Anticholinergics**	Increased anticholinergic effects
✓ **Antithyroid drugs**	Increased risk of agranulocytosis (with Clozapine)
✓ **Chloroquine**	May precipitate extra-pyramidal symptoms with Phenothiazines

✓ **Cigarette smoking**	Increased metabolism of antipsychotics; higher dose needed
✓ **Oral contraceptives**	May potentiate hyperprolactinaemia
✓ **Levodopa**	Decreased efficacy of neuroleptics
✓ **Lithium**	Enhancement of neurotoxicity and precipitation of NMS (Haloperidol)

❑ Anti-Depressants

- Depression is a **common psychiatric disorder** but the etiology of it is not clear.
- Depression could be:

1. Unipolar
a) Reactive depression
b) Endogenous depression
2. Bipolar mood disorder or manic depressive illness.

1. UNIPOLAR DEPRESSION

a) Reactive depression

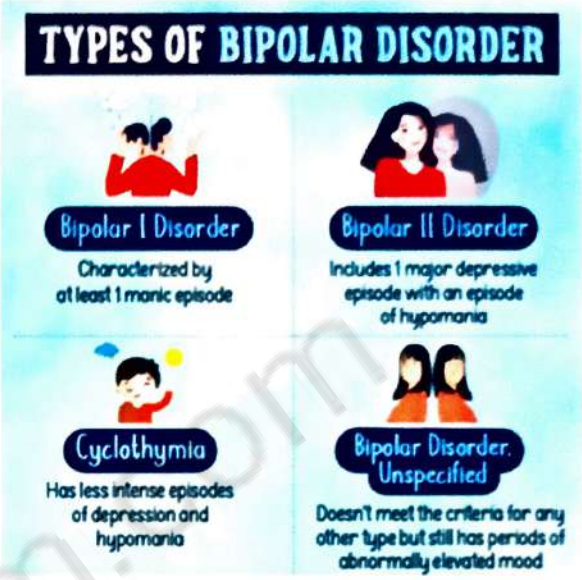
- It is due to **stressful** and **distressing** circumstances in life.

b) Endogenous depression

- It is major depression and results from a **biochemical abnormality** in the brain.
- **Deficiency of monoamine (NA, 5-HT)** activity in the CNS is thought to be responsible for endogenous depression.
- Symptoms are:

Emotional symptoms	Biological symptoms
• Sadness, misery, hopelessness, low self-esteem, loss of interest and suicidal thoughts	• Fatigue, apathy, loss of libido, loss of appetite, lack of concentration and sleep disturbances.

2. BIPOLAR DEPRESSION



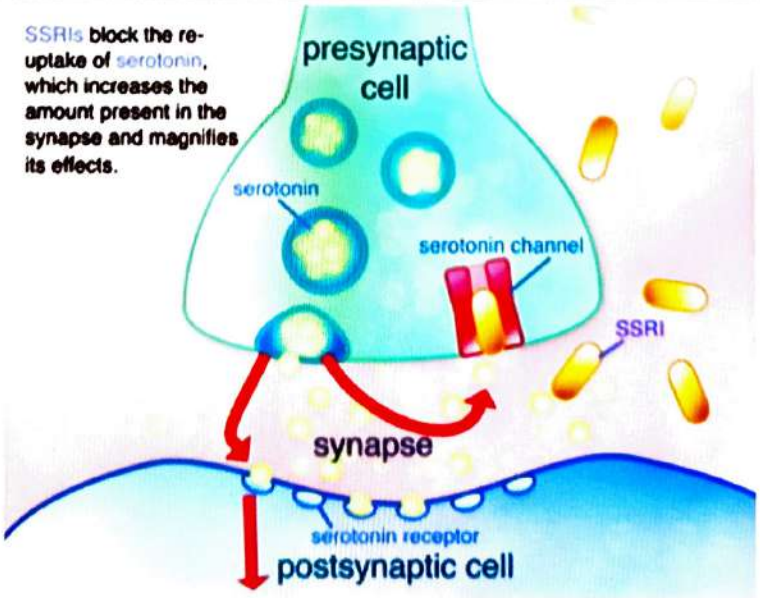
- It is characterized by **alternate episodes or periods of mania and depression.**
- The patient has **cyclical mood swings**. It is less common and is associated with a hereditary tendency.
- Mania can be considered opposite of depression with **elation, overenthusiasm, over-confidence,** often associated with irritation and aggression.

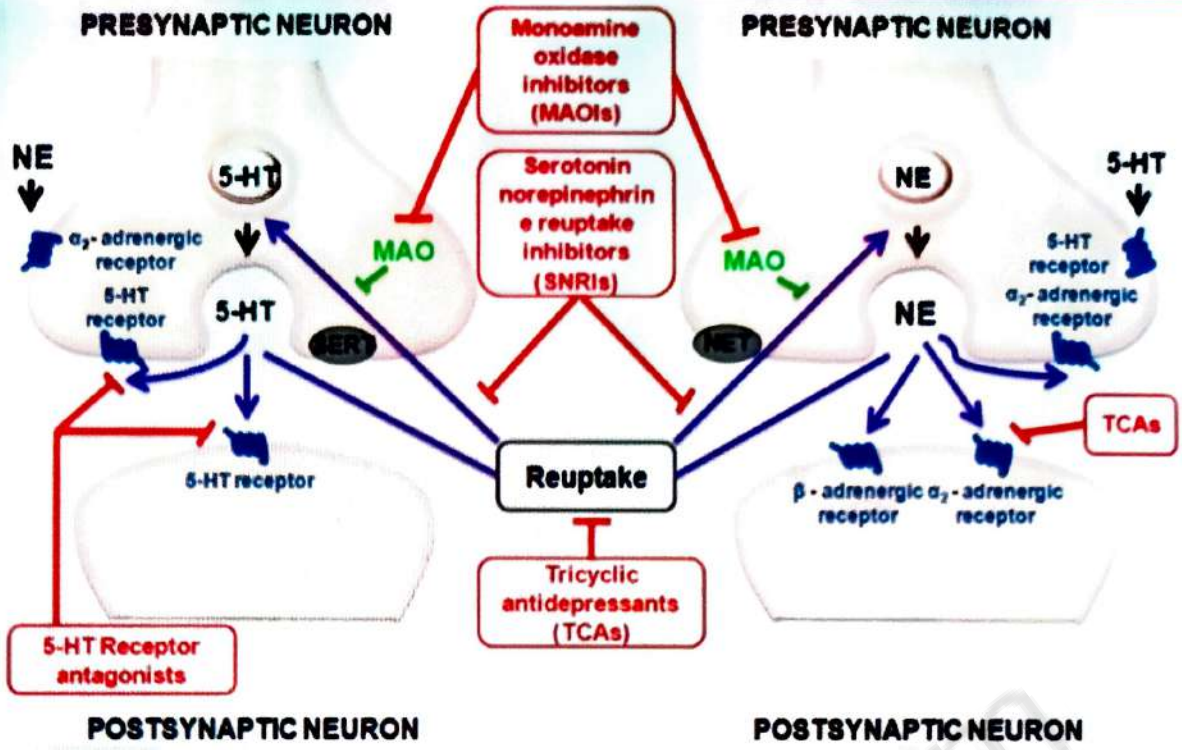
❖ Classification of Anti-Depressants

1.	**Selective serotonin reuptake inhibitors (SSRIs)**	Fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, sertraline
2.	**Tricyclic antidepressants (TCAs)**	Imipramine, desipramine, clomipramine, amitriptyline, nortriptyline, doxepin
3.	**Serotonin norepinephrine reuptake inhibitors (SNRIs)**	Venlafaxine, desvenlafaxine, duloxetin, milnacipran
4.	**Atypical antidepressants**	Mianserine, amineptine, tianeptine, bupropion, reboxetine, mirtazapine, amoxapine, atomoxetine maprotiline, trazodone, nefazodone, vortioxetine.
5.	**Monoamine oxidase (MAO) inhibitors**	Phenelzine, tranylcypromine, moclobemide.

❖ Mechanism of Action

1.	**Selective serotonin reuptake inhibitors (SSRIs)**	• SSRIs block the reuptake of serotonin from the synapse into the serotonergic nerve endings by inhibiting the serotonin transporter (SERT). • There is selectively increase levels of serotonin in synaptic cleft.
2.	**Tricyclic antidepressants (TCAs)**	• They block reuptake of NE and 5-HT into their neuron by inhibiting respective transporters. • It leads to more availability and a longer stay of NE and 5-HT at their respective receptor sites.
3.	**Serotonin norepinephrine reuptake inhibitors (SNRIs)**	• Inhibit the reuptake of both serotonin and norepinephrine at the presynaptic neurons by binding to SERT and NET like TCA. • Unlike TCA, they do not have anticholinergic, α-blocking or antihistaminic effects— hence fewer side effects.
4.	**Atypical antidepressants**	• Atypical antidepressants act by enhancing the monoamine levels in the brain either by inhibiting their reuptake or preventing their degradation.
5.	**Monoamine oxidase (MAO) inhibitors**	• Monoamine oxidase (MAO) is an enzyme which metabolizes NA, 5-HT and DA. • Drugs which inhibit this enzyme, enhance the neuronal levels of monoamines like NA, DA and 5-HT. MAO exists as two isozymes— MAOA and MAOB. MAOA is selective for 5-HT.





