**PHARM D II YEARS** **PHARMACOLOGY-I (Uncovered Portion)**

**SUBJECT CODE-2.4**

**PHARMACOLOGY OF DRUGS ACTING ON CENTRAL NERVOUS SYSTEM**

# ANTICONVULSANTS

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.

Group of drugs used primarily in the treatment of epilepsy.

Supress seizures by maintaining an effective plasma drug concentration and in brain minimising the side effects.

Single drug is best to be administered , rapid withdrawl can cause rebound seizures.

Major molecular targets of marked anticonvulsants are voltage gated sodium channels , calcium channels, components of GABA system and synaptic vesicle glycoprotein 2A(SV2A).

**PATHOPHYSIOILOGY OF SEIZURES**

Increased availability of excitatory neurotransmitter like glutamate and Ach.

Enhanced binding of these transmitters with their cationic channels receptor site.

Excessive depolarization by glutamate may also result in increased calcium concentration.

Decreased availability of GABA(inhibitory neurotransmitter),the most potent inhibitory neurotransmitter of CNS.

Normally , the GABA hyperpolarizes the resting potential or stabilizes the membrane at a high resting membrane potential.

Mutations leading to decreased sensitivity of GABA.

**TYPES OF SEIZURES**

PARTIAL SEIZURES

Localized within a focal area of the brain

Convulsions confined to a single limb,muscle group,specific localized

Sensory disturbances  Without impairment of consciousness

GENERALIZED SIEZURES :

Imparts unconsciousness

Grand mal

Petit mal

UNDETERMINED SEIZURES :

Neonatal seizure

SITUATION RELATED SEIZURES :

Toxic events due to alcohol,drugs etc.

**MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS**

Three main mechanisms

Enhancement of GABA action

Inhibition of sodium channel function

Inhibition of calcium channel function.

Other mechanisms include –

Inhibition of glutamate release and Block of glutamate receptors.

**CLASSIFICATION**

1.BARBITURATES : eg: Phenobarbital, Mephobarbital

2.HYDANTOIN DERIVATIVES : eg: Phenytoin, Phenylethyl hydantoin

3. OXAZOLIDINEDIONE DERIVATIVES : eg: Trimethadione, Paramethadione

4. SUCCINIMIDES : eg: Phensuximide, methsuximide

5. BENZODIAZEPINES : eg: Diazepam, Clobazepam

6. GABA ANALOGUES : eg: Progabide, Tiagabin

7. MISCELLANEOUS : eg: Carbamazepine, Valproate

8. NEWER ANTICONVULSANTS : eg: Denzimol, Denzinamide

**BARBITURATES**

**Phenobarbital**

First effective organic anticonvulsant drug , widely used in veterinary medicine.

Being a derivative of barbituric acid has CNS depressing action , but has low lipid solubility , slow onset and long duration of action compared to other barbiturates.

**MOA**

Decreases seizure activity primarily by enhancing responsiveness toϖ inhibitory postsynaptic effects of GABA.

Interacts with GABA receptors , opening Cl channel resulting in hyperpolarization of resting membrane potential due to increased Cl influx. Also inhibits glutamate activity and probably Ca fluxes across neuronal membrane.

Increases the seizure threshold.

**Pharmacological effects**

Depresses the motor centres of cerebral cortex , enhancing anticonvulsant properties.

Broad-spectrum anticonvulsant.

Action begins within 1-2 hours after oral administration and lasts for about 24 hrs.

Decreases cerebral blood flow and metabolism.

Most potent microsomal enzyme stimulating agent known , compared on molar basis thus , increasing the activity of liver to metabolize all drugs which are metabolised in microsomal fraction.

This induction is dose related.

**Pharmacokinetics**

Slowly but well absorbed from GI tract and its peak plasma level occurs in 4-6 hrs in dogs.

Bioavailability ranges from 88% to 95% after oral administration.

Primarily metabolised in liver by oxidative hydroxylation to form phydroxyphenobarbitol, rapidly eliminated from blood by glucoronide conjugation and excreted in urine.

**Side effects**

Polyphagia , polydypsia , weight gain, Sedation for few days

**Treatment**

In case of overdose , oral administration of activated charcoal and alkalisation of urine.

**Contraindications**

Hepatic impairment , pregnants and nursing mothers. When given by IV slow infusion

**DEOXYBARBITURATES**

**Primidone**

Is 2-deoxy analogue of Phenobarbital

Approved for use in dogs for control of convulsions associated with epilepsy , virus encephalitis, distemper, prevention of aggressive behavior and cannibalism in gilt pigs etc.

Was once a mainstay anticonvulsant in the treatment of partial and generalized seizures, but now it has declined due to availability of better drugs

**Mechanism of Action**

Believed to work via interaction with voltage-gated Na+ channelswhich inhibit high frequency repetitive firing of Action Potential.

Primidone also increases GABA-mediated chloride flux: thereby hyperpolarizing the membrane potential.

But exact mechanism is unknown, it raises seizure threshold and alters  seizure.

**Pharmacological effects**

Effectiveness of primidone correlates with serum phenobarbital concentration than with primidone dose(85% antiepileptic activity)

Primidone initially produces sedation, but this effect decrease with its continued use.

Primidone, like phenobarbital, can induced hepatic microsomal enzymes which can increase the rate of metabolism of itself and other drugs.

**Pharmacokinetics**:

Metabolized in liver to active metabolites phenylethylmalonamide (PEMA) and phenobarbital.

Pharmacological action is due to Phenobarbital(more potent and has long life)

**Side effects**

Polydipsia(excessive and constant thirst)

Tachycardia

Episodic hyperventilation

Hepatic injury

Dermatitis

Megaloblastic anaemia

Overdosage may produce Hepatotoxicity, anorexia, vomiting, nystagmus(involuntary eye movement), CNS depression(sedation to coma)

Treatment of overdose: forced alkaline dieresis

**Contraindications and precautions**

In patients with severe liver disease. Animals demonstrated hypersensitivity reactions to it.

Should be used with caution in nephritis or respiratory dysfunction.

**Drugs interactions**:

CNS depressants and pre-anaesthetics may increase the effects of primidone

Excretion is decreased by concurrent administration of chloramphenicol(inhibitor of microsomal enzyme system)

**HYDANTOINS**

Used for emergency treatment of poisoning or tetanic seizures.

**PHENYTOIN**

Used frequently for human epileptic patients , in vet medicine not used for long term due to its undesirable pharmacological profile.

**MOA**

Exact mechanism is not known , thought to be mediated by membrane stabilizing effect through slowing the rate of recovery of voltage activated Na channels thus preventing repititive firing of axons.

**Pharmacological effect**

Inhibits motor area of cortex.

Reduces the spread of seizures from an active site.

Sedation is less likely with phenytoin.

Also possess local anaesthetic and anti- arrythmatic properties.

**Pharmacokinetics**

Moderately absorbed after oral administration.Metabolised in liver into meta- and para - hydroxyphenytoin , which are then excreted in urine as glucoronide conjugates.

Induces hepatic microsomal enzymes. Short half life

**Side effects**

Sedation , anorexia

Chronic administration causes hepatocellular hypertrophy , necrosis , hepatic lipidosis.

**Benzodiazepines**

The benzodiazepines are use clinically as tranquilizer-sedative, anxiolytics, skeletal muscle relaxants and behavior modifying drugs.in addition, it has broad antiseizure properties.

E.g diazepam, clonazepam, lorozepam, oxazepam and clorazepate.

**Diazepam**

The prototypical benzodiazepamϖ Is the drug of choice for treatment of epilepticusϖ Is especially well suited for IV treatment of convulsion(as cross blood-brain barrier faster) in community, intravenous administration is not practical and so rectal diazepam

Choice for emergency control of convulsions induced by tetanus, convulsant drug poisoning.

Note: Lorazepam has a shorter pharmacokinetic half-life but stays in the brain longer than diazepam.

**Mechanism of action**

Bind to GABA inhibitory receptors to reduce firing rate.

**Pharmacological effects**

Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle- relaxant, anticonvulsant and amnestic effects.

**Pharmacokinetics**

After oral administration > 90% of diazepam is absorbed and the average time to achieve peak plasma concentrations is 1 – 1.5 hours with a range of 0.25 to 2.5 hours.

Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%).

Diazepam and its metabolites cross the blood-brain and placental barriers It is metabolized into nordiazepam and oxazepam.

Diazepam and its metabolites are excreted mainly in the urine,predominantly as their glucuronide conjugates.

Elimination half-life (50 hours); 20–100 hours (36–200 hours for main active metabolite desmethyldiazepam)

**SIDE EFFECTS**

Side effects most commonly reported were drowsiness, fatigue, muscle weakness, and ataxia , hypersalivation.

Central Nervous System: confusion, depression, dysarthria, headache, slurred speech, tremor, vertigo

Gastrointestinal System: constipation, nausea, gastrointestinal disturbances

Special Senses: blurred vision, diplopia, dizziness

Cardiovascular System: hypotension

Urogenital System: incontinence, changes in libido, urinary retention

Antegrade amnesia may occur using therapeutic dosages, the risk increasing at higher dosages.

**Contraindication** in patients with myasthenia gravis, severe respiratory insufficiency, severe hepatic insufficiency, and sleep apnea syndrome in acute narrow-angle glaucoma.

Drug interaction

Oral contraceptives, some antibiotics, antidepressants, and antifungal agents, educe the rate of elimination of the benzodiazepines leading to possibly excessive drug accumulation and increased side-effects.

The antibiotic rifampicin, and the anticonvulsants carbamazepine and phenytoin, accelerateθ elimination of many benzodiazepines and decrease their action.

**Aliphatic carboxylic acid**

Valproic acid and sodium valproate

**MOA**

Produces phenytoin like action.

Inhibits degradation of GABA.

Decreases the influx of Ca through T-type Ca channel.

Na valproate is converted rapidly to valproic acid in acidic environment of stomach.

**Side effects**

Gastrointestinal upsets

Alopecia , rashes , anemia

Hepatotoxicity

Naloxone is reported to be beneficial in reversing some CNS effects of valproic acid.

**GABA analogue- Gabapentin, Vigabatrin**

**Gabapentin**

Is an anticonvulsant medication used to treat partial seizures, neuropathic pain, hotϖ flashes, and restless legs syndrome

**Mechanism of action**

The chemical structure of gabapentin is GABA molecule covalently bound to a lipophilic cyclohexane ring.

Gabapentin is an analog of GABA. However, it does not act at GABA receptors, and it neither enhances GABA actions nor is converted to GABA.

Its precise mechanism of action is not known.

Its therapeutic action on neuropathic pain is though to involve inhibition of voltage-gated N-type calcium ions channels in CNS, which decrease pre-synaptic release of neurotransmitters.

**Pharmacological effects**

Binds to calcium channels inhibits influx of Ca++, which decrease pre-synaptic release of neurotransmitters. inhibition of α2δ-1-containing VDCCs by gabapentin appears to be responsible for its anticonvulsant, analgesic, and anxiolytic effects. Gabapentin does not bind to plasma proteins and is excreted unchanged through the kidney

**Side effect**

Common side effects include sleepiness and dizziness.

Serious side effects include an increased risk of suicide, aggressive behavior, and drug reactions. It is unclear if it is safe during pregnancy or breastfeeding

Medical uses Seizures Neuropathic pain, Migraine, Anxiety disorders

**Carboxamides**

**Carbamazepines**

Is an anticonvulsant and mood stabilizing drugs.

It is related chemically to tricyclic antidepressants, but pharmacologically with phenytoin.

**Mechanism of action**

Reduce the propagation of abnormal impulses in brain by¤ blocking sodium channel, thereby inhibiting the generation of repetitive action potential.

**Pharmacological effects**

Blocks sodium channel of brain. It is an inducer of isozyme families(UDP glucuronosyltransferase), which increase the clearance and reduce the efficacy of drugs that they metabolized.

**Pharmacokinetics**

Absorbed slowly and erratically following oral administration.¬It induces its own drug metabolism and has an active metabolites.

**Side effects**

Hyponatremia, blurred vision, blood dysrasias may be noted.

Steven’s-Johnson syndrome.

A characteristic rash may developed.

**Contraindication**

Allergic, Hypersensitivity.

**ANTICONVULSANT THERAPY**

1.Emergency therapy

2.Maintainence therapy

Emergency therapy

a. Status epilecticus

b. A single generalised seizure persists for greater than 5 minutes.

c. More than one seizure per hour for 3 consecutive hours , regardless of seizure length.

d. More than 3 seizures per day , regardless of seizure length

Maintainence therapy

Usually designed to help a primary treatment succeed.

