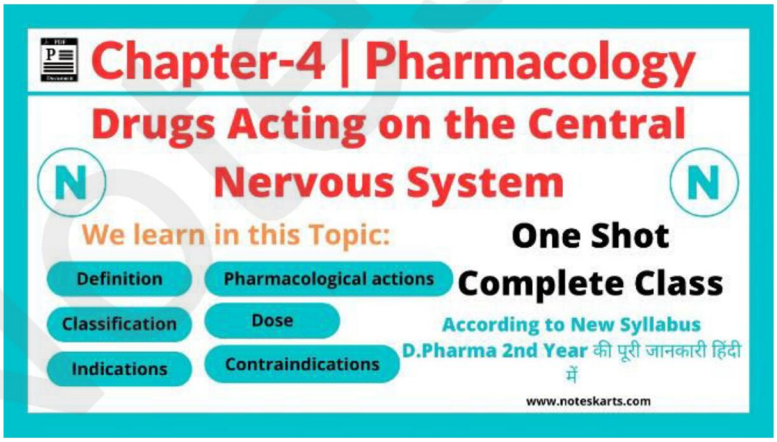
Chapter-4
Pharmacology & Toxicology

D.Pharma 2nd Year Notes

Chapter- 4

Drugs Acting on the Central Nervous System Definition, classification, pharmacological actions, dose, indications and contraindications of

1. General anaesthetics
2. Hypnotics and sedatives
3. Anti-Convulsant drugs
4. Anti-anxiety drugs
5. Anti-depressant drugs
6. Anti-psychotics
7. Nootropic agents
8. Centrally acting muscle relaxants
9. Opioid analgesics



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1. General anaesthetics:

General anaesthetics (GAS) are drugs which produce reversible loss of all sensation and consciousness.

The cardinal features of general anesthesia are:

- Loss of all sensation, especially pain
- Sleep (unconsciousness) and amnesia
- Immobility and muscle relaxation
- Abolition of somatic and autonomic reflexes.

Stage of General anaesthetics:

- General anaesthetics cause an irregularly descending depression of the CNS.
- The higher functions are lost first and progressively lower areas of the brain are involved but in the spinal cord lower segments are affected somewhat earlier than the higher segments.
- The description of these stages still serves to define the efforts of light and deep anesthesia.

Important features of different stages are –

Stage I

- **Analgesia state:** Patient is conscious and rational, with decreased perception of pain.

Stage-II

- **Delirium stage:** Patient is unconscious; body responds reflexively; irregular breathing pattern with breath holding.

Stage-III

- **Surgical anesthesia:** Increasing degrees of muscle relaxation; unable to protect airway.

Stage IV

- **Medullary depression:** There is depression of cardiovascular and respiratory centers.

Properties of an ideal anesthetic

A. For the patient

- It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. For the surgeon

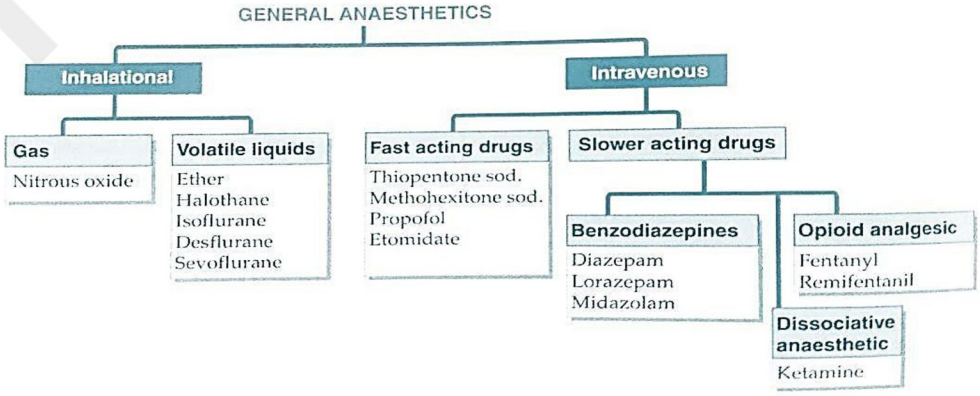
- It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and non-explosive so that cautery may be used.