❖ Pharmacokinetics

- Oral absorption of most antidepressant drugs is **good;** still the bioavailability is uncertain because of their **first pass metabolism.**
- **The plasma half-life of most antidepressants is long,**
- Plasma half-life for some antidepressants is **low.**
- The half-life is longer due to their metabolites except for Fluvoxamine, Paroxetine and Protriptyline.

❖ Therapeutic Uses

1. Endogenous depression

- Antipsychotics are used in **Endogenous depression**
- The choice of drug depends on the **side effects** and **patient factors** like age.
- **SSRIs** are the most commonly used antidepressants.
- In severe depression **with suicidal tendencies, electroconvulsive therapy (ECT)** is given.

2. Panic attacks

- **Acute, recurrent, brief episodes** of anxiety are known as panic attacks.
- **Post-traumatic stress disorders, panic attacks** and other anxiety disorders— all respond to antidepressants.

3. Obsessive compulsive disorders (OCDs)

- OCDs are characterized by **repeated anxiety—provoking thoughts and compulsive behavior to overcome such anxiety.**
- OCDs respond to SSRIs/ clomipramine along with counselling.

4. Other anxiety disorders

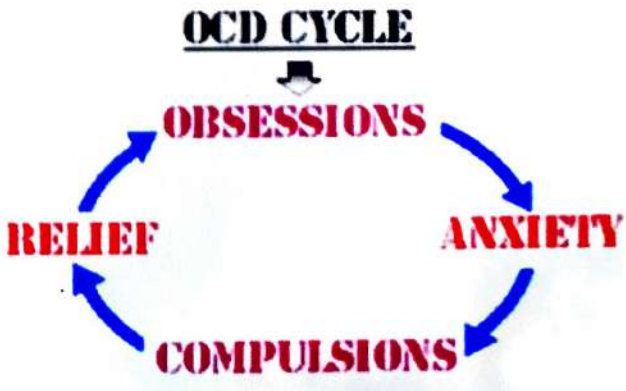
- **SSRIs** are effective in several anxiety states like **posttraumatic stress disorders**, phobias and social anxiety.

5. Disorders of pain

- Antidepressants that inhibit the **uptake of both serotonin and norepinephrine (SNRIs)** are found to influence ascending pain pathway
- They are effective in chronic pain, including diabetic neuropathy, backache, postherpetic neuralgia and fibromyalgia.

6. Other indications

- Migraine, attention deficit hyperactivity disorder, chronic fatigue, urinary stress incontinence and chronic alcoholism—may result in depression- antidepressants are tried.



❖ Adverse Effects

1.	**Selective serotonin reuptake inhibitors (SSRIs)**	• Nausea, vomiting, insomnia,headache, restlessness, anxiety and sexual dysfunction. • Inhibition of platelet function may result in ecchymosis.
2.	**Tricyclic antidepressants (TCAs)**	• Sedation, confusion, postural hypotension, • tachycardia and sweating. • weight gain due to increased appetite. • cardiac arrhythmias.
3.	**Serotonin norepinephrine reuptake inhibitors (SNRIs)**	• These drugs have serotonergic side effects like discontinuation syndrome.
4.	**Atypical antidepressants**	• Trazodone causes nausea, sedation, postural hypotension and priapism leading to impotence. • Bupropion causes agitation and insomnia • Mirtazapine and Mianserin cause sedation due to histamine H1-blockade.
5.	**Monoamine oxidase (MAO) inhibitors**	• Postural hypotension (in elders), weight gain, dizziness and sexual dysfunction.

❖ Drug Interactions

1.	**Interactions with TCAs and related drugs**
a)	TCAs potentiate effects of directly acting sympathomimetics causing rise in BP and arrhythmias; but inhibit effects of indirectly acting sympathomimetics.
b)	Phenytoin, Chlorpromazine and Aspirin displace TCAs from their protein binding sites leading to increased effect of TCAs.
c)	Anticholinergic drugs aggravate toxicity of TCAs.

2.	Interactions with MAO inhibitors
a)	Food articles containing tyramine, like cheese, beer, red wine, banana, yoghurt and pickled meat when used with MAO inhibitors can cause hypertensive crisis.
b)	MAO inhibitors with TCAs or with directly/indirectly acting sympathomimetics can cause hypertension, arrhythmias and seizures
c)	MAO inhibitors retard metabolism of drugs like morphine causing severe respiratory depression

3.	Interactions with SSRIs
a)	SSRIs inhibit metabolising enzymes like CYP2D6 and CYP3A4. As a result, plasma levels and toxicity of TCAs, Haloperidol, Clozapine, Warfarin, Dextromethorphan, Terfenadine, Astemizole and Cisapride are increased
b)	SSRIs with MAO inhibitors result in elevated levels of 5-HT causing "serotonin syndrome" leading to hyperthermia, muscle rigidity, tremors and rapid changes in mental status along with cardiovascular collapse.

❑ Anti-anxiety Agents

- Anxiety is **tension** or **apprehension** which is anormal response to certain situations in life. It is a **universal human emotion.**
- However, when it becomes **excessive** and **disproportionate** to the situation, it becomes disabling and needs treatment.

❖ Classification of Anti-anxiety Agents

S.NO	CLASS	DRUGS
1.	**Benzodiazepines**	Diazepam, chlordiazepoxide, lorazepam, alprazolam
2.	**5-HT agonist–antagonists**	Buspirone, gepirone, ipsapirone
3.	**Beta-blockers**	Propranolol
4.	**Sedative antihistamine**	Hydroxyzine

❖ Mechanism of Action

1.	**5-HT agonist–antagonists**	• These drugs act through non-GABAergic system and have low chances of side effects in comparison to BZDs. • These drugs exert their anxiolytic effects by acting as a partial agonist primarily at brain 5-HT1A receptors. • By selective activation of the inhibitory presynaptic 5-HT1A receptor, they suppress 5-HT neurotransmission through neuronal system.
2.	**Beta-blockers**	• Worrying situations may lead to palpitation, tremors, GIT upset or even hypertension die to sympathetic overactivity. • These symptoms, reinforce anxiety and thus the visicous cycle continues. • Propranolol breaks the visicious cycle. Through its β-blocking action, it decreases palpitation, tremors, GIT upset, hypertension and blood lactic acid levels. • Because of its cardiovascular actions, it is not a potential preferred anxiolytic.

3.	**Sedative antihistamine**	• Hydroxyzine is an antihistaminic with anxiolytic actions—but due to high sedation, it is not used

❖ Pharmacokinetics

- Buspirone is rapidly absorbed and metabolized in the liver, undergoes extensive first pass metabolism.
- Chlordiazepoxide Oral absorption is slow. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action.

❖ Adverse Effects

- **Sedation, light-headedness, psychomotor and cognitive impairment, confusional state** (especially in the elderly), increased appetite and weight gain, alterations in sexual function.
- Dizziness, nausea, abdominal discomfort, headache, rarely excitement

❑ Anti-maniacs

- Mania is characterized by an **excessive desire** and **too much of euphoria.**
- Majority of patients of mania experience **cyclic episodes** of mania followed by **severe depression** with periods of normal mood in between.
- Thus, The patient's condition moves between **mania** and **depression.** Hence, it is called as **manic-depressive psychosis (MDP).**
- Excessive NE/DA related activity precipitates **mania** and the drugs which reduce **NE/DA relieve mania.**
- Balanced neurotransmitter levels help in stabilization of mood.
- While manic episode is believed to result from elevated NE, depressive phase is associated with decrease in NE.

❖ Classification

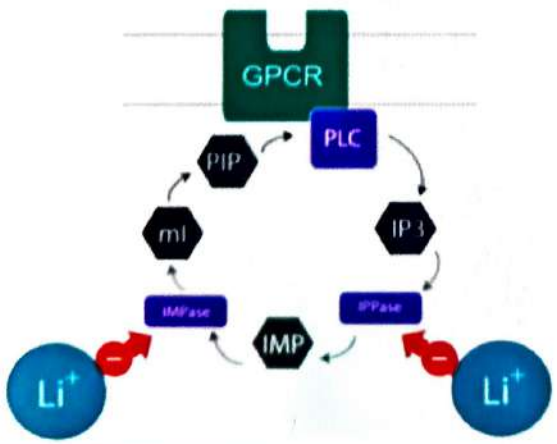
DRUGS FOR MANIA AND BIPOLAR DISORDER

- **Lithium carbonate**
- **Anticonvulsants**
  1. Sodium valproate
  2. Carbamazepine
  3. Lamotrigine
- **Atypical antipsychotics**
  1. Olanzepine
  2. Risperidine
  3. Quetiapine
  4. Aripiprazole

❖ Mechanism of Action

- The mechanism of action of Lithium is related to **second messenger involved in α-adrenergic and muscarinic neurotransmission.**
- **Inositol triphosphate (IP3)** is inactivated to **inositol diphosphate (IP2), inositol monophosphate (IP1) and then to inositol.**
- Lithium selectively inhibits **signal transduction** in overactive neurons by blocking conversion of **IP2 to IP1 and then to inositol.**
- As a result, the supply of **free inositol** to regenerate **phosphatidyl inositol-diphosphate (PIP2)** in hyperactive neurons is interrupted and ultimately release of IP3 and diacyl glycerol (DAG) is also reduced which decreases neuronal response to **NE, DA and 5-HT.**
- In addition, Lithium may uncouple receptors from their G-proteins. Sodium ions are so common for **neurotransmission**. Competition of lithium ions with sodium is also said to contribute to the **action of lithium.**

