Unit-5
Pharmacology-I

B.Pharma 4st Sem Notes

UNIT- V

Pharmacology of drugs acting on central nervous system

- Psychopharmacological agents: antipsychotics, antidepressants, anti-anxiety agents, antimanics and hallucinogens.
- Drugs used in Parkinson's disease and Alzheimer's disease.
- CNS stimulants and nootropics.
- Opioid analgesics and antagonists.
- Drug addiction, drug abuse, tolerance and dependence.

Pharmacology of drugs acting on central nervous system

Psychopharmacological agents: antipsychotics, antidepressants, anti-anxiety agents, antimanics and hallucinogens.

Psychopharmacological agents:

- Psychopharmacological agents, also known as psychotropic drugs, primarily affect mental processes and are used for treating psychiatric disorders.
- Psychopharmacology is the scientific study of how drugs impact mood, sensation, thinking, behavior, judgment, evaluation, and memory.

Drugs anting on CNS are classified in different categories:

- Antipsychotics,
- Antidepressants,
- Anti-Anxiety Agents,
- Antimanics And Hallucinogens.

Antipsychotics Drugs:

- Antipsychotic medications, also known as neuroleptics and major tranquilizers, are a class of psychotropic drugs primarily used to manage psychosis.
- They work by altering the balance of chemicals in the brain, particularly dopamine, a neurotransmitter involved in mood regulation, cognition, and perception.

Classification of Antipsychotics Drugs:

1. **First-generation antipsychotics** (Typical antipsychotics):
    - **Chlorpromazine**
    - **Fluphenazine**
    - **Haloperidol**
    - **Perphenazine**
    - **Thioridazine**
2. **Second-generation antipsychotics** (Atypical antipsychotics"):
    - **Aripiprazole**
    - **Asenapine**
    - **Brexpiprazole**
    - **Cariprazine (Vraylar)**

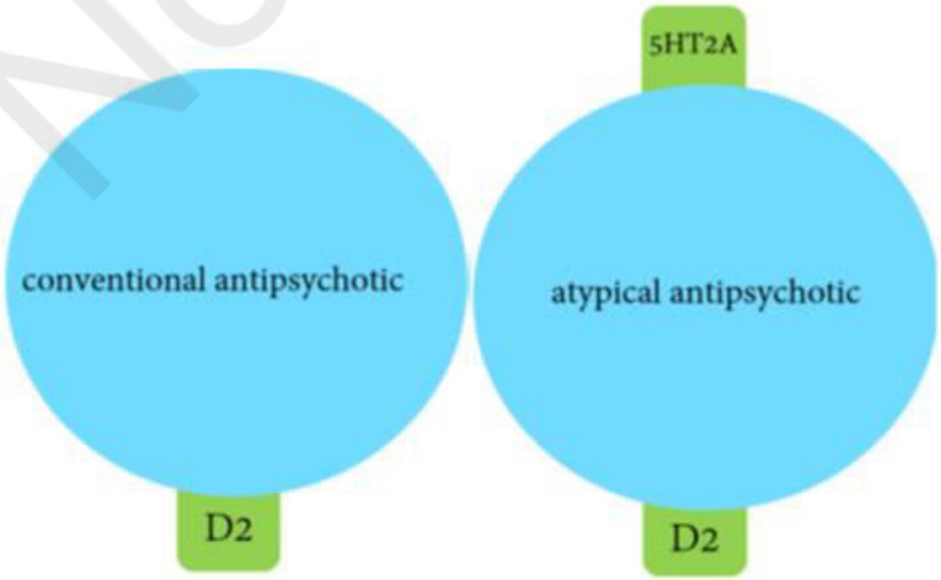
Mechanism of action of Antipsychotics Drugs:

1. Typical Antipsychotics (Conventional):

- These drugs primarily target the **dopamine system** in the brain.
- They work by binding to **dopamine D2 receptors**, which are abundant in various brain regions.
- By blocking these receptors, typical antipsychotics reduce the activity of dopamine, particularly in the **mesolimbic**, **corticolimbic**, and **nigrostriatal** systems.
- This helps alleviate the **positive symptoms** of schizophrenia (such as hallucinations and delusions).