C. For the anesthetist

- Its administration should be easy, controllable and versatile.
- Margin of safety should be wide-no fall in BP. Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anesthesia should be possible.
- It should be cheap, stable and easily stored. It should not react with rubber tubing or soda lime.

Classification of General anaesthetics:

- **Inhalational**
  - **Gas-** Nitrous Oxide
  - **Volatile Oil Liquid-** Halothane
- **Parenteral anaesthetic**
  - **Benzodiazepines-** Diazepam, Lorazepam
  - **Opioid Analgesia-** Remifentanil,
  - **Dissociative Analgesia-** Ketamine



Halothane (Fluothane)

- It is a volatile liquid with sweet odor, nonirritant and non in flammable. Solubility in blood is moderate induction is reasonably quick and pleasant.
- It is not a good analgesic or muscle relaxant, but it potentiates competitive neuromuscular blockers.
- Halothane causes direct depression of myocardial contractility by reducing intracellular Ca2+ concentration. Moreover, sympathetic activity fails to increase reflex.
- Cardiac output is reduced with deepening anesthesia.

Pharmacology Action:

- Halothane causes general anaethesia due to its actions on multiple ion channels, which ultimately depresses nerve conduction, breathing, cardiac contractility.
- Its immobilizing effects have been attributed to its binding to potassium channels in cholinergic neurons.
- Halothane's effect are also likely due to binding to NMDA and calcium channels, causing hyperpolarization.

Dose:

- 2-4% and for main tenance 0.5-1% is delivered by the use of a special vapourizer.

Indications:

- Halothane is a frequently used anaesthetic in developing countries, because it is relatively cheap and nonirritant, noninflammable, pleasant with relatively rapid action.
- It is particularly suitable for use in children, both for induction as well as maintenance.
- In adults, it is mainly used as a maintenance anaesthetic after i.v. induction.

Contraindications

- Relatively greater depression of respiration. Breathing is shallow and rapid-PP of CO, in blood rises if respiration is not assisted. Cerebral blood flow increases.

Benzodiazepines (BZDs)

- In addition to pre-anaesthetic medication, BZDs are now frequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'.

Pharmacological actions Benzodiazepines

Benzodiazepines work by enhancing a very important neurotransmitter called GABA (gamma- aminobutyric acid) at the GABA A receptor. This results in the sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties

Dose Diazepam:

- 5 to 25 mg three times a day-four times a day Maximum 40 mg/day.

Indications:

- Indications for benzodiazepine administration include, but are not limited to, anxiety disorders, insomnia, acute status epilepticus, induction of amnesia, spastic disorders, seizure disorders, and agitation.

Contraindications:

Common Contraindications

- Sedation,
- Dizziness,
- Weakness, and
- Unsteadiness.

Other side effects include: transient drowsiness commonly experienced during the first few days of treatment,

- A feeling of depression,
- Loss of orientation,
- Headache,
- Sleep disturbance,
- Confusion,
- Irritability,
- Aggression

2. Hypnotics and sedatives

Sedative & Hypnotic

Sedatives:

- A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced.
- Sedation refers to decreased responsiveness to stimulation; is associated with some decrease in alertness, ideation and motor activity.

Or

- **Sedative:-** These are the drug which reduce excitement or slow down the current physical activity.