Minimizes the recurrence of the seizures episodes.

Generally oral route is preferred for long term therapy.

Generally a single drug is given during therapy.

If control is not satisfactory then either the dose is increased or a second drug is added as per recommended protocol.

# ANALGESICS AND ANTI-INFLAMMATORY DRUGS

## ANALGESICS

A drug that selectively relieves pain by acting in CNS or on peripheral pain mechanism, without significantly altering consciousness.

**Pain (algesia)**

An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

**Mechanisms of pain and nociception**

Nociception is the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system. Pain is a subjective experience, not always associated with nociception.

Polymodal nociceptors (PMN) are the main type of peripheral sensory neuron that responds to noxious stimuli. The majority are nonmyelinated C-fibres whose endings respond to thermal, mechanical and chemical stimuli.

Chemical stimuli acting on PMN to cause pain include bradykinin, 5-HT, and capsaicin. PMN are sensitised by prostaglandins, which explains the analgesic effect of aspirin-like drugs, particularly in the presence of inflammation. Nociceptive fibres terminate in the superficial layers of the dorsal horn, forming synaptic connections with transmission neurons running to the thalamus

PMN neurons release glutamate (fast transmitter) and various peptides (especially substance P) which act as slow transmitters. Peptides are also released peripherally and contribute to neurogenic inflammation. Neuropathic pain, associated with damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus, is frequently a component of chronic pain states, and may respond poorly to opioid analgesics.

**Opioid Analgesics**

There are three main families of endogenous opioid peptides; these have analgesic activity and have many physiological functions, but they are not used as drugs. ´

Opioid drugs include:

- Phenanthrene derivativ es, structurally related to morphine
- Synthetic compounds with dissimilar structures but similar pharmacological effects

**Opioid Receptors**

**μ-receptors** are thought to be responsible for most of the analgesic effects of opioids, and for some major unwanted effects (e.g. respiratory depression, euphoria, sedation and dependence). Most of the analgesic opioids are μ-receptor agonists.

**δ-receptors** are probably more important in the periphery, but may also contribute to analgesia.

**κ-receptors** contribute to analgesia at the spinal level, and may elicit sedation and dysphoria, but produce relatively few unwanted effects, and do not contribute to dependence. Some analgesics are relatively κ-selective.

σ-receptors are not true opioid receptors, but are the site of action of certain psychotomimetic drugs, with which some opioids interact.

All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase.

They also facilitate opening of K + channels (causing hyperpolarisation), and inhibit opening of Ca2+ channels (inhibiting transmitter release).

These membrane effects are linked to the decrease in cAMP formation.

**MORPHINE**

**Pharmacological effects and Mechanisms**

**CNS effects**

Analgesia: increasing tolerance of pain are the most prominent effects. Therefore, help patients to eliminate dysphoria, anxiety. Consciousness is not lost, and the patient can usually still locate the source of pain.

Respiratory depression and suppression of cough, reducing the responsiveness of the respiratory centers in the brain stem to blood levels of carbon dioxide and inhibiting directly the respiratory center.

Nausea and vomiting: stimulating the chemoreceptor trigger zone. In most cases, after therapeutic dose, subsequent doses of morphine do not produce vomiting.

Miosis: pinpoint pupils are indicative of toxic dosage prior to asphyxia. It can be block with atropine.

**Cardiovascular effects:**

Orthostatic hypotention can occur due to vasomotor medullary depression and histamine release.

**Gastrointestinal effect:**

Reduces gastrointestinal motility, causing constipation

Decreases biliary and pancreatic secretions.

Constriction at the spincter of Oddi causes an increase in biliary pressure.

**Other systemic effects:**

Increases detrusor muscle tone in the urinary bladder, producing a feeling of urinary.

Vesical sphincter tone is also increased, making voiding

Inhibits the cellular immunity and humoral immunity, which is significant in withdrawal syndrome and tolerant in chronic administration.

**Pharmacokinetics Of Morphine**

Is well absorbed from the gastrointestinal tract.

However, the analgesic effect is greater when drug is administered intramuscularly or intrvenously.

It has a significant first-pass effect.

Morphine is metabolised to morphine-6-glucuronide, which is more potent as an analgesic.

Ninety percent of a given dose is excreted in the urine; the remaining 10% is excreted in the feces.

**Therapeutic uses**

Analgesia, such as the relief of pain from myocardial infaction, terminal illness, surgery, biliary colic and renal colic (combined with atropine).

Dyspnea due to pulmonary edema because of sedative, vascular dilataltion and inhibition of the respiratory centers responsiveness to $CO_2$ .

Treating severe diarrhea because of constipating effects.

´Treating cough (usually insteaded by codeine).

**Adverse Effects**

Respiratory depression is the most important effect.

Nausea and sometimes dysphoria can occur.

Increase biliary tract pressure.

Allergic reactions.

Bronchoconstrictive action.

Tolerance and Dependence

**Contraindications And Cautions**

Use in patients with head injures

Use during pregnancy

Use in patients with impaired pulmonary function

Use in patients with impaired hepatic or renal function

**CODEINE**

Although the pharmacologic effects of codeine are similar to those of morphine, it has about one-twelfth the analgesic potency of morphine.

Be used mainly for cough suppressant and milder pain.

It produces less sedation, respiratory depression, fewer gastrointestinal effects, and less addiction and withdrawal.

**SYNTHETIC ANALGESIC**

**PETHIDINE**

It is very similar to morphine (one-seventh to one-tenth potent) in pharmacologic effects by μ-receptor agonists.

**Therapeutic uses:** analgesic, cardiac asthma, sedation (decrease the dosage of anesthetic ) and artificial hibernation.

It has no gastrointestinal or antitussive action because of shorter-acting.

**Adverse effect:** also causes respiratory depression and possesses addiction liability, although withdrawal effects are less severe than with morphine.

**METHADONE**

It is widely used as a means of treating morphine and diamorphine addiction because of its chronic and insignificant addiction.

**Opioid Receptor Mixed Agonists/Antagonists**

Other drugs, such as nalorphine and pentazocine, produce a mixture of agonist and antagonist effects.

**Opioid Antagonists**

Pure antagonists include naloxone (short-acting) and naltrexone (long-acting).

They block μ-, κ - and - δ receptors more-or-less equally.

Naloxone does not affect pain threshold normally, but blocks stress-induced analgesia, and can exacerbate clinical pain.

Naloxone rapidly reverses opioid-induced analgesia and respiratory depression, and is used mainly to treat opioid overdose or to improve breathing in newborn babies affected by opioids given to the mother.

Naloxone precipitates withdrawal symptoms in morphine-dependent patients or animals.

**Clinical use of analgesic drugs**

The choice and route of administration of analgesic drugs depends on the nature and duration of the pain.

A progressive approach is often used, starting with nonsteroidal anti-inflammatory drugs, supplemented first by weak opioid analgesics, and then by strong opioids.

In general, severe acute pain (e.g. trauma, burns, post-operative pain) is treated with strong opioid drugs (e.g. morphine, fentanyl) given by injection.

Mild inflammatory pain (e.g. arthritis) is treated with non-steroidal anti-inflammatory drugs (e.g. aspirin) supplemented by weak opioid drugs (codeine, pentazocine) given orally if required.

Severe pain (e.g. cancer pain, severe arthritis or back pain) is treated with strong opioids given orally, intrathecally, epidurally or by subcutaneous injection.

Chronic neuropathic pain is often unresponsive to opioids, and treated with tricyclic antidepressants (e.g. amitriptyline), or other drugs, such as carbamazepine.

# ANTI- INFLAMATORY DRUGS

**Inflammation**

Inflammation is a normal protective response to tissue injury caused by

- Physical trauma
- Noxious chemicals
- Microbiologic agents

Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair

When healing is complete, the inflammatory process usually subsides

Inappropriate activation of our immune system can result in inflammation, leading to immune mediated diseases such as rheumatoid arthritis (RA)

**4 signs of inflammation**

• Redness - due to local vessel dilatation

• Heat - due to local vessel dilatation

• Swelling – due to influx of plasma proteins and phagocytic cells into the tissue spaces

• Pain – due to local release of enzymes and increased tissue pressure

**ROLE OF PROSTAGLANDINS AS LOCAL MEDIATORS**

Prostaglandins and related compounds are produced in minute quantities by virtually all tissues

Act locally on the tissues in which they are synthesized. Are rapidly metabolized to inactive products at their sites of action

Thromboxanes, leukotrienes are related lipids that are synthesized from the same precursors as the PGs

**Classification of NSAIDs**

• Salicylates: aspirin, Sodium salicylate & diflunisal.

• Propionic acid derivatives: ibuprofen, ketoprofen, naproxen.

• Aryl acetic acid derivatives: diclofenac, ketorolac

• Indole derivatives: indomethacin, sulindac

• Alkanones: Nabumetone.

• Oxicams: piroxicam, tenoxicam

•Anthranilic acid derivatives (fenamates): mefenamic acid and flufenamic acid.

•Pyrazolone derivatives: phenylbutazone, oxyphenbutazone, azapropazone (apazone) & dipyrone (novalgine).

• Aniline derivatives (analgesic only): paracetamol.

**Non-Steroidal Anti-Inflammatort Drugs**

NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities

Act primarily by inhibiting the COX enzymes that catalyze the first step in prostanoid biosynthesis

This leads to decreased PG synthesis with both beneficial and unwanted effects

**Selective Cox-2 Inhibitors**

Detection of serious cardiovascular events associated with COX-2 inhibitors has led to withdrawal of rofecoxib and valdecoxib from the market. Celecoxib is still available for the treatment of osteoarthritis, RA pain.

**ASPRIN AND OTHER SALICYLIC ACID DERIVATIVES**

Aspirin is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (inactivates) cyclooxygenase

The other NSAIDs, including salicylate , are all reversible inhibitors of cyclooxygenase

Aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate, which has antiinflammatory, antipyretic, and analgesic effects

**ASPIRIN**

NSAIDs, including aspirin, have three major therapeutic actions:

1. Anti-inflammatory actions

2. Analgesic action

3. Antipyretic action

**Anti-inflammatory action**

Because aspirin inhibits cyclooxygenase activity, it diminishes the formation of PGs and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators.

Aspirin inhibits inflammation in arthritis, but it does not stop the progress of the disease

**Analgesic action**

PGE2 sensitizes nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process

By decreasing PGE2 synthesis, aspirin and other NSAIDs repress the sensation of pain

Used mainly for the management of pain of low to moderate intensity arising from musculoskeletal disorders

**Antipyretic action**

Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated, which can be caused by PGE2 synthesis

The salicylates lower body temperature in patients with fever by decreasing PGE2 synthesis and release

This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating

Aspirin has no effect on normal body temperature

**Gastrointestinal effects**

Prostacyclin (PGI2) inhibits gastric acid secretion whereas PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine In the presence of aspirin, these prostanoids are not formed resulting in increased gastric acid secretion and diminished mucus protection

This may cause epigastric distress, ulceration, hemorrhage, and iron-deficiency anemia

Agents used for the prevention of gastric and/or duodenal ulcers include the PGE1-derivative misoprostol and PPIs like esomeprazole, lansoprazole, omeprazole PPIs can also be used for the treatment of an NSAID-induced ulcer especially if the patient will need to continue NSAID treatment

**Actions on the kidney**

Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 which are responsible for maintaining renal blood flow Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients Interstitial nephritis can also occur with all NSAIDs

**ASPIRIN AND SALICYLIC ACID DEIVATIVES THRAPEUTIC USES**

Antipyretic, antiinflammatory and analgesic

External applications

Cardiovascular applications

**Aspirin adverse effects**

GI: Epigastric distress, nausea, and vomiting. Microscopic GI bleeding.