Lithium inhibits IPPase and IMPase



- Phosphoinositide cycle:
  - Phosphoinositides: precursor of signaling molecules
  - Enzymes IPPase and IPPase: synthesis of myoinositol (mI)
  - Lithium MOA: "mI depletion hypothesis"

UNIT-V

Drugs used in Parkinson's disease & Alzheimer's disease

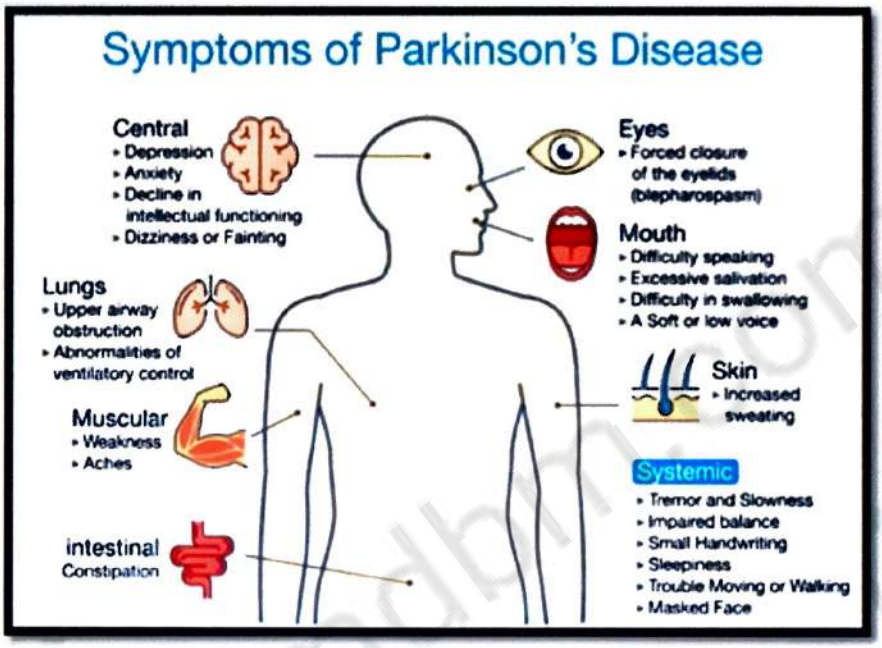
Points to be covered in this topic

- ❑ **DRUGS USED IN PARKINSONS DISEASE**
  - ❖ Introduction to Parkinson's disease
  - ❖ Drugs for Parkinson's Disease
- ❑ **DRUGS USED IN ALZHEIMER'S DRUGS**
  - ❖ Introduction to Alzheimer's Disease
  - ❖ Drugs used in Alzheimer's disease

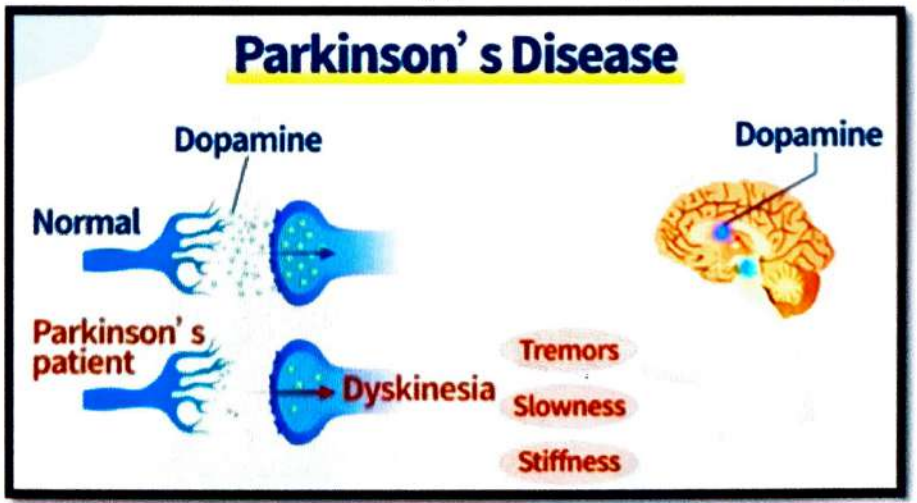
DRUGS USED IN PARKINSONS DISEASE

❑ Introduction to Parkinson's Disease

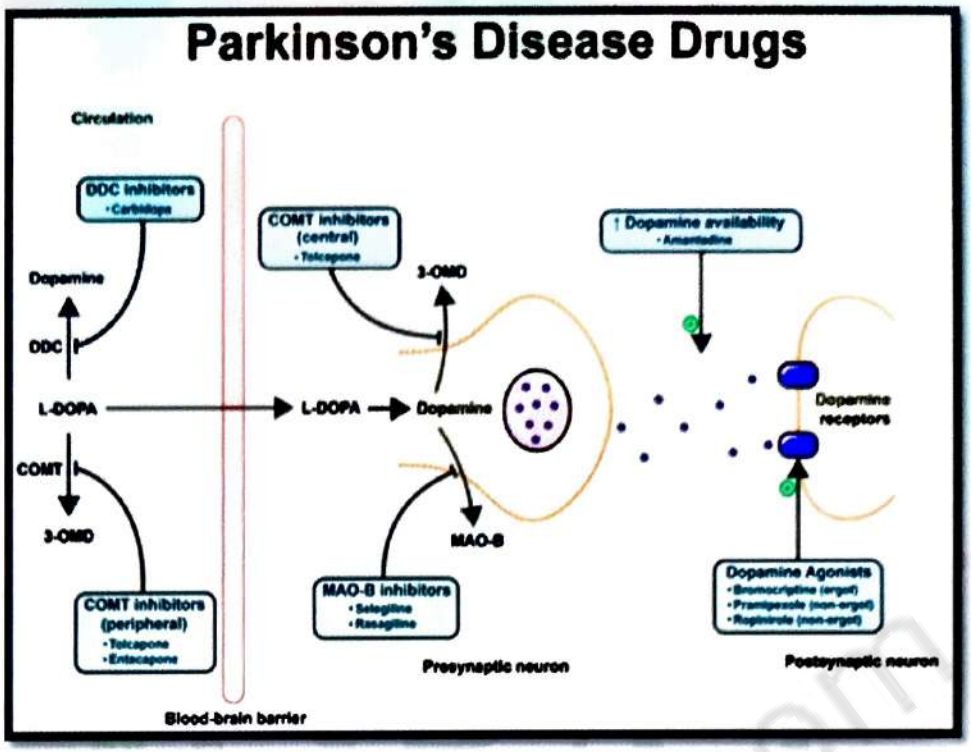
- Parkinson's disease is an **extrapyramidal motor disorder** characterized by **rigidity, tremor and hypokinesia** with secondary manifestations like **defective posture** and **gait, mask-like face** and **sialorrhea; dementia may accompany.**



- If untreated the symptoms progress over several years to end-stage disease in which the patient is **rigid, unable to move, unable to breathe** properly; succumbs mostly to chest infections/embolism.
- During functioning of brain, there is a functional balance between **dopaminergic** and **cholinergic system.**
- **In Parkinson's disease (PD), there is a loss of dopaminergic neurons.** It indirectly leads to hyperactivity of cholinergic neurons.



- The mechanism of action of drugs used in treating PD is shown-



❑ Drugs for Parkinson's Disease

Anti-cholinergics	Dopa derivatives	Adamantane derivatives
1. Biperiden 2. Procyclidine 3. Trihexyphenidyl= benzhexol 4. Diphenhydramine 5. Orphenadrine	1. Levodopa+ Benserazide 2. Levodopa+ Carbidopa 3. Levodopa+ Carbidopa SR 4. Levodopa+ Carbidopa + Entacapone	1. Amantadine
Dopamine agonists	**MAO-B inhibitors**	**others**
1. Bromocriptine 2. Pergolide 3. Lisuride 4. Cabergoline 5. Ropinirole 6. Pramipexole 7. Apomorphine	1. Selegiline 2. Rasagiline	1. Entacapone

Drug used for treating Parkinson's disease are classified in to four categories:

(i) **Drugs which prevent dopamine levels**

(ii) **Drugs which prevent dopamine degradation**

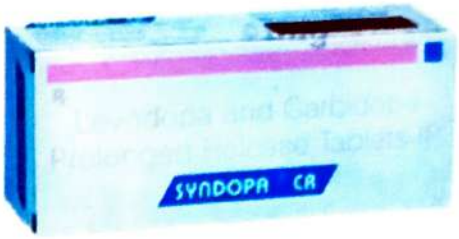
(iii) **Drugs which stimulate dopamine receptors**

(iv) **Drugs Which Restore DA-ACh Balance**

(v) **Drugs which increase dopamine levels**

❖ Drugs Which Increase Dopamine Levels

1. Levodopa with Carbidopa



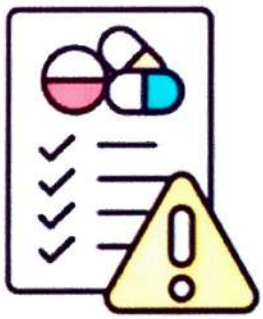
- Levodopa is the **precursor of DA.**
- Levodopa can cross BBB and **it is decarboxylated to DA(dopamine) in brain.**
- DA itself does not cross BBB.

- **If administered alone, only about 1% of Levodopa actually enters the brain.**
- **Remaining 97-99% Levodopa gets metabolized in GIT and peripheral tissues by the enzyme dopa decarboxylase to DA, which cannot enter brain because of its inability to cross BBB.**

- To prevent its peripheral degradation, Levodopa is usually **Coadministered with either Carbidopa or Benserazide, a peripheral dopa decarboxylase inhibitor.** This combination lowers the dose of Levodopa and reduces incidence of peripheral side effects.