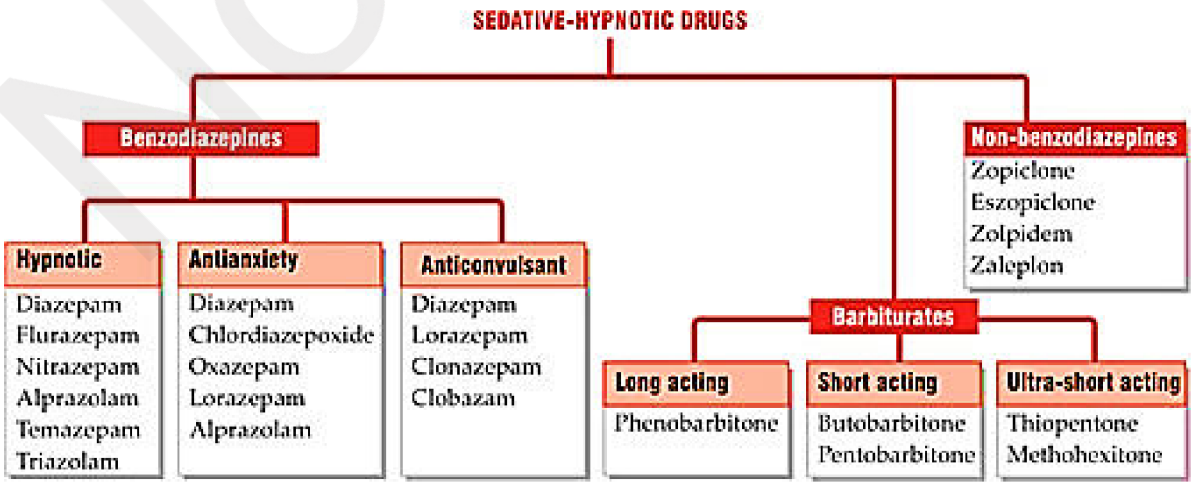
Hypnotics:

- A drug that induces and/or maintains sleep, similar to normal arousal sleep.
- This is not to be confused with 'hypnosis' meaning a trans-like state in which the subject becomes passive and highly suggestible.

Or

- **Hypnotic:-** These are the agent that induce sleep resembling natural sleep.

Classification of Sedative and Hypnotics



Diazepam:

- It is the oldest and all-purpose BZD, used as anxiolytic, hypnotic, muscle relaxant, pre-mendicant, anaesthetic and for emergency control of seizures due to its broad spectrum activity.
- Because of rapid oral absorption, it can be used for sleep onset difficulty as well as for sleep maintenance.

Pharmacological actions of Diazepam

- It generates active metabolites (desmethyl-diazepam, oxazepam). On occasional use it is free of residual effects. With regular use accumulation occurs and prolonged anxiolytic effect may be obtained.

Dose of Diazepam in Hypnotic

- 5-10 mg

Dose of Diazepam in Sedative

- 5-10 mg IV 1-2 hours before surgery; 0.03-0.1 mg/kg q30min to 6hr

Indications

- This medication is a benzodiazepine, prescribed for anxiety. It is also used for muscle spasms and seizures.
- It works by acting on receptors in the brain called GABA receptors.
- Chronic insomnia
- Anxiety
- It is less likely to cause rebound insomnia on discontinuation of chronic use. Withdrawal phenomena are mild.

Contraindications of Diazepam

- Contraindicated in patients with increased eye pressure and hypersensitivity.

Non-benzodiazepine Hypnotics:

- Non-benzodiazepine hypnotics, also sometimes referred to as "Z-drugs" due to many of their names starting with "Z", are a class of medications

used to treat insomnia. Unlike benzodiazepines, they are not chemically related but share some similar mechanisms of action and effects.

Mechanism of Action:

- Non-benzodiazepine hypnotics work by enhancing the action of a brain chemical called gamma-aminobutyric acid (GABA). GABA acts as a calming neurotransmitter in the central nervous system, and by increasing its activity, these medications promote sleepiness.

Uses:

- The primary use of non-benzodiazepine hypnotics is for the short-term treatment of insomnia, particularly difficulty falling asleep (sleep latency).