Blood: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA2 resulting in inhibition of platelet aggregation and a prolonged bleeding time

Respiration: In toxic doses, salicylates cause} respiratory depression

Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation, the energy normally used for ATP production of ATP is dissipated as heat causing hyperthermia at toxic quantities Hypersensitivity: (urticaria, bronchoconstriction)

In pregnancy:

Aspirin is classified as FDA pregnancy category C risk during the first and second trimesters Category D during the third trimester Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breastfeeding

**PROPIONIC ACID DERIVATIVES**

Ibuprofen (Trufen®, Adex®, Ibufen®, Advil®, Isofen, Nurofen®, Ultrafen®, Artofen®) Naproxen (Naprex®, Naxyn®, Naproxi®) Ketoprofen (Profenid®)

All of these drugs possess antiinflammatory, analgesic, and antipyretic activity

They can alter platelet function and prolong bleeding time

Used in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of aspirin

Reversible inhibitors of the cyclooxygenases, inhibit PG synthesis

**Adverse effects:**

GI, ranging from dyspepsia to bleeding

Tinnitus, dizziness Ibuprofen is used IV to close a patent ductus arteriosus (PDA)

**ACETIC ACID DERIVATIVES**

Indomethacin (Indocaps®, Indocin®, Indolin®, Indomed®) Sulindac (Mobicol®) Etodolac (Etodolac Teva®, Etopan®)

All have anti-inflammatory analgesic and antipyretic activity Act by reversibly inhibiting cyclooxygenase

Generally not used to lower fever

Toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, to close a PDA in neonates, in ankylosing spondylitis, and in osteoarthritis of the hip

Sulindac is an inactive prodrug that is closely related to} indomethacin

**Adverse effects**

◦ Transient renal insufficiency

◦ Jaundice

◦ Elevated liver function test values

## HETEROARYL ACETIC ACIDS

Diclofenac (Diclofen®, Rufenal®, Voltaren®, Abitern®, Betaren®, Anaflam®, Cataflam®)  Ketorolac

Approved for treatment of RA, osteoarthritis, and ankylosing spondylitis

Diclofenac is more potent than indomethacin or naproxen

**Adverse effects**: GI, renal and hepatic side effects

Ketorolac is a potent analgesic but has moderate antiinflammatory effect

Ketorolac can cause fatal peptic ulcers as well as GI  bleeding

## OXICAM DERIVATIVES

Piroxicam (Pirox®)  Meloxicam (Movalis®)

Used to treat RA, ankylosing spondylitis, and osteoarthritis

They have long halflives, which permits oncedaily administration  Excreted in urine

Adverse effects: GI disturbances

## NABUMETONE

Nabumetone (Nabuco®, Reliefex®)

Indicated for the treatment of RA and osteoarthritis

Associated with a low incidence of adverse effects

Metabolized by the liver to the active metabolite  Excreted by urine

Dose should be adjusted in low creatinine clearance

**CELECOXIB**

Celecoxib (Celebra®, Celcox®)

Significantly more selective for inhibition of COX-2 than of COX-1

This selectivity provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions

Approved for treatment of RA, osteoarthritis, acute to moderate pain

Celecoxib has both similar efficacy to NSAIDs in the treatment of pain and in the risk for cardiovascular events. When used without concomitant aspirin therapy, has been shown to be associated with less GI bleeding and dyspepsia

Etoricoxib (Arcoxia®, Tericox®) is also more selective for COX-2 inhibition

**Adverse effects:**

◦ Diarrhea, As with other NSAIDs, kidney toxicity may occur

◦ Celecoxib should be avoided in patients with chronic renal insufficiency, severe heart disease, hepatic failure

Inhibitors of CYP2C9, such as fluconazole, fluvastatin, and zafirlukast, may increase serum levels of celecoxib.

Celecoxib inhibits CYP2D6 and can lead to elevated levels of some β-blockers (propranolol), antidepressants (amitriptyline), and antipsychotic drugs (risperidone)

**ACETAMINOPHEN**

N-acetyl-p-aminophenol, or (APAP) Paracetamol} (Febramol®, Sedamol®, Otamol®, Paramol®, Tailol®, Panadol®, Dexamol®, Acamol® )

Inhibits prostaglandin synthesis in the CNS This explains its antipyretic and analgesic properties

Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak antiinflammatory activity

Acetaminophen does not affect platelet function or increase blood-clotting time

Acetaminophen is not considered to be an NSAID

**Therapeutic uses**

Analgesic

Antipyretic

Suitable for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, and those who do not require the antiinflammatory action ◦

Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox Acetaminophen

**Adverse effects**

With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects Skin rash and minor allergic reactions occur

With large doses of acetaminophen, hepatic necrosis, a very serious and potentially lifethreatening condition, can result.

Renal tubular necrosis may also occur.

**THE TNF INHIBITORS**

The TNF inhibitors decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function

Etanercept, Adalimumab , Infliximab, Golimumab, Certolizumab

A TNF inhibitor plus methotrexate be considered as standard therapy for patients with rheumatoid and psoriatic arthritis

TNF inhibitors increase risk for infections (Tuberculosis, sepsis)

Demyelinating disorders and bone marrow suppression may occur (rare)

Should be used very cautiously in those with heart failure, because they can cause and worsen preexisting heart failure

# PSYCHOTROPIC DRUGS

## Psychiatric drugs

Treat mood, cognition, and behavioral disturbances associated with psychological disorders

Psychotropic in nature

Most are not used recreationally or abused Benzodiazepines are the exception

**Psychological Disorder**

A syndrome of mood, behavior, and cognition that is dysfunctional in nature and leads to significant distress and impairment

Culturally atypical

General classes of disorders

- Mood
- Anxiety
- Psychotic

Other Disorders

- Attention Deficit Disorder

**Mood Disorders**

- Antidepressants MAO Inhibitors
- Tricyclics
- Selective Serotonin Reuptake Inhibitors
- Dual Action Antidepressants
- Selective Norepinephrine Reuptake Inhibitors
- Others

**Mood Stabilizers (Antimanic Agents)**

- Lithium Carbonate
- Valproic Acid
- Carbamazepine
- Lamotragine
- Topirimate

**MAO Inhibitors**

Accidental discovery

1950s: looking for treatment for TB .Ineffective, but elevated mood of patients. Patients became more active and more sociable due to MAO inhibition

MAO degrades 5-HT, NE & DA

Leads to increased availability of neurotransmitter for release

Use in late 1950s & ended in early 1960suse ended due to side effect (death)

MAO breaks down many chemicals including tyramine

Tyramineis present in cheeses, red wines, alcohol, smoked fish

MAO in liver breaks down tyramine

Causes a hypertensive crisis "cheese syndrome"

- increased blood pressure -stroke -death
- increased heart rate -heart attack –death

**SSRI**

Selectively block re-uptake of 5-HTWork on DA and NE as well but very little

Eliminate ACh and antihistamine effects

No more effective than MAOIs or tricyclics

Better because there are fewer side effects

On market since late 1980s & early 1990s

Fluoxetine –Prozac

Sertraline -Zoloft

Paroxetine -Paxil

Fluvoxamine -Luvo

Citalopram -Celexa

Escitalopram –Lexapro

**Other Antidepressants**

Bupropion (Wellbutrin)

No effect on either 5-HT or NE

Effective at blocking DA reuptake

May be similar action to cocaine

Lowers seizure threshold

Venlafaxine (Effexor)5-HT, DA and NE reuptake blocker

**Treatments for depression**

All of these compounds have little effect on normals but are effective in depressives

May cause agitation, restlessness or anxiety in normals

No abuse potential

Cognitive Behavioral Therapy is as effective and better in the long run.

Medications make good stabilizers

**Drugs for Bipolar**

Treat the manic phases of Bipolar Disorder

Lithium

ValproicAcid

Carbamazepine/Oxcarbazepine

Lamotragine

Topirimate Symbyax

Combo of olanzepineand fluoxetine(Zyprexa& Prozac)

**Antipsychotics**

Used to treat schizophrenia and psychotic symptoms of other disorders

Schizophrenia is a severe chronic disorderPositive symptoms: hallucinations, and delusions

Negative symptoms: amotivation, poverty of speech, flat affect

Disorganized symptoms: speech, thought, and behavior

Now being used to treat Bipolar as well

Antagonize dopamine –block a specific receptor

**Typical**

Chlorpromazine -Thorazine

Haloperidol –Haldol

**Atypical**

Risperdal-Risperidone

Olanzepine-Zyprexia

Quetiapine-Seroquel

Ziprasidone–Geodon

Aripiprazole–Abilify

Paliperidone-Invega

**Significant side effects** –Less w/newer drugs

Tardivedyskinesia

Anti-ACH

Anti-histamine

**Anxiolytics**

Treat anxiety disorders

Generalized Anxiety Disorder

Panic Disorder

PTSD

OCD

Social Anxiety Disorder (SAD)

Benzodiazepines

Facilitate GABA neurotransmission

Bind to a particular site on the GABA receptor

Xanax, Ativan, Valium, Serax, Librium

Beta-Blockers

Antagonize NE by blocking Beta receptor subtype

SSRIs

PTSD, OCD, SAD, and to some degree GAD

Others

Buspar

Does not interact with alcohol

Not highly effective

Nonsedating

**Attention Deficit Disorder**

Methylphenidate –Ritalin

DA reuptake inhibitor

So slowly it enters the brain that it is not addictive like cocaine even though they have the same mechanism

Concerta(Immediate release combined with time release)

Adderal(mixed amphetamine salts)

Has extended release

Modafinil – Provigil

Vyvanse

An amphetamine pro-drug

Less abusable

Straterra

**MIXING MEDS**

Although classified as a certain type of drug most psych meds used for many different disorders.

Antipsychotics in Bipolar Disorder

Abilify

Zyprexa

Mood stabilizers in alcoholism

Topiramate

Prescribing known to work, but there is no formal FDA indication is called “off-label prescribing

It’s perfectly legal and quite common

# ALCOHOL AND METHYL ALCOHOL

**Ethyl alcohol**

• Alcohols are hydroxy derivatives of aliphatic hydrocarbons.

• It is manufactured by fermentation of sugars.

• The major source of commercial alcohol is mollases , a byproduct of sugar industry.

Alcohol is a ***CNS depressant*** that affects in a dose dependent fashion , producing sedation, thatprogress to sleep, unconsciousness, coma, respiratory failure leading to vascular collapse.

**Other forms of alcohols:**

1. Absolute alcohol - 99% w/w ethanol.
2. Rectified spirit - 90% w/w ethanol.
3. Proof spirit – 49.29% w/w ethanol.

**Pharmacological Actions**

**1.Local actions:**

Ethanol is a mild rubefacient and counter irritant.

Injected s.c causes intense pain and inflammation.

Injected around nerve it produces permanent damage.

Alcohol is an astringent.

By precipitating bacterial proteins it acts as an antiseptic.

This effect is predominant at 70-90% alcohol.

**2. Effect on CNS:**

It is a neuronal depressant.

**Mechanism of action**

It promotes GABAA Receptor mediated synaptic inhibition (through chloride channel opening)

Inhibits NMDA and kainate type of excitatory amino acid receptor (operating through cation channels)

Ethanol can indirectly reduce neuro transmitter release by inhibiting voltage sensitive neuronal channels.

**3. On CVS:**

The effects are dose dependent.

*Small doses :* produces cutaneous and gastric vasodilatation. Skin is warm and flushed.BP is not effected.

*Moderate doses :*causes tachycardia , mild rise in BP.

*Large doses :*cause direct myocardial as well as vasomotor depression and fall in BP.

**4. On blood:**

Megaloblastic anaemia has been seen in chronic alcoholism due to foliate deficiency.

**5.On body temperature:**

It produces a sense of warmth due to cutaneous and gastric vasodilatation.

**6.Respiration:**

Alcoholic beverages acts as respiratory stimulant in collapse by irritating buccal and pharyngeal mucosa.

**7.GIT:**

Higher conc.(>20%) inhibit gastric secretions , cause vomiting , mucosal congestion and gastritis.

LES tone is reduced by alcohol- bowel movement may be altered in either directions.

**8.Skeletal muscle:**

Fatigue is allayed by small doses.

Weakness and myopathy occurs in chronic alcoholism.

**9.Liver:**

Causes alcoholic livercirrhosis

By alcohol metabolism acetaldehyde gets accumulated and damages the function of liver.

It induces inflammation and damage the hepatocytes.

Regular intake induces microsomal enzymes presentin liver.

**10.Kidney:**

Diuresis is often noticed after alcohol intake

Due to water ingested and alcohol induced inhibitionof ADH secretion.

**11.Endocrine system:**

Alcohol increases adrenalin release which causes hyperglycemia.

Acute intoxification is often associated with hypoglycemia and depletion of hepatic glycogen,because gluconeogenesis is inhibited ,glucose must be given.

**Pharmacokinetics**

**A** absorption from intestine is veryfast

Peak levels are attained after 30 min.

**D** distributed widely in the body.

**V**d = 0.7 L/Kgcrosses blood brain barrier (BBB)and also placenta.

conc. in brain =conc. in blood.

**M** gets oxidised in liver to an extent of 98% metabolism of alcohol follows zero order kinetics constant rate (8-12 ml /hr)

**E** excretion is through kidney and lungs.

Concentration in exhaled air is about 0.05% of blood concentration.

This is utilized for *medico legal* determination of drunken state using ***breath analyser***.

**Contra indications:**

Peptic ulcer , hyper acidity.