(a) Adverse effects

- Excessive and abnormal choreiform movements of limbs, trunk, face and tongue. These effects are termed as **Dyskinesias**
- **Vivid dreams**
- **Delusions**
- Hallucinations
- Confusion
- **Sleep disturbances**



- Prolonged therapy of Carbidopa + Levodopa may cause schizophrenia-like symptoms in elderly.

(b) Contraindications

- Levodopa is contraindicated in **psychoses, narrow angle glaucoma, cardiac arrhythmias** and **melanoma.**

(c) Drug interactions

- **Pyridoxine (vitamin B6)** enhances the extracerebral metabolism of Levodopa and decreases its therapeutic effects.
- **MAO-A inhibitors** potentiate toxicity of Levodopa leading to hypertensive crisis.
- Proteins ingested with meals may produce sufficient amount of amino acids, which compete with Levodopa transport both in **GIT** and **brain**; hence Levodopa should be given 30 minutes before meals.
- TCAs decrease the absorption of Levodopa leading to **hypertensive episodes.**

2. COMT Inhibitors

- COMT metabolizes **DA** and its **precursor Levodopa**, producing the **inactive metabolite.**
- Hence, **inhibition of peripheral COMT** will result in increase in plasma half-life of Levodopa.
- Selective COMT inhibitors like Tolcapone and Entacapone, not only diminish metabolism of Levodopa but also increase its bioavailability in brain.
- Pharmacological effects of **Tolcapone** and **Entacapone** are similar.

3. Amantadine

- It is an **antiviral drug.**
- It prevents DA uptake, facilitates presynaptic DA release, possesses **weak antimuscarinic action** and **blocks glutamate NMDA receptor.**
- The first two actions help in treating Parkinson's disease.
- Blocking of NMDA receptor contributes in reducing excitation-induced neurotoxicity and dyskinesia.
- Amantadine alone or in **combination with Levodopa** and **Carbidopa** is used to treat PD.
- Adverse effects include nausea, dizziness, insomnia, confusion hallucinations, odema.
- Its anti-muscarinic actions are additive to CNS effects.

❖ Drugs Which Prevent Dopamine Degradation

- Selegiline is an **irreversible inhibitor of MAO-B,** an enzyme in **dopaminergic neurons** responsible for metabolism of DA.
- It makes more **DA** available for stimulation of its receptors.
- Selegiline may retard progression of PD by reducing oxidative damage due to formation of free radicals produced during metabolism of DA.

❖ Drugs Which Stimulate Dopamine Receptors

1. Dopamine agonists

- These drugs directly **stimulate DA receptors** and do not depend on the formation of DA from **Levodopa**. They have following advantages:
  a) They do not require metabolic conversion to DA.
  b) They do not depend on the functional integrity of dopaminergic neurons.
  c) They have longer duration of action and lesser on-off phenomenon as compared to Levodopa.
  d) They are more selective than **Levodopa on DA receptors.**
  e) They are less likely to generate **damaging free radicals.**

❖ Drugs Which Restore DA-ACh Balance

- The drugs under this category are **centrally acting antimuscarinic drugs.**
- In the absence of inhibitory control of DA, the activity of **cholinergic system** becomes dominant.
- Blockade of **central muscarinic receptor** by these drugs reduces **cholinergic activity.**
- The muscarinic antagonists are most commonly used to treat following conditions:-

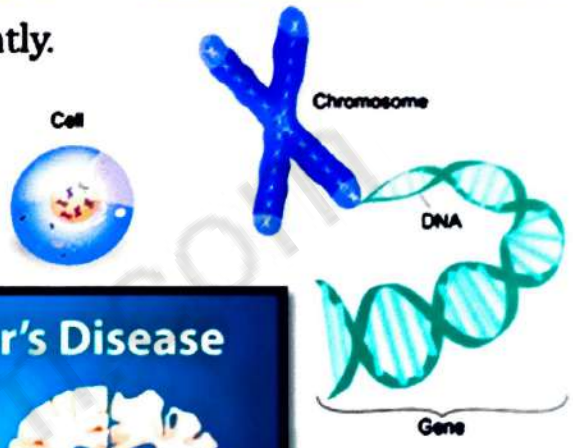
1.	Early stages of the disease.
2.	Late-stage PD as an adjunct to Levodopa + Carbidopa therapy.
3.	Neuroleptic-induced extrapyramidal side effects.

- The drugs in this category include: **Trihexyphenidyl (benzhexol), Procycliydine, Orphenadrine and Benztropine.**

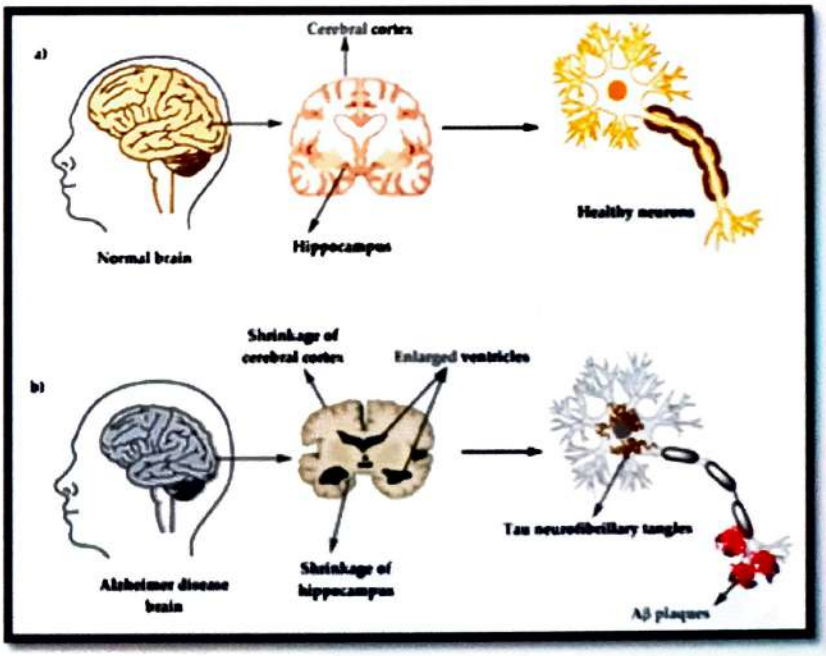
DRUGS USED IN ALZHEIMER'S DRUGS

❑ Introduction to Alzheimer's Disease

- Alzheimer's disease is a **progressive neurologic disorder**
- Alzheimer's disease is the most common cause of **dementia** — a continuous decline in **thinking, behavioral** and **social skills** that affects a person's ability to function independently.
- Problems with **genes**—even small changes to a gene—can cause diseases like Alzheimer's.



- Other symptoms like depression, anxiety and disturbed sleep may also be seen.
- Pathological features include **atrophy** of the cerebral cortex and **loss of neurons**—mainly **cholinergic neurons** with multiple senile **(amyloid) plaques** and neurofibrillary tangles in the brain.



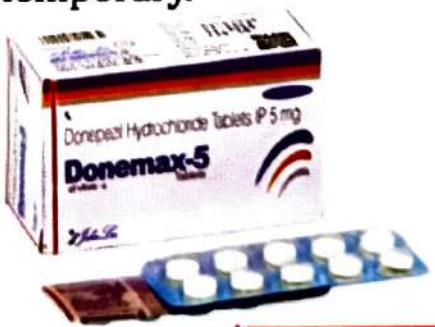
- Since there is loss of **cholinergic neurons**

❑ Drugs used in Alzheimer's disease

- ❖ **Cholinesterase inhibitors**
  - Tacrine, rivastigmine, donepezil, galantamine
- ❖ **Nootropic agents (cognition enhancers)**
  - Piracetam, aniracetam, cerebrolysin
- ❖ **NMDA receptor antagonist**
  - Memantine
- ❖ **Others**
  - Piribedil, ginkgo biloba

- The loss of cholinergic activity in brain or patients with AD led to the use of cholinesterase inhibiting drugs **which can cross BBB.**
- These drugs **block degradation of Ach** and increase availability of ACh in synaptic cleft.
- The drugs used to treat AD are: **Tacrine, Donepezil, Rivastigmine** and **Galantamine.**
- Tacrine is a long acting reversible anticholinesterase. It can be used for treatment of mild to moderate patients of AD. It is orally active and provides improvements in memory, cognition and general well being soon after initiation.
- **Donepezil, Rivastigmine** and **Galantamine** have better penetration in CNS. They are less toxic and better tolerated in comparison to Tacrine. Their clinical results are modest and temporary.

➢ Their dosages are as follows:



- ✓ **Donepezil:** 5 mg once daily in evening increased maximum up to 10 mg once daily after 4 weeks.
- ✓ **Rivastigmine:** 1.5 mg initially twice a day increased up to 3 mg twice a day after two weeks.