They may be preferred over benzodiazepines due to potentially:

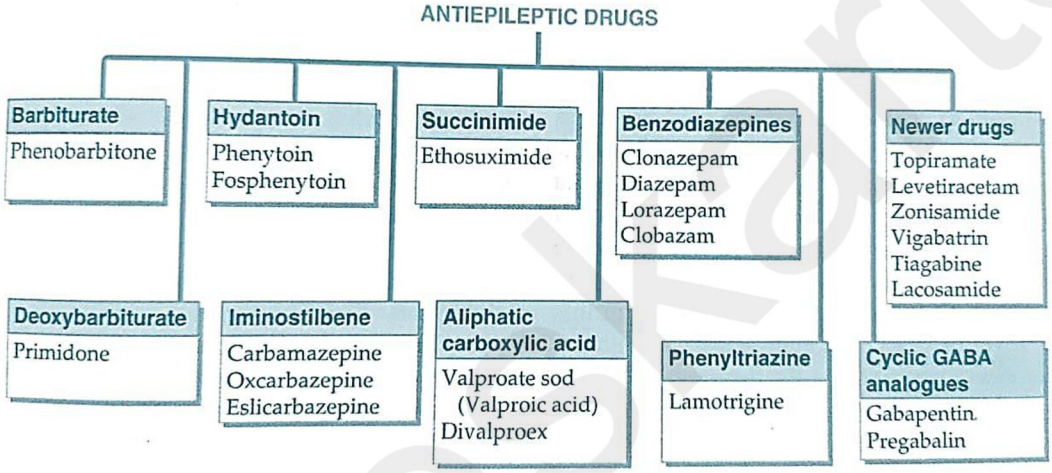
- Less disruption of normal sleep architecture
- Reduced risk of daytime drowsiness
- Lower risk of dependence and abuse
- Milder withdrawal symptoms

3. Anti-Convulsants drugs (Anti-epileptic drugs)

Anticonvulsants are a diverse group of pharmacological agents used in the treatment of epileptic seizures.

Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain.

Classification of Anti-Convulsants drugs:



Phenytoin

- Phenytoin is in a class of medications called anticonvulsants.
- Phenytoin is used to control certain type of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system.
- It works by decreasing abnormal electrical activity in the brain.

Pharmacological actions of Phenytoin

- Phenytoin is often described as a non-specific sodium channel blocker and targets almost all voltage-gated sodium channel subtypes.
- More specifically, phenytoin prevents seizures by inhibiting the positive feedback loop that results in neuronal propagation of high frequency action potentials.

Dose of Phenytoin

Capsule, immediate-release

- 30mg
- 100mg

Capsule, extended-release

- 100mg
- 200mg

Indication

- Phenytoin is indicated to treat grand mal seizures, complex partial seizures, and to prevent and treat seizures during or following neurosurgery.
    - Epilepsy
    - Status epilepticus
    - Neuropathic pain
    - Choreoathetosis
    - Myotonia

Contraindication:

- Hypersensitivity to phenytoin or other hydantoins. Because of its effect on ventricular automaticity, IV phenytoin is contraindicated in sinus bradycardia, sinoatrial block, second and third-degree AV block, patients with Adams-Stokes syndrome.

4. Anti-anxiety drugs:

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.

Or

Anxiety is a feeling of fear, dread, and uneasiness. It might cause you to sweat, feel restless and tense, and have a rapid heartbeat.

It can be a normal reaction to stress. For example, you might feel anxious when faced with a difficult problem at work, before taking a test, or before making an important decision.

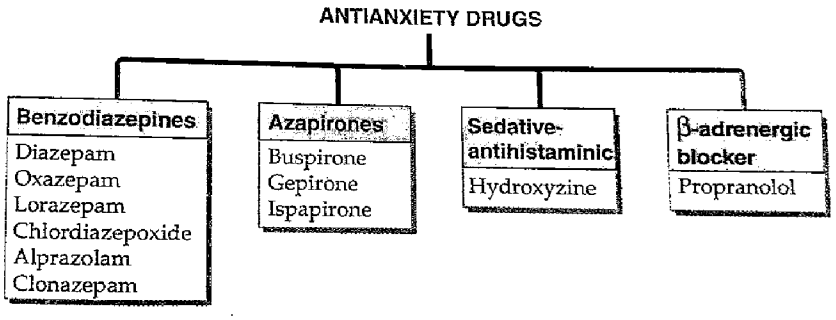
Anxiety disorders:

- Anxiety disorders are conditions in which you have anxiety that does not go away and can get worse over time.
- The symptoms can interfere with daily activities such as job performance, schoolwork, and relationships.