Epileptics : seizures may precipitated.

Severe liver disease patients.

Pregnant women :even moderate drinking cause foetal alcohol syndrome resulting in intrauterine growth retardation, low IQ, facial andother abnormalities.

**ADVERSE EFFECTS:**

***Moderate drinking*** –nausea , vomiting , flushing , hangover , traffic accidents.

***Acute alcoholic intoxication –*** hypotension ,gastritis , hypoglycemia , respiratory depression , coma , death.

***TREATMENT:***

Gastric lavage

Correction of hypoglycaemia by glucose infusion. (thiamine 100 mg in 500 ml glucose solution)

***Chronic alcoholism -***

Physical dependence occurs

Impaired mental and physical performances

Neurological problems are common – pellagra , tremors , seizures , psychosis…

Alcoholic liver cirrhosis , hypertension ,cardiomyopathy , stroke , acute pancreatitis , infertility and skeletal myopathy.

***Withdrawal syndrome***

Anxiety ,sweating , tremor , impairment of sleep ,confusion , hallucination , convulsions..

***TREATMENT***

• Benzodiazepines (chordiazepoxide , diazepam)

• Naltrexone – opioid receptor antagonist.

• Acamprostate – weak NMDA receptor antagonist.

• Ondansetron – 5-HT3 antagonist.

•Topiramate – anti-epileptic

**Aldehyde dehydrogenase inhibitors**

**Disulfiram**

It inhibits enzyme aldehyde

dehydrogenase

***Symptoms:***

Flushing , burning sensation , throbbing headache ,perspiration,uneasiness,tightnessin chest, dizziness,vomiting,mental confusion.

***Duration***(1-4 hrs).

Disulfiram has been used in chronic alcoholics who are motivated andsincerely desire to leave the habit.

***Side effects:***

- Rashes
- Metallic taste
- Nervousness
- Abdominal upset

**Drugs:**

ESPERAL – 250mg

ANTADICT -250mg

***CLINICAL USES:***

As antiseptic

Rubefacient and counter irritant forsprains , joint pains.

As appetite stimulant and carminative: 30-50ml of 7-10% alcohol may be taken as beverages and tinctures.

To treat methanol poisoning

## METHYL ALCOHOL

Methanol is also a CNS depressant as ethanol.

Even 15 ml of methanol causes blindness

30 ml causes death

75-100 ml is regarded as fatal dose.

***Manifestations of methanol poisoning***

Vomiting , headache , epigastric pain , uneasiness , bradycardia , hypotension

Methanol is metabolised to formaldehyde and formic acid.

The specific toxicity of formic acid is ***retinal damage.***

**Treatment:**

Gastric lavage with sod.bicarbonate.

Pot.chloride infusion.

Haemodialysis.

***Fomepizole*** –is a specific inhibitor of alcohol dehydrogenase.

# CNS STIMULANTS AND COGNITIVE ENHANCERS

Drugs which primarily stimulate the CNS globally or to improve specific brain functions

Mostly – generalized action – high doses cause convulsion

**Classification** based on clinical use:

1. **Convulsants**: Strychnine, Picrotoxin, Bicuculline, Pentylenetetrazole (PTZ)
2. **Analeptics**: Doxapram
3. **Psychostimulants:** Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine

## CONVULSANTS

Strychnine (*Nux-vomica*), Picrotoxin (*fish berries*), Bicuculline, Pentylenetetrazole (PTZ)

Limited – almost Nil therapeutic indications

Experimental Use in the evaluation of Antiepileptic drugs

## ANALEPTICS (RESPIRATORY STIMULANTS)

Drugs which stimulate respiration and have resuscitative value in coma and fainting

Advantage is that they stimulate in sub-convulsive doses – however, narrow therapeutic margin – Mechanical support is the Best – also other measures

Limited Role in Therapeutics:

As an expedient in hypnotic drug poisoning

Suffocation in drowning and acute respiratory insufficiency

Apnoea in premature infant

Failure to ventilate spontaneously after GA

Doxapram: Continuous IV infusion – apnoea in premature infants not responding to Theophylline

**PSYCHOSTIMULANTS**

Amphetamines, Methylphenidate, Atomoxetine, Modafinil, Armodafinil, Pemoline, Cocaine, Caffeine

Amphetamines and Methylphenidate: Central sympathomimetics – higher central: peripheral activity ---- dextroamphetamine, methamphetamine

By releasing NA and DA in brain

Used in ADHD (Methylphenidate is better) – lesser tachycardia and growth retardation

Also used in adults for conc and attention deficit and narcolepsy

High doses produce convulsions

Atomoxetine: Selective NA reuptake inhibitor – unrelated to amphetamine

Improves attention span and behaviour in ADHD - >6years

Extensive metabolizer (EM) and poor metabolizers (PM) in CYP2D6 polymorphism – inhibitors of CYP2D6 – fluoxetine, paroxetine – toxicity

Modafinil: Newer – night shift (call centre) workers – acts by inhibiting NA and DA reuptake and also altering GABA and glutamate concentration

Used in narcolepsy day-time sleepiness, sleep apnoea syndrome and shift-work disorder and cocaine withdrawal syndrome

**CAFFEINE**

Pharmacological actions: CNS stimulant, sense of well-being, alertness, beats boredom, allays fatigue, clearer thinking

Improves performance and motor activity

High doses: nervousness, restlessness, panic, insomnia, excitement - higher doses - delirium and coma

Kinetics: Poorly water soluble, rapidly absorbed from GIT, completely metabolized in liver – demethylation and oxidation

ADRs: Extension of pharmacological actions – gastric irritation, nausea and vomiting

Nervousness, insomnia, agitation, rise in body temperature, convulsion – tachycardia – should be avoided in peptic ulcer and gout

Uses:

In analgesic mixture – benefits headache

Migraine – in combination with ergotamine

Apnoea in premature infants

## COGNITIVE ENHANCERS

In simple terms it is the Brain process of acquiring and exploiting knowledge

Mental processes involved in gaining knowledge and comprehension, including thinking, knowing, remembering, judging and problem-solving

higher-level functions of the brain and encompass language, imagination, perception and planning

Multiple levels of Neurobiological process – learning, memory, attention and motivation

Hippocampus – encoding new information

Strio-frontal circuit – decision making

Frontal lobe - retrieval

Cognition Enhancers are the drugs used in the disorders of these functions

Amnesia---- Alzheimer`s Disease

**Dementia**

Deterioration of intellectual faculties, such as memory, concentration, and judgment to previously unimpaired person

Lost: Memory, capacity to solve problems of day to day, learned motor skills, social skills, control of emotions

Retained: Consciousness and motor functions

Causes:

Aging

Alzheimer`s Disease

Most common cause of dementia

Progressive neurodegenerative disorder of older individuals leading to a total vegetative state

Atrophy of cortical and subcortical areas with deposition of amyloid protein in the form of senile plaques - marked cholinergic deficiency

TIA, CVA and stroke etc.

Organic brain syndrome and sequelae head injury, ECT and brain surgery of Infarction

**CLASSIFICATION**

**Cholinergic activators**

Tacrine, Rivastigmine, Donepezil, Galantamine

Glutamate (NMDA) antagonist: Memantine

Miscellaneous

Piracetam, Pyritinol, Dihydroergotoxine, Piribedil, Ginko biloba

Herbs and Nutrients

They are believed to act by:

Increasing Blood Flow

Increased Brain (!)

Neurotransmission Enhancement

Increased Neuronal metabolism – Stimulation of Hormones and Enzymes

Increased Nerve growth

Improvement of Cerebral Functions – Memory

**CHOLINERGIC ACTIVATORS**

Brain Ach is markedly reduced and also reduction in cholinergic transmission

Precursors of Ach have been tried – choline and lecithin – failed (no shortage in brain)

Other cholinergic drugs like bethanechol or AChE inhibitors (Physostigmine) gives good results but marked side effects

But, 4 AChE inhibitors are found to be best and used – Tacrine, Rivastigmine,

**Donepezil and Galantamine**

Tacrine is no more in use now – hepatotoxicity, no alteration of underlying disease process and other side effects

**RIVASTIGMINE**

Carbamate derivative of Physostigmine

Inhibits both AChE and BuChE – more selective to G1 isoform of AChE which is

predominant in brain

Highly lipid soluble – CNS penetration

MOA: Introduces carbamyl residues to AChE and renders inactive which dissociates slowly

Uses: Useful in mild to moderate Alzheimer`s disease – other symptoms like apathy, delusion and hallucination etc. are also improved. But, disease progression is not stopped

Available as 1.5, 3, 4.5, 6 mg caps (twice daily)

**Donepezil:** Cerebroselective and reversible anti-AChE

Improves Ach concentration in cortex especially in projecting neurons from basal ganglia to cortx

Improvement maintains upto 2 years

Long duration of action (half life – 70 hours) and usefull in severe cases of AD – onceDaily

**Galantamine**: Natural alkaloid – selective inhibition of cerebral AChE and also

direct agonistic action on Nicotinic receptors – twice daily dose

Memantine

Different mechanism of action than rivastigmine and others

It’s a new NMDA receptor antagonist and related to amantadine

Known for slowing down of the process of dementia in moderate to severe dementia

MOA: Blocks the excitotoxic glutamate neurotransmitter competitively

Also useful in Parkinsonism

Better tolerated than anti-ChEs

ADRs: constipation, tiredness, headache and drowsiness etc.

**Gingko biloba**

Ginko meaning naked Maidenhair Tree - Chinese and Japanese plant

Contains ginkgoflavon glycosides – PAF antagonist

Used in a variety of cognitive and behavioural disorders in Elderly

Prevents cerebral impairment in Multiple infarct disease (MID)

ADRs: GIT upset and arrhthmia etc

Doses: 40 mg tds for 4 weeks

Preparations: Ginkocer, Bilovas, Ginkoba

Efficacy is doubtful – also used with Gotu Kola (Brahmi)

# LOCAL ANAESTHESIA (LA)

Local anaesthetics are the drugs that blocks the generation & conduction of nerve impulse without affecting consciousness.

The generation & transmission of nociception (pain) can be prevented by **blocking voltage gated Na+ channel** in afferent neuron.

They can act on any part of the nervous system & on every type of nerve.

**Advantages of LA over GA:**

Unaltered consciousness, function of vital organ is unaffected, safe for patients, useful for minor & major operations.

**Classification:**

**Injectable**

• Low potency, short duration: Procaine, Chloroprocaine

• Intermediate potency & duration: Lignocaine (Lidocaine), Prilocaine

• High potency, long duration: Bupivacaine, Ropivacaine, Tetracaine

**Surface Anaesthetic**

• Soluble: Cocaine, Lidocaine, Tetracaine

• Insoluble: Benzocaine, Oxethazaine

**Chemistry**

Local anaesthetics are weak bases with ampiphilic (lipohilic & hydrophilic) property linked through ester/amide linkage.

**Ester linked**: cocaine, procaine

**Amide linked**: lignocaine, bupivacaine

**Systemic action of LA**

**CNS**

• Stimulation followed by depression

• Cocaine causes CNS stimulation

**CVS**

• Cardiac depressant

• Tend to fall BP except cocaine

**Blood vessels**

• Vasodilation leading to fall in BP

**Others**

• Ganglionic blockade, neuromuscular blockade

**Adverse Effects**

• Occurs due to escape of local anesthetics to systemic circulation

• CNS: lightheadness, dizziness, auditory & visual disturbance, confusion

• CVS: myocardial depression & vasodilation, occasional

Hypersensitivity

**Lignocaine**

• Versatile LA used for surface application & injection.

• Has fast onset of action (within 3 min)

• Causes vasodilation in injected area

**Uses**: Surface application, infiltration, nerve block, spinal & intravenous regional block anaesthesia.

Also used as antiarrhythemic drug.

**Adverse effects**: drowsiness, dysphoria & altered taste. Overdose may cause convulsion, coma & respiratory arrest.

**Dose**: 2-4% gel (Xylocaine gel), 100mg/ml spray, 1- 2% injection (with or without adrenaline)

**Bupivacaine**

• Potent & long acting LA.

• Causes more sensory block than motor block.