2. Atypical Antipsychotics:

- Typical antipsychotics, atypical ones have a multimodal mechanism of action.
- They not only affect dopamine but also modulate other neurotransmitters:
  - Serotonin (5-HT): Atypical antipsychotics interact with 5-HT receptors, contributing to their broader efficacy.
  - Norepinephrine: Some atypical drugs also influence norepinephrine transmission.
  - Histamine: Histamine receptors are involved, impacting both mood and cognition.
- This diverse action explains why atypical antipsychotics are effective not only in psychosis but also in mood disorders (such as depression and anxiety).
- Novel experimental drugs with dual antipsychotic and antidepressant potential also exhibit similar multimodal effects on central neurotransmission



Therapeutic Uses of Antipsychotics Drugs:

- Antipsychotic medications work by altering brain chemistry to help reduce psychotic symptoms like hallucinations, delusions and disordered thinking.
- They can also help prevent those symptoms from returning.

Adverse Effect:

- Drowsiness
- Mental Confusion
- Blurring of vision
- Phenothiazines
- Hypotension, Seizures, etc.

Antidepressant Drugs:

Depression:

- It is a mental disorder that is marked by pathological mood changes, low self-worth, low energy, poor focus, lack of interest or pleasure, and feelings of guilt.

Symptoms:

- Weight loss
- Fatigue
- Loss of Appetite
- Lack of concentration

Antidepressant Drugs:

- Antidepressants are drugs which can elevate mood indepression illness.
- Practically all depressants affect monoaminergic transmission in the brain in one way.
- They are used to relief of the symptoms of moderate and severe depression.

Classification of Antidepressant Drugs:

I. Reversible Inhibitors of MAOA (RIMAs)

Moclobemide, Clorgyline

II. Tricyclic Antidepressants (TCAs)

a. ***NA + 5HT reuptake inhibitors*** Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine
b. ***Predominantly NA reuptake inhibitors*** Desipramine, Nortriptyline, Amoxapine, Reboxetine

III. Selective Serotonin Reuptake Inhibitors (SSRIs)

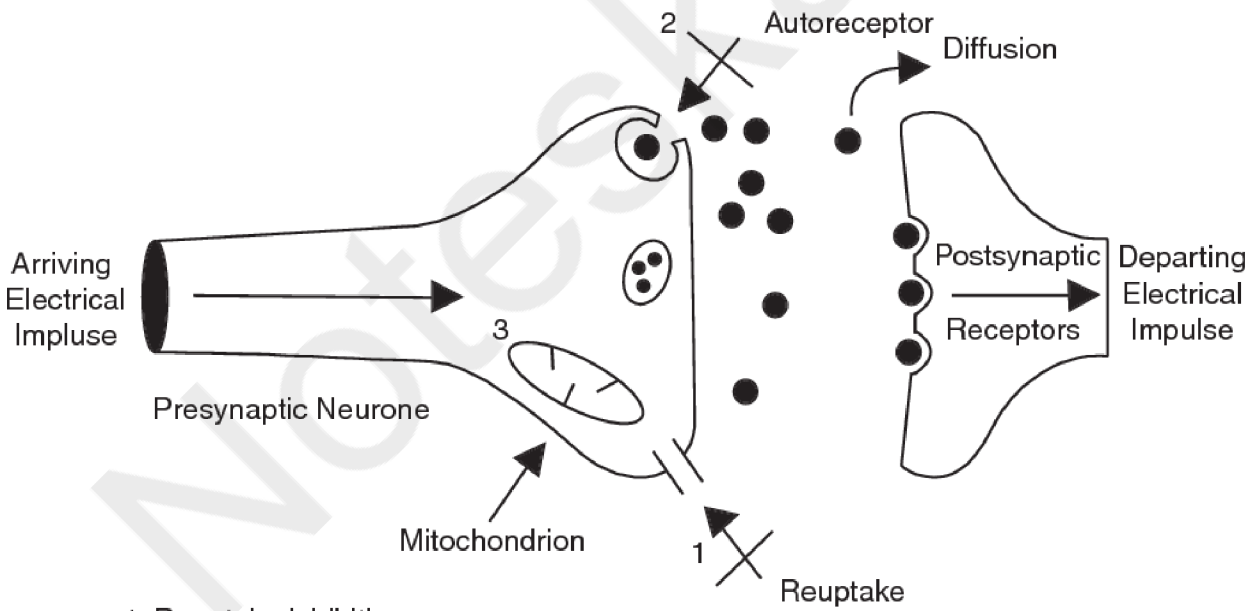
- Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram, etc.