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 drugs:



Alprazolam

- Alprazolam is used to treat anxiety and panic disorders. It belongs to a class of medications called benzodiazepines which act on the brain and nerves (central nervous system) to produce a calming effect.
- It works by enhancing the effects of a certain natural chemical in the body (GABA).

Pharmacological Action of Alprazolam

- Alprazolam is a benzodiazepine.
- Benzodiazepines presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system at the GABA receptor complex.
- All benzodiazepines cause a dose-related central nervous system depressant activity.

Dose

- 0.25-1.0 mg TDS up to 6 mg/day in panic disorder.

Indication:

- Anxiety disorder
- Panic disorder
- Sedative

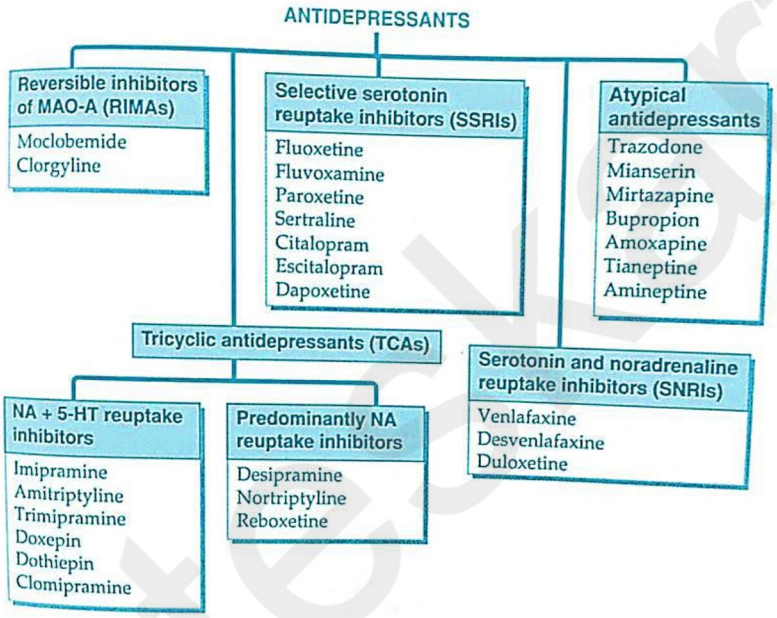
Contraindications:

- Respiratory depression, especially seen with coexistent respiratory disease or myasthenia gravis.
- There is potential for growing dependence, therefore only short-term recommended. use is
- Acute porphyria.
- Narrow-angle glaucoma.

5. Anti-depressant drugs

- These are drugs which can elevate mood in depressive illness.
- Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other, and many of them have other associated properties.
- Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines.

Classification of Anti-depressant drugs:



Escitalopram.

- Escitalopram belongs to a class of drugs known as selective serotonin reuptake inhibitors (SSRIs)
- Escitalopram is used to treat depression and anxiety. It maintains the serotonin level in the brain which is responsible for the anxiety or depression.

Pharmacological action of Escitalopram:

- Escitalopram binds with the site of the serotonin transporter (Primary and allosteric site) while other SSRIs and SNRI binds only with primary site.
- So, it gave the more advantage for managing the anxiety disorder, recently it is commonly use.

Dose:

- **Tablets-** 5mg, 10mg, 20mg Oral solution-5mg/5ml.

Indication:

- Anxiety and depression.