**Uses**: infiltration, nerve block, epidural & spinal anaesthesia. Popular in obstetrics & postoperative pain relief.

**Adverse effect**: cardiotoxic

**Dose**: 0.25-0.5% injection

**Ropivacaine**

• It is a congener of bupivacaine but less cardiotoxic

**Uses & Techniques of LA**

**1. Topical anaesthesia**

• LA is directly applied to the skin & mucous membrane of nose, mouth, throat, tracheo-bronchial tree, esophagus & genitourinary tract

• Only superficial layer is anaesthesised

**2. Infiltration anaesthesia**

• LA is injected directly into the tissue

• Motor function is not affected

• Used for minor operations: incision, hydrocele, hernia

**3. Conduction block**

• Field block: s.c. injection, all nerves coming to a field are

blocked

• Nerve block: injection around nerve trunk or plexuses

**4. Spinal anaesthesia**

• LA is injected in subarachnoid space betweenL2-3 or L3-4

• Acts on nerve roots in caudaequina

• Lower abdomen & hind limb are anaesthesised & paralysed.

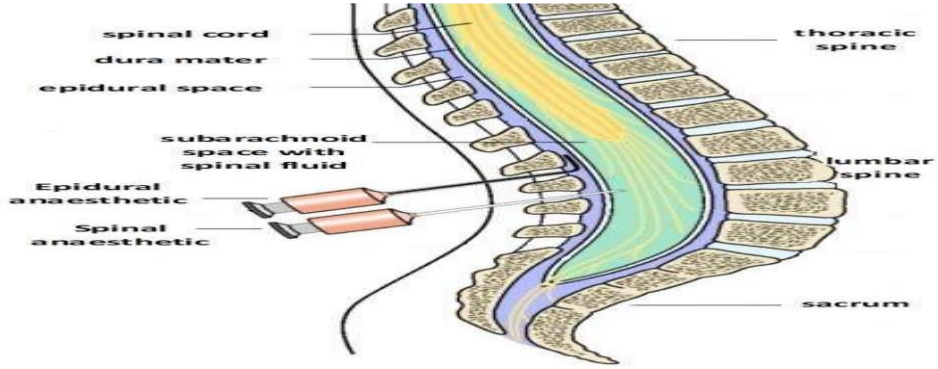
• Level of anaesthesia depends on volume & speed of injection & posture of patient.

• Bupivacaine(0.5-0.75%), lidocaine(1.5-5%), tetracaine(0.25- 0.5%) is commonly used.

**Uses**: operation on lower limbs, pelvis, lower abdomen, prostatectomy, fracture setting, obstetric procedures, caesarean section

**Adverse effects**: headache, nausea, vomiting, septic meningitis, hypotension, respiratory paralysis & cauda equina syndrome

**Contraindication**: hypotension & hypovolemia, mentally ill patient, infant & children




**5. Epidural anaesthesia**

• LA is injected in the epidural space that acts on nerve roots

• It can be thoracic, lumbar or caudal depending on site of injection

• Lidocaine 1-2% & Bupivacaine 0.25-0.5% are used.

• Epidural catheter allows continuous or repeated administration

• Lesser complications

**6. Intravenous regional anaesthesia**

• LA is injected in veins

• 0.5% lidocaine is injected i.v.

• Used for upper limb & orthopedic procedures

## PHARM D II YEARS PHARMACOLOGY-I (Uncovered Portion)

**SUBJECT CODE-2.4 UNIT 5**

### PHARMACOLOGY OF DRUGS ACTING ON RESPIRATORY TRACT

The respiratory tract may be divided into upper and lower portions. The upper portion consists of the nose, sinuses, oropharynx, and larynx. The lower portion comprises the trachea and lungs with their associated airways. Disorders and drug therapy of the upper respiratory system differ from those of the lower respiratory tract.

Disorders of the upper respiratory tract are those associated with infections (most commonly uncomplicated viral rhinotracheitis) and seasonal allergies (allergic rhinoconjunctivitis and rhinotracheitis). For the most part, these dysfunctions are self-limiting, and the drug classes used to treat them may be obtained without a prescription (over-the-counter, OTC). Disorders of the lower respiratory tract may be broadly classified as parenchymal infections (e.g., pneumonia) and obstructive airway (bronchial) conditions. In general, the latter disorders limit expiratory airflow. They are divided into bronchial asthma, which is characterized by acute episodes, and chronic obstructive airway disorders. Chronic obstructive airway disorders are further subdivided into chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis. The treatment of infections in all parts of the respiratory tract.

Manifestations of upper respiratory tract dysfunctions include mucous and watery discharges and vasodilation, mediated in part through histamine and other substances released from mast cells. Mast cells are important “gate-keeper” cells that are concentrated in the skin and other tissues near external body surfaces.

Histamine is produced from the amino acid histidine and is stored in vesicles. The four histamine receptor subtypes characterized to date are designated $H_1$ to $H_4$. $H_1$ receptors mediate mucous discharge and vasodilation, $H_2$ receptors are important in gastric acid secretion $H_3$ receptors are found in the central nervous system (CNS), and $H_4$ receptors may modulate inflammatory reactions by chemotactic effects on eosinophils and mast cells. Secretion of histamine and other mast cell mediators causes vasodilation of the nasal vasculature, leading to the nasal congestion and "runny nose" commonly associated with seasonal allergies and viral infections. Drugs used to decrease these manifestations include $H_1$ receptor antagonists (antihistamines) to decrease mucus production and vasodilation, nasal decongestants to decrease vasodilation, and mast cell stabilizers.

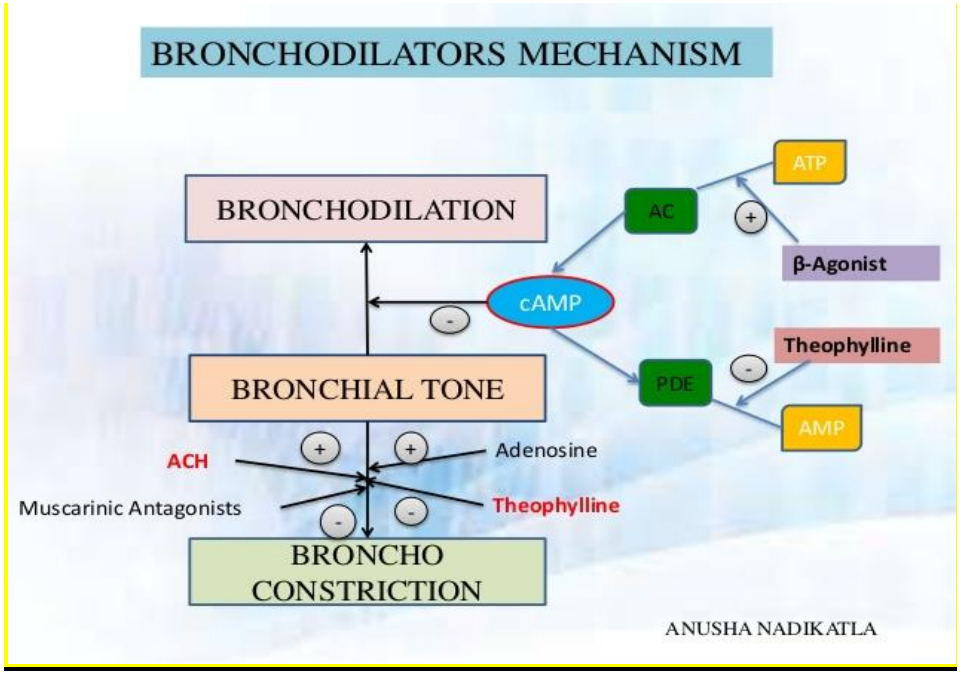
# BRONCHODILATORS

Bronchodilators are a type of medication that make breathing easier by relaxing the muscles in the lungs and widening the airways (bronchi). They're often used to treat long-term conditions where the airways may become narrow and inflamed, such as: asthma, a common lung condition caused by inflammation of the airways.

Bronchodilators may be either:

- Short-acting – used as short-term relief from sudden, unexpected attacks of breathlessness
- Long-acting – used regularly to help control breathlessness in asthma and COPD, and increase the effectiveness of corticosteroids in asthma

## Mechanism Of Bronchodilator




## Classification of Bronchodilator

The 3 most widely used bronchodilators are:

- Beta-2 agonists, such as salbutamol, salmeterol, formoterol and vilanterol
- Anticholinergics, such as ipratropium, tiotropium, aclidinium and glycopyrronium
- Theophylline

Beta-2 agonists and anticholinergics are available in both short-acting and long-acting forms, whereas theophylline is only available in a long-acting form.

## BETA-2 AGONISTS

Beta-2 agonists are used for both asthma and COPD, although some types are only available for COPD. They're usually inhaled using a small handheld inhaler, but may also be available as tablets or syrup.For sudden, severe symptoms, they can also be injected or nebulised.A nebuliser is a compressor that turns liquid medication into a fine mist, allowing a large dose of the medicine to be inhaled through a mouthpiece or face mask.

Beta-2 agonists work by stimulating receptors called beta-2 receptors in the muscles that line the airways, which causes them to relax and allows the airways to widen (dilate).

They should be used with caution in people with:

- An overactive thyroid (hyperthyroidism) – a condition that occurs when there's too much thyroid hormone in the body
- Cardiovascular disease – conditions that affect the heart or blood vessels
- An irregular heartbeat (arrhythmia)
- High blood pressure (hypertension)
- Diabetes – a lifelong condition that causes a person's blood sugar level to become too high

In rare cases, beta-2 agonists can make some of the symptoms and possible complications of these conditions worse.

***SALBUTAMOL***

***Inhaled Salbutamol:***

***It bronchodilation with in 5mins and the action lasts for 2-4hrs.***

***Dose: 100-200 µ gm.***

***Adverse effects: Muscle tremors, palpitation, restlessness, nervousness, throat irritation, ankle edema.***

***Oral Salbutamol :***

***Oral bio availability is 50%.***

***Duration of action is 4-6hrs.***

***Side effects are more frequent.***

***Dose:2-4 mg.***

***TERBUTALINE:***

***It is similar to salbutamol in properties and use.***

***Inhaled salbutamol and terbutaline causes quick reversal or bronchospasum.***

***Ragular use of these drugs does not reduce bronchial hyper reactivity: may even worsen it.***

***β2 agonist inhalers are restricted to symptomatic relief of wheezing.***

***SALMETEROL:***

***It is first long acting selective β2 agonist with slow on set of action.***

***It is more lipophillic which probably accounts for its longer action.***

***BAMBUTEROL:***

***It is bicarbamate ester prodrug of terbutaline***

***It is hydrolised by pseudo choline esterase to release the active drug over 24hrs.***

***It is indicated in chronic bronchial asthma in a single evening dose of 10-20mg.***

***SALMETEROL:***

***It is first long acting selective β2 agonist with slow on set of action.***

***It is more lipophillic which probably accounts for its longer action.***

***FORMOTEROL:***

***It has faster onset of action compared to salmeterol.***

***It is used on a regular morning-eveningschedule for round the clock bronchodilation.***

***It acts for 12hrs when inhaled.***

***EPHEDRINE:***

***It has α+β1+β2 actions.***

***It causes mild slowly developing bronchodilation lasting for 3-5hrs.***

***Because of low efficacy and frequent side effects it is not preffered now.***

**ANTICHOLINERGICS**

Anticholinergics (also known as antimuscarinics) are mainly used to treat COPD, but a few can also be used for asthma. They're usually taken using an inhaler, but may be nebulised to treat sudden and severe symptoms.

Anticholinergics cause the airways to widen by blocking the cholinergic nerves. These nerves release chemicals that can cause the muscles lining the airways to tighten.

They should be used with caution in people with:

- Benign prostate enlargement – where the prostate gland becomes enlarged, which can affect how you pee

- A bladder outflow obstruction – any condition that affects the flow of urine out of the bladder, such as bladder stones or prostate cancer
- Glaucoma – a build-up of pressure in the eye

If you have benign prostate enlargement or a bladder outflow obstruction, anticholinergics can cause problems, such as difficulty peeing and not being able to empty your bladder fully.Glaucoma can get worse if anticholinergic medication unintentionally gets into the eyes.

***Ipratropium Bromide:***

***Patients with asthmatic bronchitis , COPD and psychogenic asthma respond better to anticholinergics.***

***Combination of inhaled ipratropium with β2 agonist produces more marked and long lasting bronchodilation***

***Dose: 2-4 puffs 6 hourly***

***Adverse effects: Dry mouth, Systemic anticholinergic effects such as urinary retention and constipation.***

**THEOPHYLLINE**

Theophylline is usually taken in tablet or capsule form, but a different version called aminophylline can be given directly into a vein (intravenously) if your symptoms are severe.

It's unclear exactly how theophylline works, but it seems to reduce any inflammation (swelling) in the airways, in addition to relaxing the muscles lining them.

The effect of theophylline is weaker than other bronchodilators and corticosteroids.

It's also more likely to cause side effects, so is often only used alongside these medicines if they're not effective enough.