IV. Atypical Antidepressants

- Trazodone, Mianserin, Mirtazapine, Venlafaxine, Duloxetine, Tianeptine, Amineptine, Bupropion, etc.

Mechanism of Action of Antidepressant Drugs:

- Tricyclic Antidepressant (TCAs) norepinephrine and serotonin reuptake into the neuron.
- Inhibition of neurotransmitter reuptake:- TCAs is potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals.
- At therapeutic concentrations they don't look dopamine transporters.
- TCAs cause increased concentration of monoamines in the syneptic left ultimately resulting in antidepressant effect.
- Blocking of receptors:
- TCAs also block serotonergic alpha adrenergic histamine and muscarinic receptors.
- It is not known if any of these action produce TCAs therapeutic benefit.



1. Reuptake inhibition
2. Receptor blockade
3. MAO enzyme inhibition

Pharmacokinetics:

- Oral absorption of most antidepressant drugs is good still the bioavailability is uncertain because of there first pass metabolism.
- The plasma half life of most antidepressants is long.
- Plasma half life is longer due to their metabolites except for fluvoxamine paroxetine and prothiptyline.

Therapeutic Uses:

- Antidepressants are mostly used to treat depression in adults.

Antidepressants can also be used to help treat other mental health conditions, including:

- Anxiety disorder.
- Obsessive compulsive disorder (ocd)
- Panic disorder.
- Serious phobias, such as agoraphobia and social anxiety (social phobia)
- Bulimia.
- Post-traumatic stress disorder (PTSD)

Anti-anxiety agents:

Definition of Anxiety:

- It is an emotional state, unpleasant in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat.
- Somatic symptoms like anorexia, breathlessness, palpitation, paresthesia, etc. often accompany.
- Some degree of anxiety is a part of normal life.

Anti-anxiety drugs

- These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind with out interfering with normal mental or physical functions.
- The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics.

Classification of Anti-anxiety agents:

1. Benzodiazepines

- Diazepam
- Chlordiazepoxide
- Oxazepam
- Lorazepam
- Alprazolam

2. 5-HT aginist Antagonists

- Buspirone
- Gepirone
- Ispapirone

3. Sedative antihistaminic

- Hydroxyzine

4. β-blocker

- Propranolol

Mechanism of Action:

1. 5-HT aginist 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. Sedative antihistamine:

- Hydroxyzine is an antihistaminic with anxiolytic actions but due to high sedation it is not used.

3. Beta-Blockers:

- Propranolol breaks the visicious cycle. Through its beta-blocking action it decreases palpitation tremors, GIT upset, hypertensions and blood lactic acid levels. Because of its cardiovascular acion it is not a potential preferred anxiolytic.

Pharmacokinetics:

- Buspirone is rapidly absorbed and metabolized in the liver undergoes extensive five pass metabolism.
- Chlordiazepoxide oral absorption is slow. It $t^1/_2$ is 6-12 hours, but active metabolites are produced which extend the duration of action.

Therapeutics Uses:

- Endogenous depression.
- Anxiety disorder
- Neuropathic Pain
- Migrain

Adverse Effects:

- Dizziness,
- Nausea,
- Abdominal discomfort,
- Headache, etc.

Antimanics:

Mania:

- Mania is a mental and behavioral disorder that causes an abnormally elevated state of arousal, affect, and energy level.