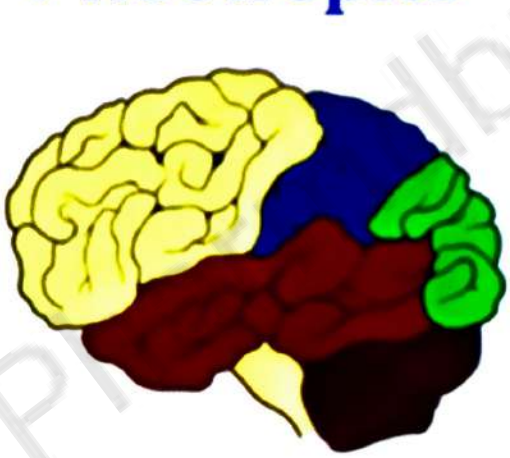
- ✓ **Galantamine:** 4 mg twice initially, increased up to 8 mg twice a day after one to two weeks. Transdermal Rivastigmine patch, to be applied once in a day is available. Use of these drugs is not associated with hepatotoxicity except for peripheral cholinergic side effects like diarrhea, nausea, vomiting and increased urination.

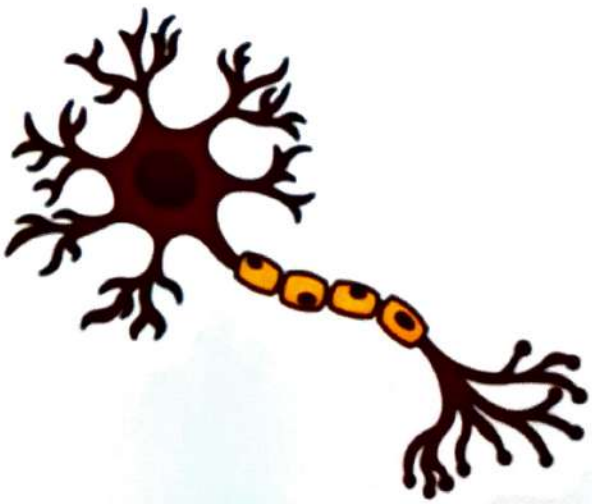
UNIT-V

CNS Stimulants & Nootropics

Points to be covered in this topic

- ❖ CNS stimulants
- ❖ Nootropics





CNS STIMULANTS & NUTROPICS

❑ CNS Stimulants

- The drugs in this category have a marked influence on **mental functions** and **behavior** to produce excitement, euphoria, increase in motor activity and reduction in fatigue. They are sub-classified as follows:

❖ **Respiratory stimulants**

- **Doxapram, nikethamide**

❖ **Psychomotor stimulants**

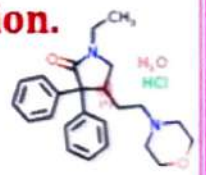
- **Amphetamine, cocaine, methylxanthines**

❖ **Convulsants**

- **Leptazol, strychnine**

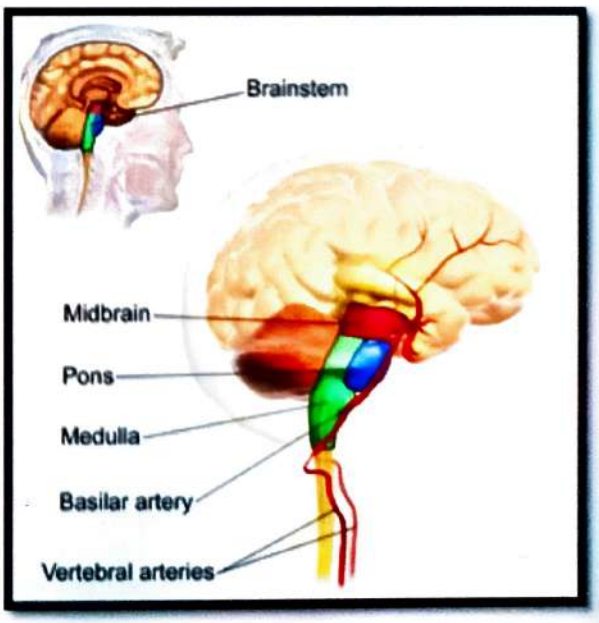
❖ Respiratory stimulants

- Respiratory stimulants are also called **Analeptics.**
- These drugs **stimulate respiration** and are sometimes used to **treat respiratory failure.**
- They may bring about **temporary improvement in respiration.**
- They have a low safety margin and may produce convulsions.



1. Doxapram

- It appears to act mainly on the **brainstem** and **spinal cord** and increase the activity of **medullary respiratory and vasomotor centers.**
- Doxapram in low doses can selectively stimulate **respiration.**
- DOSE:- 1–2 mg/kg/hr or 40–80 mg IM.



➢ Adverse effects

- Nausea, Cough, Restlessness, Muscle twitching, Hypertension, Tachycardia, Arrhythmias and Convulsions.

➢ Uses

1. It is occasionally used IV as an analeptic in **acute respiratory failure.**
2. **Apnoea in premature infants** not responding to theophylline.

❖ Psychomotor Stimulants

- **Amphetamine** and **dextroamphetamine** are sympathomimetic drugs.
- Cocaine is a CNS stimulant, produces euphoria and is a drug of abuse.

1. Methylxanthines

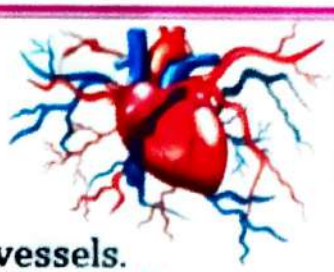
- Caffeine, theophylline and theobromine are the naturally occurring xanthine alkaloids.
- The beverages—coffee contains **caffeine**; tea contains **theophylline** and caffeine; cocoa has caffeine and theobromine.

➢ Actions

a) CNS

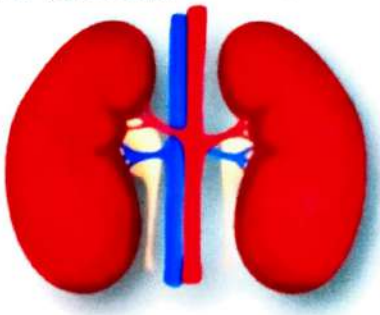
- **Mental alertness.**
- Reduces fatigue, produce a sense of well-being.
- Improve motor activity and performance with a clearer flow of thought.
- Caffeine stimulates the **Respiratory center.**
- Higher doses produce **Irritability, nervousness, restlessness, insomnia, excitement and headache.**
- High doses can result in **convulsions.**

b) CVS



- Increase the **cardiac output.**
- produce peripheral **vasodilatation.**
- Caffeine causes vasoconstriction of cerebral blood vessels.

c) Kidney

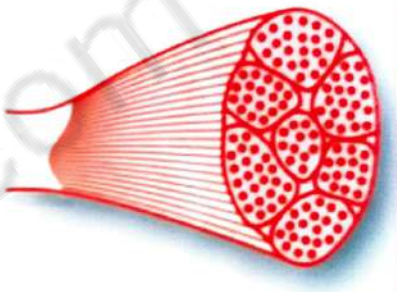


- The xanthine's have a diuretic effect and **increase the urine output.**

d) Smooth muscle

- Xanthine's cause relaxation of smooth muscles especially the bronchial smooth muscle.

e) Skeletal muscle



- Xanthine's enhance the power of muscle contraction and increase the capacity to do muscular work by both a central stimulant effect and the peripheral actions.

➢ Pharmacokinetics

- Methylxanthines are well absorbed orally, widely distributed and are metabolized in the liver; **t½ 7–12 hr.**
- In higher doses, t½ may be prolonged due to saturation of metabolizing enzymes. Premature infants have a longer **t½ of 24–36 hr.**

➢ Adverse Effects

- Nervousness, Insomnia
- Tremors
- Tachycardia
- Hypotension
- Arrhythmias
- Headache
- Gastritis, nausea, vomiting, epigastric pain and diuresis.

➢ Uses

- Headache
- Bronchial asthma
- Apnoea in premature infants

❖ Convulsants

1. Strychnine

- It is an alkaloid obtained from the seeds of **Nux vomica.**
- On administration, it produces **tonic convulsions—opisthotonos followed by coma and death.**
- It acts as a **competitive antagonist** of the inhibitory neurotransmitter glycine—mainly stimulates the spinal cord and in higher doses the entire nervous system.
- Strychnine is of **NO THERAPEUTIC VALUE.**

2. Leptazol or pentylene tetrazol

- It is a **CNS stimulant.**
- By a direct effect on the central neurons, it produces convulsions.
- It is mostly used as an **experimental drug** to induce convulsions. Poisoning with leptazol is **treated with diazepam.**

Mechanism of Action

- These drugs enter the nerve ending by active transport and displace DA/NE from storage vesicles by altering their pH.
- They have some property to inhibit DA metabolism by inhibiting MAO-B in the nerve ending. Due to inhibition of the enzyme, concentration of intraneuronal DA increases.
- This reverses the direction of transport mechanism so that DA is now released in to synapse by reverse transport rather than by usual exocytosis.
- This further increases DA concentration in the **synaptic cleft.**

❑ Nootropics

- Nootropics are drugs that improve memory and cognition. They are also called **Cognition Enhancers.**
- Nootropics can overcome or **retard cognitive decline** occurring in old age and in some diseased conditions.
- They can prevent the disruption of the process of memory consolidation by **hypoxia, trauma, seizures, Hypoglycemia** and other factors.

❖ Nootropics should possess following properties:

- ✓ They should facilitate **learning acquisition** and **memory consolidation** and prevent or mitigate impairment of memory induced by ageing, amnestic agents and other aversive factors.
- ✓ They should facilitate **inter-hemispheric transfer of information.**
- ✓ They should improve tonic cortical control over **sub-cortical centers.**
- ✓ They should not induce any overt **behavioral** or **autonomic effects** on long term administration.