***Mechanism of action:***

***• Inhibition of phosphpdiesterase which degrades cyclic nucleotides intracellularly.***

***• Blockade of adenosine receptors.***

***Pharmacokinetics***

***: • It is well absorbed orally. • Only 10% is excreted unchanged in urine. • t 1/2 : 7-12hrs.***

***Adverse effects :***

***• CNS toxicity in children.***

***• Gastric pain (oral).***

***• Rectal inflammation (suppositories).***

***• Ventricular arrhythmias.***

***Interactions:***

***Plasma conc. of theophylline is decreased by rifampicine , Phenytoin and phenobarbitone (Induces p450 enzyme). Plasma conc. of theophylline is increased by erythromycin, Clarithromycin and ciprofloxacin(Inhibits p450 enzyme).***

Theophylline should be used with caution in people with:

- An overactive thyroid
- Cardiovascular disease
- Liver problems, such as liver disease

- High blood pressure
- Open sores that develop on the stomach lining (stomach ulcers)
- A condition that affects the brain and causes repeated fits (seizures) (epilepsy)

Theophylline may make these conditions worse. In people with liver problems, it can sometimes lead to a dangerous build-up of medication in the body.

Other medicines can also cause an abnormal build-up of theophylline in the body. This should always be checked by your doctor.

Elderly people may also need additional monitoring while taking theophylline.

**Side Effects of Bronchodilators**

General side effects of bronchodilators include:

- Trembling, particularly in the hands
- headaches
- A dry mouth
- Suddenly noticeable heartbeats (palpitations)
- Muscle cramps
- A cough
- Nausea and vomiting
- Diarrhoea

# MUCOLYTICS

Drugs which render sputum less visous so that sputum is more easily cleared from chest.

## CLASSIFICATION OF MUCOLYTICS

A) **Chemical classification of mucolytics**:
Alkaloid derivative: Bromhexine.
Amino acid derivative: Carbocisteine.

B) **Pharmacological classification of mucolytics:**
i) Inhalational Mucolytics :Acetylcysteine, Tyloxapol.
ii) Oral Mucolytics :
Acetylcysteine, Bromhexine, Carbocisteine,Methylcysteine.

C) **Therapeutic classification of mucolytics:**
i) Chronic bronchitis :Carbocisteine, Bromhexine.
ii) Bronchial asthma :Tyloxapol, Bromhexine
iii)Mucoviscidosis:Bromhexine, Acetylcysteine, methylcysteine.

**BROMHEXINE**:

It is a derivative of alkaloid vasicine obtained from Adhatoda vasica. It is potent mucolytic and mucokinetic, capable of inducing thin copious bronchial secretion. It depolymerises mucopoly saccharides directly as well as by liberating lysosomal enzymes. The network of fibers in tenacious sputum is broken. It is particularly used when mucous plugs are present. Dose: 8mg.Adverse effects : Rhinorrhoea, Lacrimation, Gastric irritation, Hypersensitivity

**ACETYL CYSTEINE**:

It opens di sulfide bonds in muco proteins present in sputum makes it less viscid.

It has to be administered directly in to the respiratory tract.

**AMBROXOL:**

It is metabolite of bromhexine.

Dose:15-30mg.

**CARBOCYSTEINE:**

It liquefies viscid sputum in the same way as acetyl cysteine.

It is administered orally .

Some patients of chronic bronchitis have been shown to benefit.

Adverse effects: G.I.irritation Rashes.

# EXPECTORANTS

**Definition:**

Drugs which ↑ bronchial secretions or reduces its viscosity facilitating its removal by coughing

**MECHANISM OF ACTION OF EXPECTORANTS**

a. **Directly acting:-**

Stimulate secretory cells of respiratory tract directly & produces demulcent effect by decreasing irritation and viscosity of mucous.

Since these drugs stimulate secretion more fluid get produced in resp tract and sputum is diluted, there by helping in easy removal of sputum.

b. **Indirectly/ reflex acting**:-

Act indirectly to relieve cough by irritating gastric mucosa and increases resp tract fluid secretion and decreasing viscosity of sputum.

## CLASSIFICATION OF EXPECTORANTS

A) **Chemical classification of expectorants**:
Alkaloids - Ipecacuanha
Glycosidal saponins -Senega, Squill.
Iodides - Sodium iodide, Potassium iodide.

B) **Pharmacological classification of expectorants** :
i) Drugs acting reflexly : Ipecacuanha, Ammonium chloride, Ammonium bicarbonate, Guaifenesin, Cocillana, Senega,Squill, Terpen hydrate.
ii) Drugs acting directly : Sodium iodide and Potassium iodide.

D) **Therapeutic classification of expectorants**:
i) Irritant to Gastric mucosa : Ipecacuanha, Squill, Senega, Ammonium chloride and Ammonium bicarbonate.
ii) Carminative use : Ammonium bicarbonate
iii) Decrease viscosity of sputum : Guaifenesin, Sodium and Potassium iodide.
iv) Chronic bronchitis: Sodium iodide.

**Ammonium salts**

- Gastric irritants(nauseating) — enhance bronchial secretions.
- Expectorant doses are subemetic, having unpleasant taste.
- Used in combination with antitussives.

**Ipecacuanha**

- Used as expectorant in small doses & emetic in large doses.
- It liquefies thick secretions and relieve the irritated mucosa.
- It also irritates the gastric mucosa and enhances the expulsion of secretion.
- It is mainly used for emesis in accidental poisoning.

**Guaiphenesin**

**Mechanism of Action**

Decrease sputum viscosity and increase sputum volume thereby decreasing difficulty in expectoration.

**Uses:**For symptomatic relief of dry, non productive cough in the presence of mucus in respiratory tract.

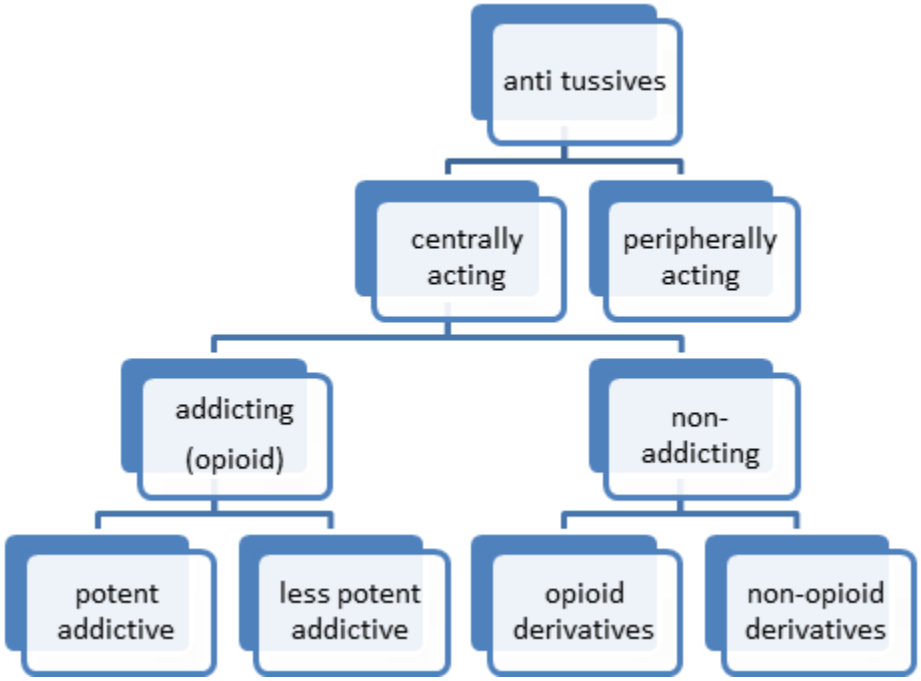
**Adverse effects**: Gastric disturbances and drowsiness.

## ANTI-TUSSIVE

Drugs which suppress cough & are used for symptomatic treatment of cough.

**Types:**

**Two** types according to mechanism of action



**1. Centrally acting anti-tussives:**

Suppress cough by a direct action on medullary cough center.

**2. Peripheral Anti–tussives**

They suppress cough reflex by decreasing the input of stimuli from cough receptors in respiratory passages.

**Anti-tussive Drugs should be used to suppress unproductive / useless cough.**

## Classification of Anti-tussive Drugs

**(A) Central Anti-tussives**

**(a) Opioid / Narcotic /Addicting Anti-tussives**

(i) **Less addicting Drugs**

- Codeine phosphate,
- Pholcodine,
- Dihydrocodeine tartrate.

(ii) **Potent addicting Drugs**

- Morphine,
- Dihydromorphinone.

**(b) Non-Addicting Anti-tussives**

**Opioid derivatives :**

- Dextromethorphan,
- Noscapine.

**Non Opioids:**

- Benzonatate,
- Diphenhydramine –antihistamine 1$^{st}$ gen, having sedative, anticholinergic actions, crosses BBB

**(2) Peripheral Anti-tussives**

(a) **Pharyngeal Demulcents** (soothing action on irritating mucosa)

(b) **Steam inhalation** With tincture bezoin / menthol.

(c) **Drugs with Local Anesthetic Activity-** Benzonatate, Lignocaine

**Mechanism of action of antitussives**

**Centrally acting**

Depression of medullary centres or associated higher centres.

Increased threshold of cough centre.

**Peripherally acting**

Interruption of tussle impulses from respiratory tract, having soothing effect.

*Opioids:*

**Codeine**

An opium alkaloid**.**

- It is more selective for cough centre.
- Centrally acting anti tussives increase threshold for cough.
- Suppresses cough for about 6 hours.
- The antitussive action is blocked by **naloxone** indicating that its action may be exerted through Opioid receptors in the brain.
- Cough suppression occur with low doses of opioids than those needed for analgesia.(sub-analgesic dose 15 mg)
- Abuse liability is low, but present.

**Adverse Effects**

- Constipation.
- Respiratory depression & drowsiness

- Driving may be impaired.
- Contraindicated in asthmatics & in patients with diminished respiratory reserve.

**Pholcodeine:**

- Centrally acting, suppresses center in medulla
- Little/ no analgesic or addicting property.
- Similar efficacy as antitussive to codeine
- Is longer acting——acts for 12 hours or more.
- Given once or twice daily.
- Dose: 10-15 mg.

**Adverse Effects**

- Nausea
- Drowsiness.

Non-addicting Anti-tussives:

**Noscapine:**

- Depresses cough but has no narcotic, analgesic or dependence inducing properties.
- Efficacy same as codeine, specially useful in **spasmodic cough.**

**Adverse Effects**

- Headache & nausea can occur.

**Dextromethorphan:**

- A synthetic compound
- The d-isomer has selective antitussive action (raises threshold for cough & depresses cough center in medulla.).
- It has been found to enhance the analgesic action of morphine & other μ receptors agonists

- As effective as codeine, does not depress mucociliary function of the airway mucosa.
- Devoid of addicting actions.
- Produces less constipation than codeine.
- No CNS depression.
- Antitussive action for 6 hours.
- Naloxone does not antagonize it, indicating it does not act through opioids receptors.
- Available as combination with anti asthmatics drugs, bronchodilators, expectorants and anti histamines. Extended release preparation is available which is administered two times daily.

**Side effects:** Dizziness, nausea, drowsiness & ataxia.

**Dose:** 15-30mg three or four times daily

**Levopropoxyphene:**

Devoid of opioid effect but has some sedative property.

**Adverse Effects-**Sedation.

Antitussive dose- 50-100mg 4 hrly.

**Antihistamines**

- 1st generation drugs are used as anti tussives.
- Many antihistamines have been added to antitussive / expectorant formulations.
- They relieve cough due to their sedative and anticholinergic actions, but lack selectivity for the cough centre.
- Useful in allergic cough.
- They may reduce secretions by anticholinergic action (2-5 mg)

Diphenhydramine (15-25 mg) , Promethazine (15-25 mg) are commonly used.

Only first generation antihistamine are used, 2nd generation drugs cannot cross BBB, so having no sedative effect.

Peripheral Antitussives

**Demulcents.**

- They provide relief to throat.
- Promotes salivation & inhibit impulses from inflamed mucosa.

**Linctus**

Thick liquid preparation containing sucrose and medicinal substance.

These have sedative, demulcent properties.

**Throat lozenges:**

- Small medicated tablets intended to dissolve slowly in mouth
- They have lubricating and soothing effect on irritated tissue of throat.
- Lonzenges may contain **benzocaine or dextromethorphan.**

**Bronchodilators**

- If cough is due to bronchospasm, D2 agonists are given.
- Bronchodilators relieve cough in patients with bronchial hyperreactivity.
- They shoud be used only when an element of bronchoconstriction is present**.**

**Benzonatate:**

Chemically related to Procaine, which is local anesthetic. It has both central and peripheral actions.