Antimanics (Mood Stabilizing Drugs):

- Antimanic drugs are psychotropic drugs that are used to treat symptoms of mania.
- Though there are different causes of mania, the majority is caused by bipolar disorder, therefore antimanic drugs are mostly similar to drugs treating bipolar disorder.

List of drugs:

Below is the list of common antimanic drugs.

First-line treatment	
Lithium	Lithium carbonate
	Lithium citrate
Valproate (anticonvulsants)	Valproate sodium
	Valproic acid
Other common drugs	
Anticonvulsants	Carbamazepine
	Gabapentin
	Lamotrigine
Antipsychotics	Asenapine
	Haloperidol
	Olanzapine
	Quetiapine
	Risperidone
	Ziprasidone

Mechanism of actions:

A. Anticonvulsants

- Although some mechanisms of actions of anticonvulsants are still unknown or suspected, there are mainly several types of mechanism of actions.
- The most common mechanism is affecting voltage-dependent sodium channels, which is mainly adopted by both carbamazepine and lamotrigine. Other mechanisms include affecting calcium currents, GABA activity and glutamate receptors.

B. Antipsychotics:

- The mechanism of actions of most antipsychotics is post-synaptic blockage of brain dopamine D2 receptors. Second generation antipsychotics also bind with serotonin 5HT2 receptors at a high affinity, which is suggested to be the cause for the lowered risk of extrapyramidal side effects compared with first generation antipsychotics.

Therapeutics Uses:

- Antimanic drugs are used to stabilise mood by controlling symptoms of mania in patients with bipolar disorder.
- They may be used in conditions when patients periodically display periods of great excitement or over-activity.

Hallucinogens:

- Hallucinogens are psychedelic drugs that can potentially change the way people see, hear, taste, smell or feel, and also affect mood and thought.

Classification:

1. **Indole Amines:** Lysergic diethylamide, Harmine.
2. **Phenyl Alkylamines:** Mescaline, Methylenedioxymethamphetamine (MDMA)
3. **Alycyclohexyl Amines:** Phencyclidine
4. **Cannabinoids:** Tetrahydrocannabinod.

Pharmacological Action:

- Lysergic diethylamide has hallucinogenic effects.
- It is most potent psychedelic.
- Lysergic acid amide is lotimes less potent than LSD.

Therapeutics use:

- Used in Analgesic, Antiemitic, Antiinflamatory.

Drugs used in Parkinson's disease and Alzheimer's disease.:

Parkinson's Disease:

- Parkinson's Disease is an autonomic neurogenic disorder in which the muscle are permanently contract.
- Parkinson's disease (PD) is a chronic brain disorder that affects the central nervous system's motor and non-motor systems.
- In this disease the release of acetycholic is increase and release of dopamine is less.
- When high amount of acetylcholine is bind with cholinergic receptor then it cause continuous and permanent construction.
- Dopamine is responsible for muscle relaxation but in parkinson's disease their secretion is decrease.

Cause:

- Genetic Factor
- Age
- Degeneration of Dopamine neurotransmitters.
- More alcohol consumption.

Symptoms:

- Tremor in hands, arms, legs, jaw, or head.
- Muscle stiffness, where muscle remains contracted for a long time.
- Slowness of movement.

Classification of Anti-Parkinson's drugs:

1. Drugs affecting brain dopaminergic system

a. **Dopamine Precursor :** Levodopa (ldopa)
b. **Decarboxylase Inhibitors :** Carbidopa, Benserazide.
c. **Agonists:** Bromocriptine, Ropinirole, Pramipexole
d. **MAO-B Inhibitor**: Selegiline
e. **COMT Inhibitors:** Entacapone, Tolcapone
f. **Dopamine Facilitator:** Amantadine.

2. *Drugs affecting brain cholinergic system*

a. **Central Anticholinergics:** Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.
b. **Antihistaminics *:*** Orphenadrine, Promethazine.

Levodopa (L-dopa):

- Levodopa is the precursor to dopamine. Most commonly, clinicians use levodopa as a dopamine replacement agent for the treatment of Parkinson disease.