❖ They belong to diverse chemical category. Some of them are listed below:

- ✓ Piracetam and its congeners: **Aniracetam, Oxiracetam.**
- ✓ Hydergine (dihydroergotoxin)
- ✓ **Vincamine**
- ✓ **Meclofenoxate**
- ✓ **Pentoxifylline**
- ✓ Pyritinol
- ✓ Cyclangate
- ✓ **Nicergoline**
- ✓ Herpestis monniera (Brahmi)
- ✓ **Ginkgo biloba extract**

1. Piracetam

- Piracetam is a **cyclized derivative of GABA.**
- It was first introduced as a **nootropic agent.**
- It has been shown to be beneficial in **cognitive deficit** occurring in several types of brain disorders.
- Mental performance is improved in children and ageing individual with memory deficits. Piracetam is devoid of significant autonomic, motor or behavioral effects, even at relatively high doses.
- **Aniracetam and Oxiracetam are derivatives of Piracetam.**
- The derivatives have actions similar to Piracetam. Dose of Piracetam is **2-3 gm daily in divided doses.**

➢ Uses

- In **cognitive defects** associated with presenility (Alzheimer's disease) and ageing.
- In children with **learning and attention deficit.**
- Amnesia following **cerebral trauma, drug abuse** including **alcoholism, seizures.**
- Coexisting memory deficits in neurological and **psychiatric illnesses.**

MECHANISM OF ACTION

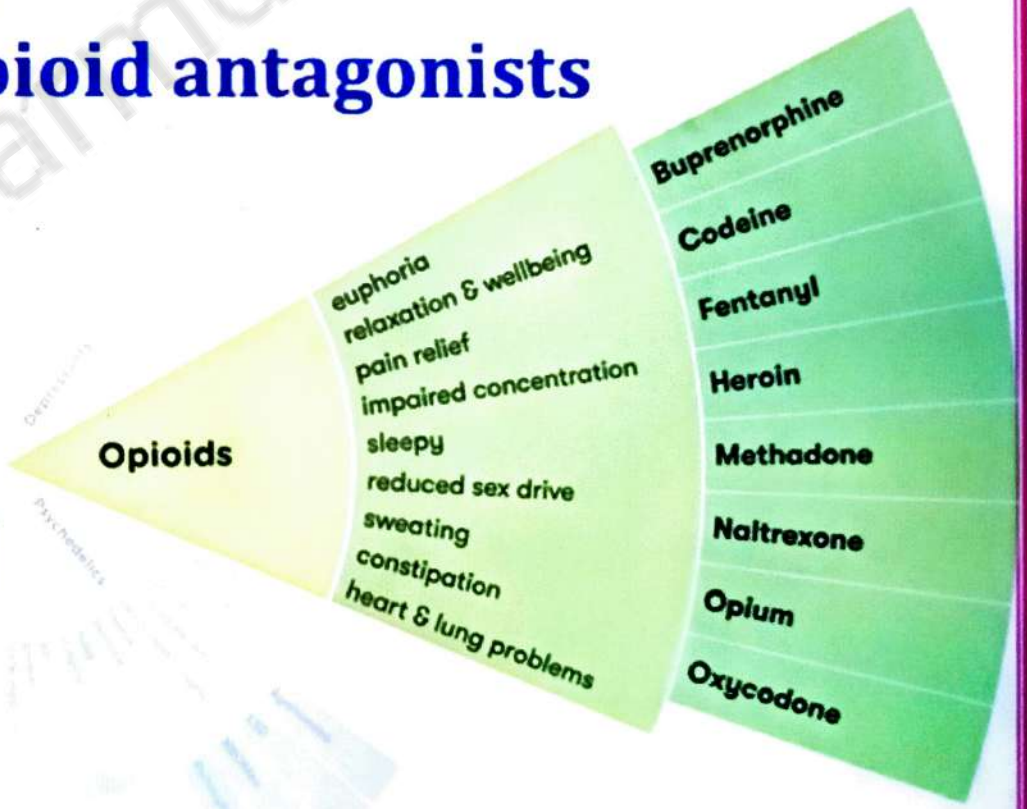
- Nootropics like Pentoxifylline, Pyritinol, Cyclandate and Nicergoline function like cerebral protectors improving cerebral circulation.
- Improvement in brain metabolism and energy utilization may be involved, as also effects on central neurotransmitters.
- There is evidence that **central cholinergic synapses** may be part of the intrinsic system controlling memory storage. Nootropics may induce environment of neurotransmitters conducive to learning acquisition and memory retention.
- The mechanism of action includes increase in central cholinergic, noradrenergic and dopaminergic activity with concomitant reduction in serotonergic function.

UNIT-V

Opioid Analgesics & antagonists

Points to be covered in this topic

- ❖ Introduction
- ❖ Opioid analgesics
- ❖ Opioid antagonists



OPIOID ANALGESICS & ANTAGONISTS

❑ Introduction

- Pain or algesia is an **unpleasant subjective sensation.**
- Pain is a **warning signal** and indicates that there is an impairment of structural and **functional integrity of the body.**
- It is the most important symptom that brings the patient to the doctor and demands immediate relief.

❖ Types of Pain

SOMATIC PAIN	• Pain arising from the skin and integumental structures, muscles, bones and joints is known as **Somatic pain.** • It is usually caused by inflammation and is well-defined or sharp pain.
VISCERAL PAIN	• Pain arising from the viscera is vague, dull aching type, difficult to pinpoint to a site and is known as **Visceral pain.** • It may be accompanied by autonomic responses like sweating, nausea and hypotension. • It may be due to spasm, ischemia or inflammation.
REFERRED PAIN	• When pain is referred to a cutaneous area which receives nerve supply from the same spinal segment as that of the affected viscera, it is known as **referred pain.** • E.g. Cardiac pain referred to the left arm.

❖ Analgesics

- Analgesic is a drug which relieves pain without loss of consciousness.
- Analgesics only afford Symptomatic relief from pain without affecting the cause.
- Analgesics are of 3 classes:

1.	**Opioid or morphine** type of analgesics
2.	**Non-opioid or aspirin** type of analgesics
3.	**Adjuvant analgesics**
a.	**Antiepileptics**—pregabalin, gabapentin, carbamazepine, lamotrigine.
b.	**Antidepressants**—amitriptyline, venlafaxine, duloxetine, citalopram, escitalopram.

❖ Endogenous Opioid Peptides

- Three types of **endogenous peptides with analgesic activity** are endorphins, enkephalins and dynorphins. They are derived from distinct precursor polypeptides.
- They are involved in modulating pain and **form part of the complex pain** inhibiting mechanisms in the brain and spinal cord.

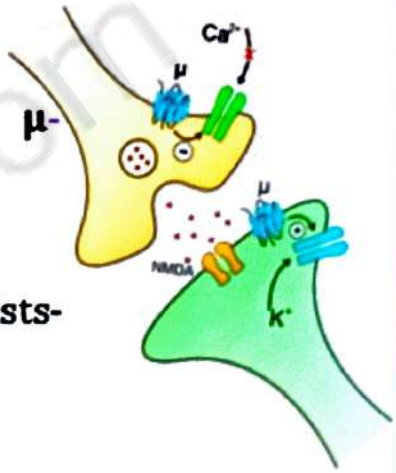
❖ Opioid Receptors

- Four major categories of **endogenous opioid receptors** have been identified. They are as follows:

✓ **μ (mu)**
✓ **κ (kappa)**
✓ **δ (delta)**
✓ **σ (sigma)**

- **The μ, k and σ receptors mediate the main pharmacological actions of narcotic analgesics.**
- **μ and k receptors are important for analgesia while sigma receptors are responsible for psychotomimetic effects.**
- **The δ-receptors inhibit excitatory neurotransmission in the brain and periphery.**
- **It is postulated that opioid receptor activation leads to decrease in c AMP production in the brain, opening up of K^+ channels and inhibition of intraneuronal Ca^{++} transport, all of which induce inhibition of neuronal activity.**

❑ Opioid Analgesics



- **Drugs having agonistic activity, especially on μ-receptors are used as analgesics.**
- **Morphine is the prototype drug in this category.**
- **Other morphine agonists and mixed agonists-antagonists have actions similar to morphine.**

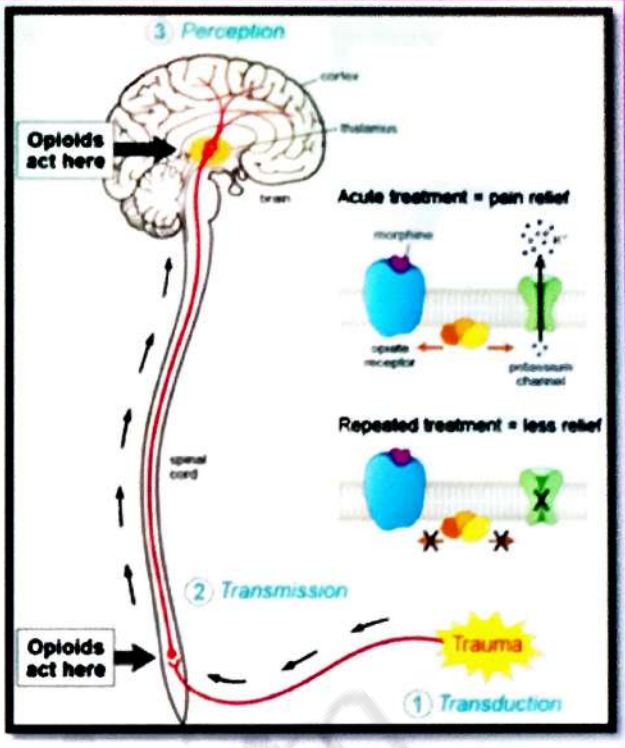
❖ Pharmacokinetics

- **Morphine is readily absorbed from GIT.**
- **Because of extensive first-pass metabolism, bioavailability is poor.**
- **The drug is usually administered by intramuscular route.**
- **Half-life is 2.5 hours, peak effect is at 1 hour and duration of analgesia is 4 hours.**
- **Morphine is metabolized by N-dealkylation and oxidation followed by glucuronide or sulphate conjugation.**
- **It has relatively poor access through BBB.**

❖ Mechanism of Action

- **Morphine acts through different receptors mentioned above.**
- **It influences the activity of some neurotransmitters in brain.**
- **It increases cholinergic and 5-HT activity; and inhibits nor-adrenergic, dopaminergic and GABAergic activity.**

- It releases histamine but **inhibits release of substance P.** These wide ranging effects contribute to various pharmacological actions.