**Mechanism of Action**

- Exerts its antitussive action on stretch or cough receptor in lungs (Local anaesthetic effect).

- It has some central effects as well.

**Adverse Effects:**

- Headache,
- Dizziness,
- Pruritis
- Nasal Congestion,
- Burning of eyes &
- Tightness in chest.

**Benzonatate** –has central and peripheral actions, local anesthetic so action on stretch receptors in lung bronchi

**Lignocaine** by nebulizer –not anti tussive, only used in special cases (CA bronchus)

**Uses**

1) For dry unproductive cough.

2) If cough is unduly tiring.

3) Disturb sleep.

4) If patient is suffering from hernia, piles or underwent abdominal surgery

## NASAL DECONGESTANT

Definition: "These are α agonists which on topical application as dilute solution (0.05–0.1%) produce local vasoconstriction."

Simply, nasal decongestants are the drugs that reduce congestion of nasal passages, which in turn open clogged nasal passages and enhances drainages of the sinuses.

Nasal decongestants are prescribed in patients with allergic or vasomotor rhinitis and in acute rhinitis in patients with upper respiratory infections.

Major limitation with chronic nasal decongestants therapy or withdrawal of therapy is loss of efficacy, “rebound” hyperemia, and worsening of symptoms may due to receptor desensitization and damage to the mucosa.


**Classification Of Nasal Decongestant :**

A. Depends upon duration of action;

1. Short acting decongestants administered topically; Ex-Phenylepherne, Phenylpropanolamine. 2.Long acting decongestants administered orally ; Ex-Ephedrine, Pseudoephedrine, Naphazoline. 3. Long acting topical decongestants; Ex- Xylometazoline, Oxymetazoline

B. Depends upon α Receptor agonists/ Sympathomimetic decongestants :

These agents used with great caution in patients with hypertension and in men with prostatic enlargement, and they are contraindicated in patients who are taking MAO inhibitors.

1. α1 agonist: Ex- Phenylephrine, Phenylephrine .

2. α2 receptors agonists/ Imidazoline compounds : Ex-Clonidine. Naphazoline, xylometazoline oxymetazoline.

A. **α1 agonist:**

Definition: "These drugs probably decrease resistance to airflow by decreasing the volume of the nasal mucosa; this may occur by activation of αlpha receptors in venous capacitance vessels in nasal tissues that have erectile characteristics" Ex- Phenylephrine.

At high concentration it has negligible β action. These are less likely to induce mucosal damage but on I/V infusion causes marked arterial vasoconstriction causes raises BP

Phenylephrine & epinephrine: Chemically, phenylephrine differs from epinephrine only in lacking a hydroxyl group at position 4 on the benzene ring. Pseudoephedrine is less potent than ephedrine in producing tachycardia, increased blood pressure, and CNS stimulation. Uses: Used as nasal decongestant in acute rhinitis. Topically used as mydriatic when cycloplegia is not required. It reduces intraocular tension by constricting ciliary body blood vessels.

B. α2 receptors agonists/ Imidazoline compounds :Ex- Clonidine, naphazoline, xylometazoline and oxymetazoline. α2 receptors may mediate contraction of arterioles that supply nutrition to the nasal mucosa but intense constriction may cause structural damage to the mucosa. They may cause initial stinging sensation (specially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction They can be absorbed from the nose and produce systemic effects, mainly CNS depression and rise in BP. These drugs should be used cautiously in hypertensives and in those receiving MAO inhibitors.

They have a longer duration of action (12 hours) than ephedrine.

**Clonidine**

It is an imidazoline derivatives , was originally tested as a vasoconstrictor acting at peripheral α2 receptors. During clinical trials as a topical nasal decongestant, clonidine was found to cause hypotension, sedation, and bradycardia.

Pharmacological Effects It changes in blood pressure and heart rate. Intravenous infusion of clonidine causes an acute rise in blood pressure.

Common mechanism of action: Decongestant α 1 adrenergic receptor stimulate Release Enhansing noradrenaline and adrenaline activity vasoconstriction and constricting nasal vasculature Decongestion of nasal mucosa and paranasal sinuses Reduced inflammation/ swelling and mucus formation in these areas.

**Side effects:**

The effects are not limited to the nose, and these medicines may cause hypertension (high blood pressure) through vasoconstriction; it is for this reason that people with hypertension are advised to avoid them.

The common side-effects include Sleeplessness, Anxiety, Dizziness, Excitability and nervousness.

Topical nasal or ophthalmic decongestants quickly develop tachyphylaxis (a rapid decrease in the response to a drug after repeated doses over a short period of time). Long-term use is not recommended, since these agents lose effectiveness after a few days.

## PHARM D II YEARS PHARMACOLOGY-I (Uncovered Portion)

**SUBJECT CODE-2.4**

### PHARMACOLOGY OF DRUGS ACTING ON ENDOCRINE SYSTEM

### THYROID AND ANTI-THYROID DRUGS

**Thyroid gland secretes thyroid hormones**—

Triiodothyronine ($T_3$)

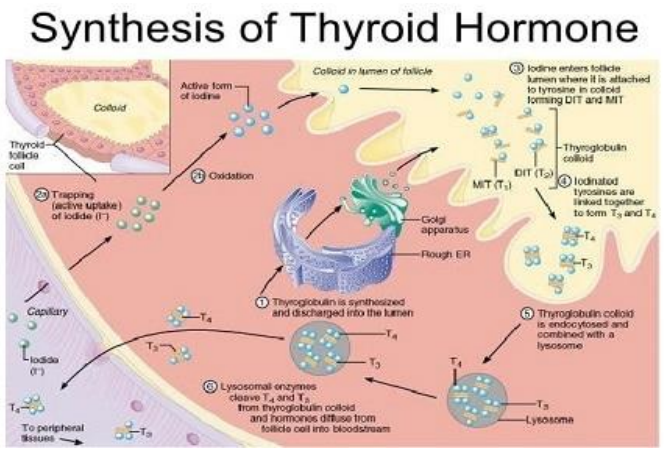
Tetraiodothyronine($T_4$,thyroxine)

Calcitonin

**Thyroid Hormone Synthesis**

Thyroid Hormone: Synthesis

- Iodide Uptake
- Oxidation and Iodination
- Coupling
- Storage and release
- Peripheral conversion of T4 to T3




**Thyroid Hormone: Transport**

Avidly bound to plasma proteins; 0.03%-0.08% T4 & 0.2-0.5% T3 in free form

Bound to 3 plasma proteins:

- Thyroxine Binding Globulin (TBG)
- Thyroxine Binding prealbumin (trans-thyretin)
- Albumin

Plasma bound Iodine: mostly is thyroid hormone (90-95% T4 )

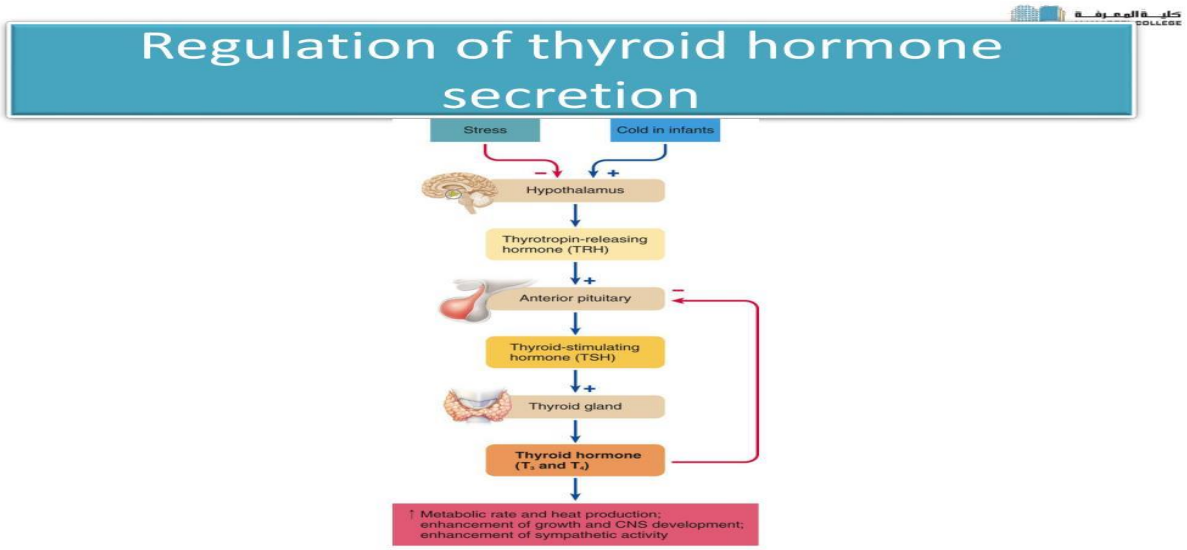
Normal Concentration of PBI = 4-10mcg/dl (0.1-0.2 T3 )

**Thyroid Hormone: Metabolism and Excretion**

Metabolic inactivation occurs by deiodination and glucuronide/sulphate conjugation

Primary site: Liver, others: salivary glands, kidney  significant undergoes deconjugation Excreted in bile  finally excreted in urine enterohepatic circulation

**Thyroid Hormones: Regulation of Secretion**




**Mechanism of Action:** binds to nuclear thyroid hormone.  Penetrates cells by active transport  ◊receptor bound to the thyroid hormone response element (TRE) conformation changes occur (heterodimerization of receptor with retinoid X  releases coreporessor and binding of coactivator occurs ◊receptor (RXR))  production of specific mRNA and proteingene transcription induced  metabolic and anatomic effects. synthesis  tachycardia, Sensitization of adrenergic receptors to catecholamines  arrhythmia, raised BP, tremor, hypoglycaemia

**Uses**

- Cretinism
- Adult Hypothyroidism

• Myxoedema coma

• Nontoxic Goiter

• Thyroid Nodule

• Papillary carcinoma of thyroid

• Emperical use

## ANTI-THYROID DRUGS

**Classification**

•Inhibits Hormone synthesis - Propylthiouracil, Methimazole, Carbimazole

• Inhibits iodine trapping (ionic inhibitors) -Thicynates, Perchlorates, Nitrates

• Inhibits hormone release - Iodine, Iodides of Na and K, Organic Iodide

• Destroy Thyroid Tissue - Radioactive iodine (131I, 125I, 123I)

**Mechanism of Action:**

Binds to the Thyroid Peroxidase and prevent oxidation of iodide/iodotyrosil residues thereby: Inhibit iodination of tyrosine residues in thyroglobulin

Inhibit coupling of iodotyrosine residues to for T3 and T4

Thyroid colloid is depleted over time and blood levels of thyroid hormones are progressively lowered.

Additionally for Propylthiouracil: inhibits peripheral conversion of T4 to T3 by Deiodinase (D1)

**Thioamides**:

Pharmacokinetics

Well absorbed orally

Widely distributed (enters milk and placenta)

Higher concentration in thyroid, longer intrathyroid half life

Metabolised in liver

Excreted in urine

**Adverse Effects**

Due to Overtreatment:

Hypothyroidism, goiter

**Important side effects**:

Gastrointestinal intolerance, skin rashes, joint pain

Infrequent side effects:Loss or graying of hair, loss of taste, fever, liver damage

Rare but serious: Agranulocytosis

**Uses**

Control Thyrotoxicosis in Grave's Disease

Toxic Nodular Goiter

Can be used as:

Definitive therapy

Preoperatively Along with 131I

**Ionic Inhibitors**

**Mechanism of Action**

T3Inhibits iodide trapping by NIS into the thyroid and T4 not synthesised

Toxic and not clinically used these days

**Iodine and Iodides**

Fastest acting thyroid inhibitor

Peak effects seen after 10-15 days followed by “thyroid escape”

Seen more in multinodular goiter

**Mechanism of Action** (not clear): Inhibition of hormone release- termed as ‘thyroid constipation’ Endocytosis of colloid and proteolysis of thyroglobulin comes to halt. Excess of iodine inhibits its own transport by interfering with expression of NIS Attenuates TSH and cAMP induced thyroid stimulation Rapid and brief intereference with iodination of tyrosil and thyronil residues of Thyroglobulin

**Uses** Preoperative preparation , Thyroid storm , Prophylaxis of endemic goiter , As antiseptic

**Adverse Effects**

Acute Reaction ,Chronic overdose (iodism)

Long term use of high doses: Hypothyroidism and goitre

Flaring of acne in adolscents

Pregnancy/Lactating mothers: Foetal/infantile goitre and hypothyroidism

Aggravation of thyrotoxicosis in multinodular goiter

**Radioactive Iodine**

131I emits X-rays and β-particles

X-rays: tracer studies • β-particles: destructive effect on thyroid tissues

**Mechanism of Action:** emits Concentrated by thyroid, incorporated into colloid undergo pyknosis and necrosis radiation from within the follicle followed by fibrosis Partial ablation can be achieved

Administered as sodium salt of 131I dissolved in water and taken orally.