- It is most effectively used to control bradykinetic symptoms apparent in Parkinson disease.

Mechanism of Action:

$$\text{L} - \text{dopa} \xrightarrow[Decarboxylase]{DOPA} Dopamine \rightarrow Interacts\ with\ D2\ receptor \rightarrow Relieves\ Symptoms\ of\ Parkinsonism$$

Adverse Effects:

- Nausea Vomiting
- Cardiac Arrhythmias
- Alteration in taste sensation.

Selegiline:

- Selective irreversible inhibitors of MAO-B.

Advantage:

- Increase Ant-Parkinson Effect of Dopamine.
- Decrease On-Off Wearing off Phenomena.

Mechanism of Action:

- Breakdown of dopamine in CNS.
- Blockage of presynaptic dopamine receptors.
- Inhibiting of dopamine reuptake from the synapse.

Drugs used in Alzheimer's disease.

Alzheimer's disease:

- Alzheimer's disease is a progressive neurologic disorder.
- Alzheimer's is the most common cause of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life.
- The symptoms like depression, Anxiety and disturbed sleep may also be seen.

Classification of Anti-Alzheimer's Drugs:

1. Cholinergic Activators: Tacrine, Rivastigmine, Donepezil, Galantamine
2. NMDA Antagonist: Memantine
3. Miscellaneous Drugs: Piracetam, Pyrithioxine

Rivastigmine:

MOA:

Rivastigmine

↓

Selectively Binds With Enzyme Acetyl Choline Esterase (Ache)

↓

Inactivates Ache Enzyme In Brain + There By Prevents The Breakdown Of Acetylcholine To Choline + Acetate

↓

Leads To Accumulation Of Acetylcholine In The Brain

↓

Relief From Alzehimers Disease

CNS stimulants and nootropics:

CNS stimulants:

- These are drugs whose primary action is to stimulate the CNS globally or to improve specific brain functions.
- The CNS stimulants mostly produce a generalized action which may, at high doses, result in convulsions.

Classification

1. Convulsants: Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazol (PTZ).
2. Analeptics: Doxapram
3. Psychostimulants: Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine. Many other drugs are capable of causing CNS stimulation as side effect or at high doses.

I. Convulsants:

Strychnine:

- It is an alkaloid from the seeds of Strychnos nux-vomica, and a potent convulsant. The convulsions are reflex, tonic-clonic and symmetrical.

MOA:

- Strychnine acts by blocking post-synaptic inhibition produced by the inhibitory transmitter glycine.
- One of the sites that has been clearly demonstrated is the Renshaw cellmotoneurone junction in the spinal cord through which inhibition of antagonistic muscles is achieved.
- Due to loss of synaptic inhibition, any nerve impulse becomes generalized, resulting in apparent excitation and convulsions.

II. Analeptics (Respiratory stimulants):

Doxapram:

- It acts by promoting excitation of central neurones. At low doses it is more selective for the respiratory centre than other analeptics.
- Respiration is stimulated through carotid and aortic body chemoreceptors as well. Falling BP rises.
- Continuous i.v. infusion of Doxapram may abolish episodes of apnoea in premature infant not responding to theophylline.

Dose: 40–80 mg i.m. or i.v.; 0.5–2 mg/kg/hr i.v. infusion. CAROPRAM 20 mg/ml in 5 ml amp.

- Reflex stimulation Smelling ammonia or a drop of alcohol in the nose may be enough for hysterical fainting; analeptics should not be used.

III. Psychostimulants:

1. Amphetamines:

- These are central sympathomimetics. Compared to amphetamine, higher central: peripheral activity ratio is exhibited by dextroamphetamine and methamphetamine.
- They stimulate mental rather than motor activity; convulsive doses are much higher.

2. Caffeine: caffeine is used as a CNS stimulant.

Pharmacokinetics:

- Caffeine has poor water solubility; is rapidly but irregularly absorbed after oral administration.
- It is < 50% bound to plasma proteins, distributed all over the body, and nearly completely metabolized in liver by demethylation and oxidation.
- Metabolites are excreted in urine; plasma t½ is 3–6 hours in adults.