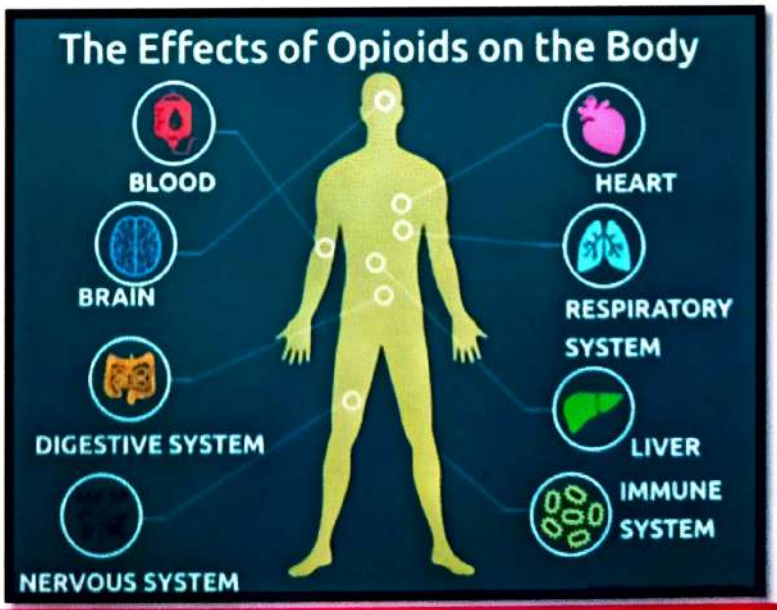
❖ Pharmacological Actions

1. Effects on CNS

- ✓ **Analgesia**
- ✓ **Euphoria**
- ✓ **Sedation**
- ✓ Respiratory depression
- ✓ Pupillary constriction
- ✓ Nausea and vomiting
- ✓ **Antitussive effect**
- ✓ Neuroendocrine effects

2. Effects on GIT

- ✓ Increase in tone and **reduces motility in many parts of GIT.**
- ✓ **Severe constipation.**
- ✓ Gastric emptying is delayed.
- ✓ Intra-biliary pressure is increased due to constriction of biliary sphincter and **contraction of gall bladder.**
- ✓ Gastric, intestinal, pancreatic and biliary secretions are decreased by morphine.



3. Effects on CVS

- ✓ Morphine causes **hypotension and bradycardia.**

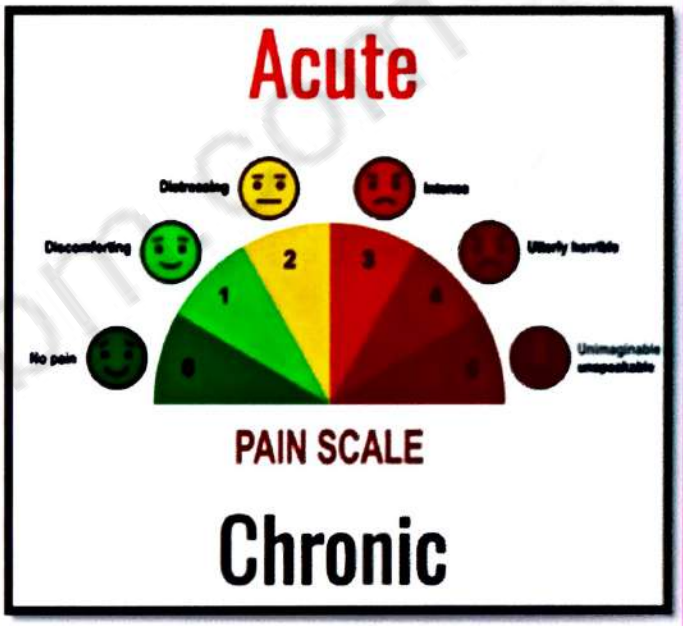
4. Other actions

- ✓ **Bronchoconstriction** is due to release of histamine and increased **vagal activity.**
- ✓ **Contraction** of uterus, ureters and urinary bladder occurs occasionally.
- ✓ **Immunosuppressant** effect is probably due to actions on CNS.
- ✓ Morphine addicts may have risk of **AIDS.**

❖ Therapeutic Uses

1. For analgesia

- ✓ For relief of **acute severe pain** in trauma, burns, post-operative pain, myocardial infarction, renal and intestinal colic.
- ✓ In Terminal cancer patients for analgesia and euphoria.



2. In left ventricular failure

- ✓ Relieves symptoms by inducing marked **Veno-dilatation** and **decrease in pre-load.**
- ✓ Reduced sensitivity of **respiratory center** to stimuli from **Congested lungs** and **increased** CO_2 levels also contribute to decreased dyspnea.

3. In anesthetic pre-medication

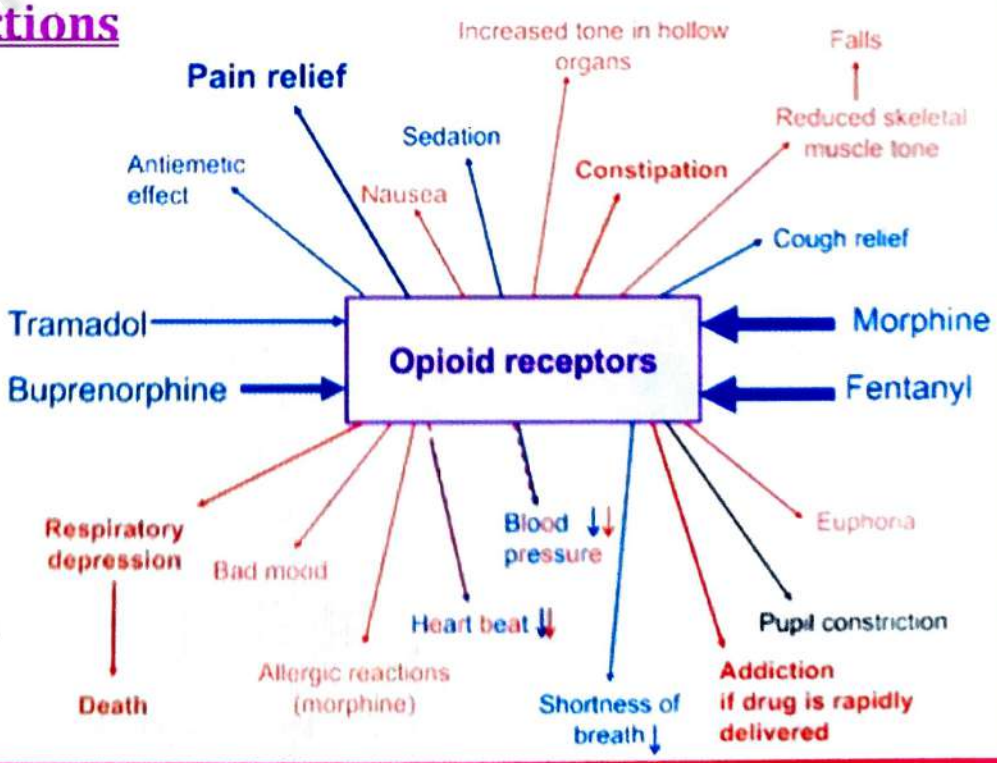
- ✓ Morphine sulphate (8-12 mg) or Pethidine (50-100 mg) is given intramuscularly 1 hour **before surgery to reduce pain during surgery.**

❖ Contraindications

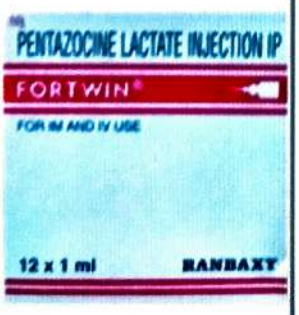
1.	**Acute abdomen**	✓ Morphine can mask the symptoms; hence it should not be given in undiagnosed abdominal pain.
2.	**Head injury**	✓ Morphine induced respiratory depression and rise in intra-cranial tension, together with miosis and vomiting may interfere with diagnosis.
3.	**Bronchial asthma**	✓ Morphine may aggravate bronchial spasm and respiratory depression.
4.	**Chronic lung disease**	✓ Respiratory insufficiency by morphine can aggravate the symptoms
5.	**Hypothyroidism**	✓ Slow metabolism of morphine can cause increased toxicity.
6.	**Hepatic failure**	✓ Reduced metabolism can cause higher toxicity leading to hepatic coma.
7.	**Biliary colic**	✓ Morphine can cause constriction of biliary sphincter. It is also to be avoided after cholecystectomy.
8.	**Ulcerative colitis**	✓ Production of colonic dilatation by morphine can complicate ulcerative colitis.