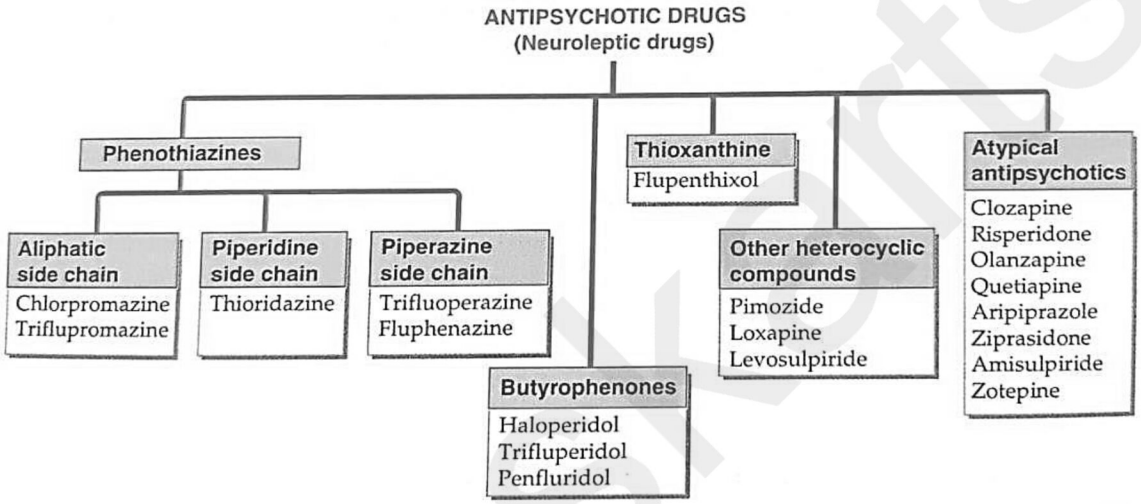
Contraindications-

- Long term use of these drug may cause the sexual impotency and ejaculation disorders.
- Insomnia, sedation also may occur.

6. Anti-psychotics

- Antipsychotics, also known as neuroleptics are a class of psychotropic medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia but also in a range of other psychotic disorders.

Classification of Anti-Psychotic drugs:



Chlorpromazine

- Chlorpromazine is a member of the typical antipsychotic or neuroleptic drug class, also known as first-generation antipsychotics (FGAs).
- Chlorpromazine is a phenothiazine (FEEN-oh-THYE-a-zeen) that is used to treat psychotic disorders such as schizophrenia or manic-depression in adults.
- Chlorpromazine is also used in adults to treat nausea and vomiting, anxiety before surgery, chronic hiccups, acute intermittent porphyria, and symptoms of tetanus.

Pharmacological Action

- The post-synaptic blockade at the D2 receptors in the mesolimbic pathway. However, the blocking of D2 receptors in the nigrostriatal pathway is responsible for its extrapyramidal side effects.

- The antiemetic effect of chlorpromazine stems from the combined blockade of histamine H1, dopamine D2, and muscarinic M1 receptors in the vomiting center.
- Chlorpromazine is extensively metabolized by the liver (CYP450 enzymes A12 and 2D6; it is a CYP3A4 substrate.) It also undergoes metabolism in the kidney and GI tract.
- It is excreted in the urine, bile, and feces. It has a half-life of between 23 and 37 hours for the parent drug, and its active metabolite has a half-life of 10 to 40 hours.

Dose

- **Tablet:** 10, 25, 50, 100 mg
- **Syrup:** 5 mg/5 ml and 25 mg/5 ml
- **Injection:** 50 mg/2 ml

Indications:

- Schizophrenia (primarily the positive symptoms)
- Bipolar I acute manic type of manic-depressive illness.
- Acute agitation marked by explosive hyper excitable behavior out of proportion to the initial provocation.
- To control nausea and vomiting, including intraoperative nausea and vomiting.

Contraindication:

- Hypersensitivity or allergy to phenothiazines.
- Pheochromocytoma.
- Breast cancer.
- A condition with low thyroid hormone levels.
- Low levels of parathyroid hormone.
- A high prolactin level.
- Overweight.
- Decreased function of bone marrow.