Adverse effects:

- Toxic effects of caffeine are extensions of its pharmacological actions. Caffeine poisoning is rare, and it is less toxic than theophylline.
- Gastric irritation, nausea and vomiting may occur as side effects. Excitatory and motor effects such as nervousness, insomnia, agitation, muscular twitching, rigidity, rise in body temperature, delirium and convulsions are produced at toxic doses.
- Tachycardia, occasionally extrasystoles occur at high doses.
- Caffeine is to be avoided in peptic ulcer patients.
- It is not contraindicated in gout because it is not converted in the body to uric acid.
- Moderate coffee drinking does not contribute to development of hypertension.

Uses:

- They most commonly use caffeine for mental alertness, headache, migraine, athletic performance, memory, and obesity.
- It is also used for asthma, gallbladder disease, ADHD, low blood pressure, depression, and many other conditions, but there is no good scientific evidence to support most of these other uses.

Nootropics:

- Nootropics are drugs that improve memory and cognition. They are also called cognition Enhancers.
- Nootropics are class of cognitive enhancing supplement that improve concentration and boost memory.
- Nootropics are often used to increase attention spans, help individuals focus and as studying aids.
- Nootropics referred to as "smart drugs "as they are associated with increased intelligence, motivation, and mental energy.
- Nootropics also called smart drug, memory enhancers, neuro enhancers, cognitive enhancers, and intelligence enhancers, motivational, and stress management are drugs, supplements, nutraceuticals, and functional foods that improve one or more aspects of mental function.
- Nootropics have actually been found as one of the reliable supplements for the mind; for that reason, its relevance has actually additionally led folks in the renovation of their memory as well as finding out ability or intellectual procedures.

Mechanism of Action of nootropics:

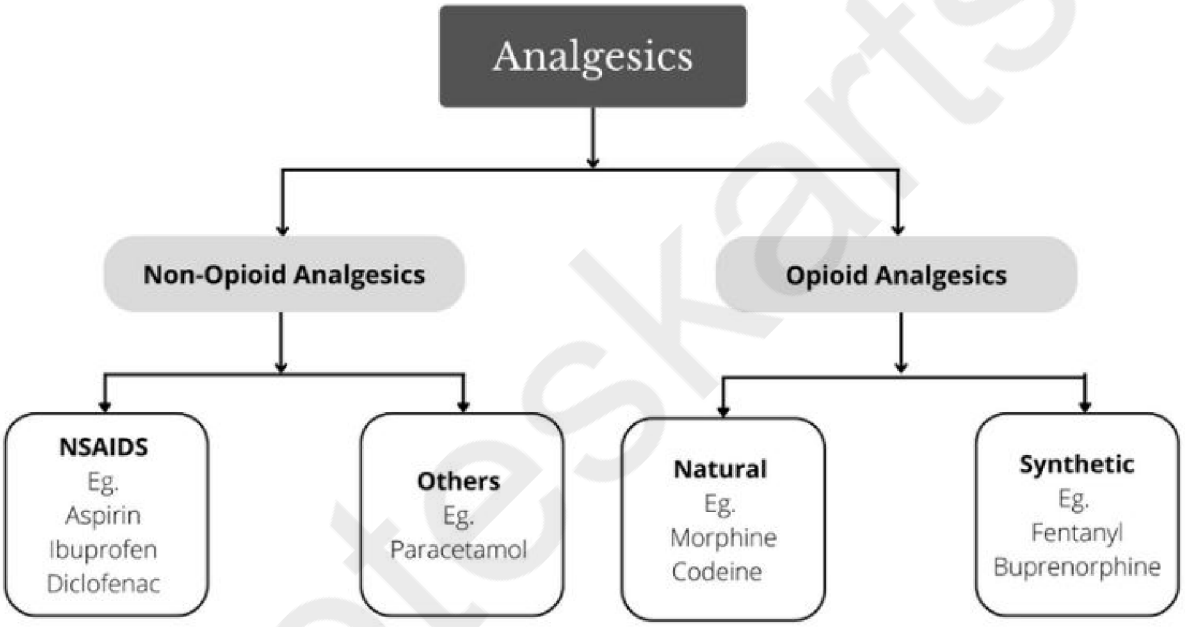
- Nootropics like Pentoxifylline, Pyritinol, Cyclandate and Nicergoline function like cerebral protectors improving cerebral circulation.
- Improvement in brain metabolism and energy utilization may be involved, as also effects on central neurotransmitters.
- There is evidence that central cholinergic 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.