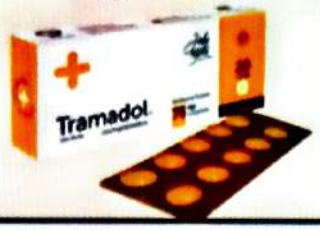
❖ Adverse Reactions

- ✓ Nausea
- ✓ Vomiting
- ✓ Drowsiness
- ✓ Sweating
- ✓ Prurites
- ✓ Piloerection
- ✓ Bradycardia
- ✓ Hypotension
- ✓ bronchospasm



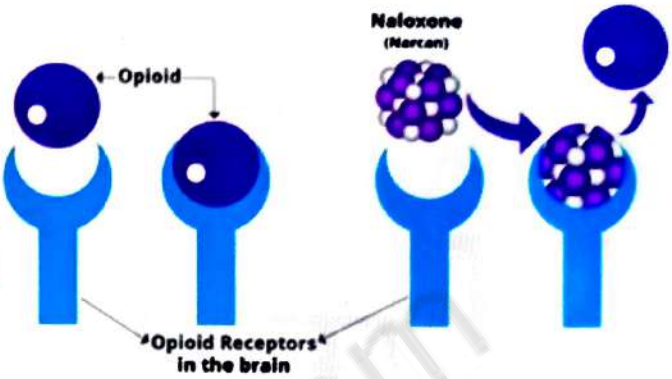
❖ Morphine Related Drugs (Opioids)

1.	**Pethidine** 	✓ Less potent than morphine as analgesic but causes equal respiratory depression and vomiting ✓ Shorter duration of action ✓ Less sedative, antitussive and constipating agent. ✓ It is used as an analgesic and preanaesthetic medicant
2.	**Heroin** 	✓ More effective than morphine as analgesic. It crosses BBB. ✓ It is metabolized to morphine in brain. It is most addictive and is not used clinically.
3.	**Methadone** 	✓ Equipotent to morphine ✓ Oral active and longer duration of action ✓ used in the treatment of morphine deaddiction.
4.	**Fentanyl** 	✓ Have shorter duration (30-60 minutes) of action ✓ Their uncontrolled use may lead to marked respiratory depression.
5.	**Codeine** 	✓ Codeine and its derivatives Oxycodone, Dihydrocodeine, Hydrocodone are less effective as analgesics ✓ Large doses can induce excitement Tolerance and physical dependence are less marked. ✓ It is mainly used for antitussive action
6.	**Pentazocine** 	✓ Pentazocine is an intermediate beween morphine and Pethidine for its potency as an analgesic ✓ It is an agonist at k-receptor and antagonist at μ-receptor ✓ Its potency is much less than that of Nalorphine or Naloxone

7.	**Tramadol** 	✓ Its analgesic activity is partly mediated through μ-receptors. It is useful ✓ in chronic neuropathic pain. Toxicity includes dependence, seizures and anaphylactoid reactions.

❑ Opioid Antagonists

❖ Naloxone



- It acts as a **competitive antagonist** to all types of opioid receptors and is a **pure antagonist.**
- In normal individuals, it does not produce any significant actions.
- But in opium addicts, when given IV, it promptly **antagonizes all the actions of morphine including respiratory depression and sedation and precipitates withdrawal syndrome.**
- It also blocks the action of endogenous opioid peptides—endorphins, enkephalins and dynorphins.
- Given orally it undergoes high first pass metabolism and is metabolized by the liver. Hence, it is given intravenously. Duration of action is **1–2 hours** . It is metabolized by glucuronide conjugation.

DOSE: 0.4 mg IV. NARCOTAN 0.4 mg/ml and 0.04 mg/ml Ampoules.

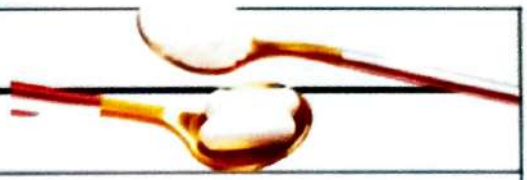
➢ Uses

- Naloxone is the drug of choice for **Morphine overdosage.**
- It is also used to **Reverse neonatal asphyxia** due to opioids used in labour.
- Diagnosis of **opioid dependence.**
- Naloxone has been found to be beneficial in **Reversing hypotension.**

❖ Naltrexone

- It is another **pure opioid antagonist.** It is

1.	**More potent** than naloxone.
2.	**Orally** effective.
3.	Has a longer duration of action of **1–2 days.**
4.	Naltrexone is well **absorbed** when given orally but undergoes first pass metabolism.

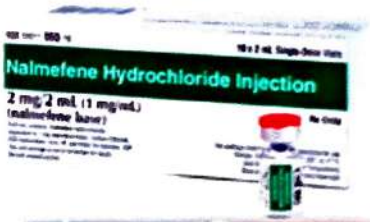


DOSE: 50–100 mg/day. NALTIMA 50 mg tab.

➢ Uses

- Naltrexone is used for **'opioid blockade'** therapy in post-addicts is found to be effective.
- Alcohol craving is also reduced by naltrexone and is used to prevent relapse of heavy drinking.

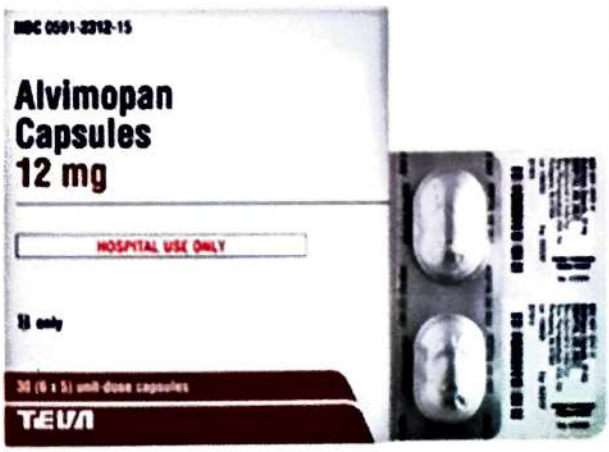
❖ Nalmefene



- **Nalmefene is a derivative of naltrexone.**
- It is orally effective (but only an IV preparation is available) and **longer acting.**
- It has better bioavailability and is not **hepatotoxic.** It is used in **opioid overdosage.**

❖ Alvimopan

- It blocks the μ receptors in the gut and does not significantly **penetrate CNS.**
- It is used in the treatment of **postoperative ileus following bowel resection.**



UNIT-V

Drug Addiction, Drug abuse , Tolerance & Dependence

Points to be covered in this topic

- ❖ Drug addiction
- ❖ Drug abuse

- ❖ Drug tolerance
- ❖ Drug dependance

DRUG ADDICTION , DRUG ABUSE, TOLERANCE & DEPENDANCE

❑ Drug Addiction

- Drug addiction has following features:

1.	The **detrimental effects** of drugs not only harm the individual but the society as well.
2.	There is always an **intense craving** to procure the drug by any means.
3.	There is development of tolerance and hence a need to increase the dose to get the same **rewarding experience**
4.	There are **life-threatening** or **alarming withdrawal effects** after **cessation** of the drug and hence there is a **physical need** to continue with use of the drug for the fear of abstinence syndrome.

❑ Drug Abuse

- Drug abuse has following features:

1.	Recurrent substance use results in failure to fulfil his/her major obligations at work, school or home, e.g. **poor performance at work, expulsion from school.**
2.	Recurrent substance use even in **situations** where it should not be used e.g. during driving, operating a machine or even operating on the patient.
3.	Recurrent substance **use punitive action**, e.g. punishment for disorderly conduct.
4.	Recurrent substance use despite having **interpersonal or family problems,** e.g. arguments or physical fight with spouse about consequences of abuse.

❑ Drug Tolerance

- Tolerance develops if, after **repeated administration**, a given dose of a drug produces a **decreased effect than expected.**
- Larger doses are needed to obtain the same effects with previous dose.
- It is classified as **pharmacokinetic** (e.g. Barbiturates) or **pharmacodynamic** (e.g. opioids).
- There is another related Term: **CROSS-TOLERANCE**. When tolerance to primary drug develops, the individual also exhibits cross-tolerance to related classes of drugs, e.g. a patient with tolerance to morphine may show cross-tolerance to heroin.

❑ Drug Dependence

- Dependence is a **physiological state of neuroadaptation** resulting from **repeated administration** of the drug, necessitating its continued use to prevent the appearance of **distressing withdrawal syndrome** which is manifested as opposite to the **pharmacological effects of drugs.**
- **Withdrawal** or **abstinence syndrome** is a term used for the adverse (sometimes life-threatening) psychologic or physiologic reactions to an abrupt discontinuation of a dependence-producing drug.
- The drugs of abuse which can endanger dependence are as follows:

1.	Drugs/agents having only **mild psychological dependence**. There are low withdrawal symptoms and no physical dependence, e.g. coffee, tea.
2.	Drugs/agents with **moderate to severe psychological dependence.** There are low withdrawal symptoms but slight physical dependence, e.g. Marijuana, Hashish, LSD, Amphetamine, Cocaine, Nicotine.
3.	Drugs/agents having **moderate to severe psychological dependence with mild physical dependence**, e.g. Benzodiazepines, Alcohol (moderate use).

4.	Drugs/agents having **severe psychological and physical dependence,** e.g. Opioids Barbiturates and Alcohol (heavy use).