7. Nootropic agents

- Drugs used to specifically facilitate learning or memory, particularly to prevent the cognitive deficits associated with dementias.
- Nootropics, also known as "smart drugs" are a diverse group of medicinal substances whose action improves human thinking, learning, and memory,
- These drugs act by a variety of mechanisms. While no potent nootropic drugs have yet been accepted for general use, several are being actively investigated.

Classification Nootropic agents

- **Cholinergic Activators :** Piracetam
- **Seratonergics :** Theamine
- **Dopaminergic :** L- Dopa
- **Some other examples** Aniracetam , Oxiracetam , Hydergine , Vincamine Meclofenoxate, Phenylethylamine

Phenylethylamine

- Phenethylamine is a chemical that is found naturally in the body. It can also be made in the laboratory.
- Phenethylamine is used for athletic performance, depression, weight loss, and to improve mood and attention, but there is no good scientific evidence to support these uses.

Pharmacological Action

- In the brain, phenethylamine regulates monoamine neurotransmission by binding to trace amine- associated receptor 1 (TAAR1) and inhibiting vesicular monoamine transporter 2 (VMAT2) in monoamine neurons.
- To a lesser extent, it also acts as a neurotransmitter in the human central nervous system.
- In mammals, phenethylamine is produced from the amino acid L-phenylalanine by the enzyme aromatic L-amino acid decarboxylase via enzymatic decarboxylation.

Dose

- Phenylethylamine (PEA) suggested dosage for cognitive benefit is 500 mg up to 3-times per day.
- PEA has a half-life of 5 – 10 minutes. But the effects of PEA can be extended by using it with a MAO-B inhibitor.
- If you do use a potent MAOI like selegiline (l-deprenyl) make sure you keep the dose low (i.e. 2.5 mg).

Indication

- Depression
- Anxiety
- Neuroprotector
- Attention Deficit Disorder (ADHD)

Contraindication

- Headache,
- Heart problems,
- Shivering,
- Confusion, and anxiety.

8. Centrally acting muscle relaxants

- Centrally acting muscle relaxants, also known as spasmolytics, target the central nervous system (CNS) to reduce muscle tone and alleviate muscle spasms.
- These drugs reduce skeletal muscle tone by a selective action in the cerebrospinal axis without altering consciousness.
- Spasticity is characterized by an increase in tonic stretch reflexes and flexor muscle spasm along with muscle weakness.
- It is associated with disease like cerebral palsy and multiple sclerosis.

Classification of Centrally acting muscle relaxants

- **Barbiturates :** Phenobarbitone
- **Benzodiazepines :** Diazepam
- **GABA derivatives :** Baclofen
- Mephenesin Congeners : Mephenesin , Meprobamate ,Chlormezanon

Pharmacological Actions

1. **Central Nervous System Depression**: These drugs typically function by depressing neural activity within the CNS, leading to muscle relaxation and reduced muscle spasms.
2. **Inhibition of Excitatory Pathways**: They inhibit excitatory neuronal pathways, which decreases muscle tone and involuntary contractions.
3. **Enhancement of Inhibitory Pathways**: Some agents enhance inhibitory pathways by increasing GABAergic activity, a neurotransmitter that reduces neuronal excitability.

Common Centrally Acting Muscle Relaxants

- **Baclofen**: Acts on GABA_B receptors to inhibit neurotransmitter release.
- **Cyclobenzaprine**: Primarily acts at the brainstem to reduce tonic somatic motor activity.
- **Tizanidine**: Acts as an alpha-2 adrenergic agonist to inhibit spinal cord synaptic transmission.

Dose

- **Baclofen**: 5 mg three times daily, gradually increased by 5 mg every three days until optimal response (maximum 80 mg/day).
- **Cyclobenzaprine**: 5-10 mg three times daily, with a maximum duration of 2-3 weeks.
- **Tizanidine**: 2 mg up to three times daily, adjusted based on response (maximum 36 mg/day).