Opioid analgesics and antagonists

Analgesics:

- Analgesics, also known as painkillers or pain relievers, are medications that treat pain and reduce fever.
- They include several classes of drugs, such as: Acetaminophen (Tylenol), Nonsteroidal anti-inflammatory drugs (NSAIDs), Antidepressants, Antiepileptics, Local anesthetics, and Opioids (narcotics).

Classification of Analgesics:



Opioid analgesics:

- Opioid analgesics, also known as narcotic analgesics, are a class of medications widely used to treat moderate to severe pain.
- Opioid Derived from or mimic natural substances from the opium poppy plant.

Morphine:

- Morphine is the principal alkaloid in opium and still widely used to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and when other pain medicines did not work well enough or cannot be tolerated.

Pharmacokinetics:

- Morphine is readily absorbed from GIT.
  Because of extensive first-pass metabolism, bioavailability is poor.

- The drug is usually administered by intermuscular 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 Blood Brain Barrier (BBB).

Mechanism of Action:

- Morphine acts through different receptor mentioned above. It influence the activity of some neurotransmitters in brain. It increase cholinergic and 5-HT activity and inhibits noradrenergic, dopaminergic and GABA activity.
- It releases histamine but inhibits release of substance. These wide ranging effects contribute to various pharmacological actions.

Therapeutics Uses:

- They are used to provide analgesia and supplement sedation in an inpatient setting, particularly in the perioperative setting.

Opioid Antagonists:

Nalorphine

- It is N-allyl-normorphine; was the first opioid antagonist introduced in 1951 which could reverse morphine action.
- Later it was found to have agonistic actions as well. Nalorphine is a κ agonist and μ antagonist; has analgesic action with a lower ceiling, but is not used clinically because of dysphoric and psychotomimetic effects.
- Naloxone has replaced it as a morphine antidote.

Uses:

- Naloxone is the drug of choice for morphine overdosage.
- Diagnosis of opioid dependence.
- It is also used to reverse neonatal asphyxia due to opioids used in labour.

Drug addiction, drug abuse, tolerance and dependence

Drug addiction:

- The term "drug addiction" describes a recurrent, chronic illness marked by obsessive drug seeking, continuing drug use despite negative effects, and long-lasting brain alterations.
- Drugs alter the structure and function of the brain, resulting in compulsive usage and uncontrolled desires, which is why it is sometimes seen as a brain condition.

Drug abuse:

- The use of drugs excessively, inappropriately, or illegally is a common form of drug abuse.
- It can apply to the use of illicit narcotics like heroin or cocaine as well as legal ones like prescription drugs.
- Drug misuse frequently has detrimental effects on one's relationships, health, and legal situation, among other areas of one's life.

Tolerance:

- When the body grows accustomed to a drug's effects, tolerance develops and higher dosages are needed to get the same results.
- It is a typical physiological reaction to long-term drug use.
- People may get tolerant to a drug's beneficial and detrimental effects, which raises the possibility of overdosing since they may need to take more of the medication to have the intended effect.

Dependence:

- Drug dependency is a condition in which the body has become used to the presence of drugs and now needs them in order to operate properly.
- Dependency can manifest as either physical or psychological, with the former including cravings and an emotional reliance on the substance, and the latter involving withdrawal symptoms in the body upon stopping use.
- Since dependency may arise from both the medicinal and recreational use of pharmaceuticals, dependence does not always entail addiction.