Indications

1. **Muscle Spasms**: Relief from muscle spasms due to acute musculoskeletal conditions.
2. **Spasticity**: Management of spasticity in conditions such as multiple sclerosis, spinal cord injury, or cerebral palsy.
3. **Pain Relief**: Adjunctive treatment for acute painful musculoskeletal conditions.

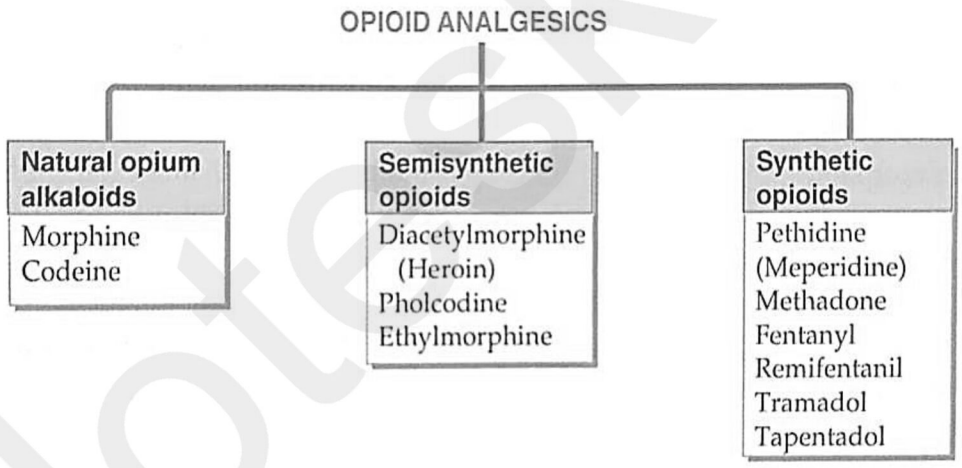
Contraindications

1. **Hypersensitivity**: Known hypersensitivity to the drug or its components.
2. **Severe Liver Impairment**: Especially for drugs like tizanidine, which can cause hepatotoxicity.
3. **Severe Renal Impairment**: Drugs like baclofen should be used cautiously.
4. **Concurrent Use with MAO Inhibitors**: Particularly for cyclobenzaprine due to the risk of hypertensive crisis.
5. **Pregnancy and Lactation**: Should be used with caution and only if clearly needed.

9. Opioid analgesics

- Opium a dark brown, resinous material obtained from poppy (Papaver somniferum) capsule.
- A pharmacist, isolated the active principle of opium in 1806 and named it 'morphine' after the Greek god of dreams Morpheus. In the last century a large number of semisynthetic and synthetic compounds have been developed with morphine-like, antagonistic and mixed agonistic-antagonistic properties.
- Compounds that are derived from opium or are chemically related to morphine are called 'opiates', while all those having morphine-like action, irrespective of chemical nature, are called 'opioids'.

Classification of Opioid Analgesics



Morphine:

- Morphine may be habit forming, especially with prolonged use. Take morphine exactly as directed.
- Morphine is an opioid agonist used for the relief of moderate to severe acute and chronic pain.

Pharmacological Action

Morphine is in a class of medications called opiate (narcotic) analgesics. It works by changing the way the brain and nervous system respond to pain.

Dose

Tablet, extended-release (MS Contin): Schedule II

- 15mg, 30mg, 60mg, 100mg, 200mg

SC/IM (opioid-naïve patients):

- 5-10 mg q4hr PRN; dose range, 5-20 mg

IV (opioid-naïve patients):

- 2.5-5 mg q3-4hr PRN, infused over 4-5 minutes; dose range, 4-10 mg

Indication

- Morphine is used for the management of chronic, moderate to severe pain.
- Musculoskeletal pain
- Abdominal pain
- Chest pain
- Arthritis, and even headaches

Contraindication

- Nausea, vomiting, constipation, lightheadedness, dizziness, drowsiness, increased sweating, or dry mouth may occur

Note: Codeine, Diacetylmorphine (Heroin), Ethylmorphine are also Important Drugs for Exam Point of View So read yourself