**Use:** Diagnostic: 25-100 mcCurie is given: no damage to thyroid cells occur at this dose Therapeutic: Hyperthyroidism due to Grave's disease or Toxic nodular goitre

Average Dose: 3-6 mCurie; higher dose for toxic multinodular goitre

**INSULIN, INSULIN ANALOGUES AND ORAL HYPOGLYCEMIC AGENTS**

**Insulin**

• Two chain polypeptide having 51 amino acids (AA), held together by 2 sulphide bonds

• A-chain 21 AA

• B-chain 30 AA

• Molecular Weight: 6000

• Pork insulin more homologous to human insulin

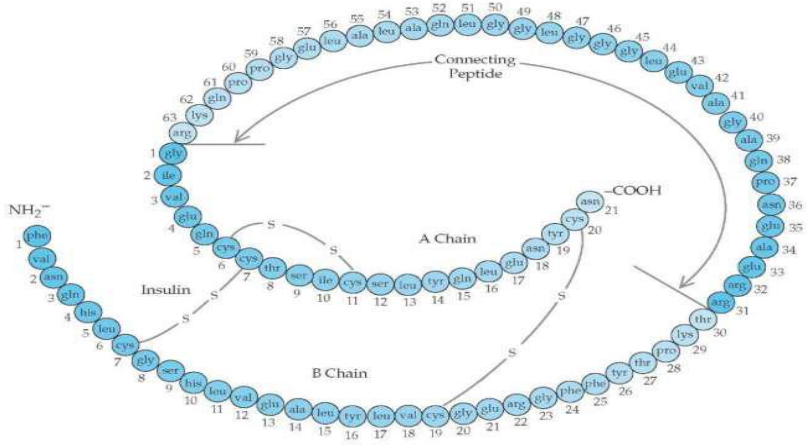
• Secreted by β-cells of pancreatic islets as

**Preproinsulin** (110 AA)

• After removal of 24 AA, **proinsulin** is formed.

• C-peptide is split by proteolysis and both fragments are stored in granules within the cell.

• Both are secreted together in the blood




**Regulation of Insulin Secretion**

• Basal condition ~1U/hr; larger quantity following meals

• Regulated by following Mechanisms:

- Chemical
- Hormonal
- Neural

**Chemical Regulation of Insulin Secretion**

Beta cells have glucose sensing mechanism activated by:
Entry of glucose into beta cells (aegis of glucose transporter GLUT1)
Phosphorylation of glucose by glucokinase→Upon activation, it indirectly inhibits the ATP-sensitive K+ channels (K+ATP)→Partial depolarization of the β-cells→Increases Ca2+ availability (increased influx, decreased efflux and release from intracellular stores)→Exocytotic release of insulin from storing granules.
Response varies when nutrients are given orally and parenterally

**Hormonal and Neural Regulation of Insulin Secretion**

**Hormonal Regulation**

• Intra-islet pancreatic interaction
• Growth Hormone,
Corticosteroids and Thyroxine shows effect in on insulin release in response to glucose.

**Neural Regulation**

Adrenergic alpha2 -Decreases
Adrenergic beta -Increases
Cholinergic(muscuranic) (Ach or vagal mediated)-Increases

**Insulin as an Anabolic Hormone:**

Actions
• Glucose transport across cell membrane

• Expression of glucose transporters into the membrane

• Intracellular utilization of glucose

• Effects on gluconeogenesis

• Effects on Lipid metabolism

• Effect on Very Low Density lipoprotein and Chylomicrons

• Effects on Protein Metabolism

**Insulin: How it acts**

• Binds to alpha subunit of receptor tyrosine kinase (RTK) present in cell membrane - Activates tyrosine kinase activity of beta subunit - phosphorylates tyrosine residue present on eachother, Insulin Receptor Substrate proteins (IRS1, IRS2) Activates a casacade of phosphorylation and

dephosphorylation reactions- Amplification of signals -stimulation and inhibition of enzymes responsible for rapid action of insulin

• Translocation of glucose transporter GLUT4 to plasma membrane and expression of genes directing synthesis of GLUT4 is promoted

• Long term effects exerted by generation of transcription factors promoting proliferation and differentiation of specific cells

**Insulin: Its Fate**

• Distributed only extracellularly

• Degraded if given orally

• Injected insulin/insulin released from pancreas: metabolised in liver (kidney and muscles also contributes)

• Biotransformation results into reduction of disulphide bonds: chains are separated.

**Insulin: Its Preparations**

• **Older commercial preparations:** beef and pork insulin, ~1% (10,000 ppm) other proteins (proinsulins, polypeptides, pancreatic proteins, insulin derivatives)

• **Newer preparations**: single peak and monocomponent, highly purified pork/beef insulin, recombinant human insulin/insulin analouges, <10 ppm proinsulin

• **Regular Insulin:** Soluble, buffered neutral pH of unmodified insulin stabilized by a small

amount of zinc. Given sub cutaenously, slow absorption, peak activity after 2-3 hrs, lasts for 6-

8 hrs. Needs to be injected ½ - 1 hr before meal: else risk of early postprandial hyperglycaemia and late postprandial hypoglycaemia. Cannot be mixed with insulin glargine/detemir

## INSULIN ANALOUGES

**Insulin lispro:**

Weak hexamers, dissociates rapidly

Quick and more defined peak

Injected immediately before or even after meal: better control of meal-time

glycaemia and lower incidence of post prandial hypoglycaemia

Multiple injections, fewer incidence of hypoglycaemia

**Insulin aspart:**

Similar to insulin lispro

**Insulin glulisine:**

Used for continuous subcutaneous insulin infusion (CSII)

**Insulin glargine:**

Remains soluble at pH4, precipitates at neutral pH

Delayed onset of action, maintained for up to 24hrs: “smooth peakless effect”

**Insulin detemir:**

Binds to albumin and action is prolonged

Twice daily dose is required

**Insulin: Unwanted Efects**

• Hypoglycaemia

• Seen more in labile diabetes patients

• Sympathetic symptoms and neuroglucopenic symptoms

• Hypoglycaemic unawareness

• Local Reactions

• Swelling, stinging, erythema; Lipodystrophy

• Allergy

• Utricaria, angioedema, anaphylaxis

• Edema

**Uses of Insulin**

• Diabetes Milletus:

• Mandatory in Type 1 DM (Insulin Dependent DM), post pancreatectomy diabetes, gestational diabetes (0.4-0.8 u/Kg/day)

• Some cases of Type 2 DM (Non Insulin dependent DM): not controlled by diet/exercise, failure of OHA, under weight, temporary situtations, during complications (0.2-1.6 U/kg/day)

• Given as Split-mix regimen and Basal Bolus regimen Diabetes Ketoacidosis

• Regular insulin, 0.1-0.2 U/kg i.v. bolus followed by 0.1U/kg/hr infusionadjusted according to the fall in blood glucose levels

• Hyperosmolar (non ketotic) Hyperglycaemic Coma

## ORAL HYPOGLYCEMICS

These agents are useful in the treatment of type 2 DM who do not respond adequately to non-medicalinterventions (diet, exercise and weight loss).

Newly diagnosed Type 2s (less than 5 years) often respond well to oral agents, patients with long standing disease (often diagnosed late) often require a combination of agents with or without insulin.

The progressive decline in β-cell function often necessitates the addition of insulin at some time in Type II diabetes. Oral agents are never indicated for Type I DM.

**CLASSIFICATION**

**Sulphonylureas–**

First generation-Tolbutamide, Chlorpropamide

Second generation(24hrs)-Glybenclamide or glyburide, Gliclazide, Glipizide, Glimepiride

**Biguanides----**Metformin, Phenformin

**Meglitinide Analogues—** Repaglinide, Nateglinide

**Thiazolidinediones-** Rosiglitazone , Pioglitazone

**Glucosidase Inhibitors--** Acarbose , Miglitol,Voglibose

**Incretin-mimetics** -Exenatide

**DPP-4 Inhibitors- S**itagliptin, Vildagliptin,Saxagliptin

**Amylin-mimetic drugs-** pramlintide

**Sodium- glucose cotransporter-2(SGLT-2)**- Dapaglifozin, Serglifozin, Remoglifozin

**Sulphonylureas**

Tolbutamide, Glyburide, Glipizide and Glimepride.

They bind to SURI(sulfonylurea receptors) and promote the release of insulin from β-cells (secretogogues)

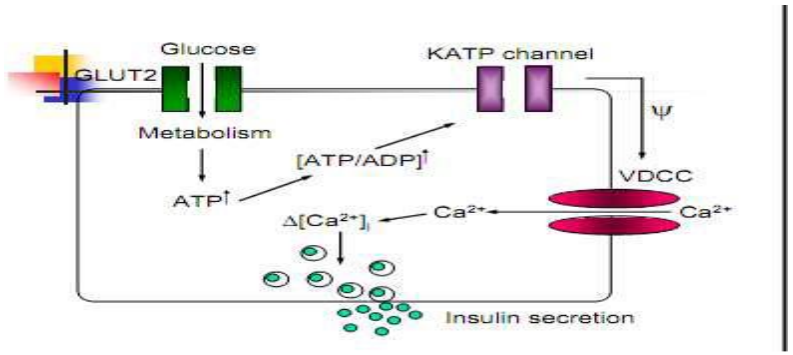
**Mechanism:**

These agents require functioning β-cells, they stimulate release by blocking ATP-sensitive K+

channels resulting in depolarization with Ca2+ influx which promotes insulin secretion.

They also reduce glucagon secretion and increase the binding of insulin to target tissues.

They may also increase the number of insulin Receptors



**Pharmacokinetics-** These agents bind to plasma proteins, are metabolized in the liver and excreted by the liver or kidney.

Orally active, low volume of distribution, 90% bound

to plasma proteins

Onset and Duration

- Short acting: Tolbutamide - 6-12 hrs
- Intermediate acting: Glipizide , Glyburide
- Long acting: Glimepiride, glyclazide
- Glybenclamide-150 times potent than tolbutamide

**Adverse effects**

These agents tend to cause weight gain due to fluid retention and oedema Hyperinsulinemia and hypopglycemia.

Hepatic or renal insufficiency causes accumulation of these agents promoting the risk of hypoglycemia.

Elderly patients appear particularly susceptible to the toxicities of these agents.

Tolbutamide is associated with high incidence of cardiovascular mortality.

Nausea, vomiting, abdominal pain, diarrhea Hypoglycaemia Dilutional hyponatraemia & water intoxication (Chlorpropamide)

Disulfiram-like reaction with alcohol (Chlorpropamide) Weight gain Hypersensitivity reactions

**Biguanides- Insulin Sensitizer**

Two classes of oral hypoglycemics work by improving insulin target cell response; the biguanides andthiazolidinediones.

Indicated in most Type 2 DM

**MOA-**Act by inhibiting liver gluconeogenesis & increasing insulin sensitivity in other tissues. Enhances insulin mediated glucose disposal in muscle and fat

Retards intestinal absorption of glucose, Metformin is not metabolized, but excreted intact in 2-5h Perpetuates weight loss

Can be combined with insulin to reduce insulin requirements

Enhances insulin mediated glucose disposal inmuscle and fat. It also reduces hyperlipidemia (↓LDL and VLDL cholesterol and ↑ HDL).

Lipid lower requires 4-6 weeks of treatment.

Metformin also decreases appetite.

It is the only oral hypoglycemic shown to reduce cardiovascular mortality.

Metformin:

Dosing from 500mg twice daily to

1 gram thrice a day

Demerits

Nausea, Vomiting and diarhorrea(5%)

Phenformin withdrawn for higher risk of lactic acidosis lactic acidosis is associated with metformin use particularly in diabetics with CHF

**Drug interactions** with cimetidine, furosemide, nifedipineand others have been identified.

**Contraindication**

a) Malabsorption or GI disturbances

b) Low BMI

c) Organ Failure: Creatinine: >1.4mg/dl Liver failure, Active Vitamin B12 Deficiency

GI intolerance

**Thiazolidinediones- Rosiglitazone , Pioglitazone**

These agents are **insulin sensitizers**, they do not promote insulin secretion from β-cells but insulin is necessary for them to be effective.

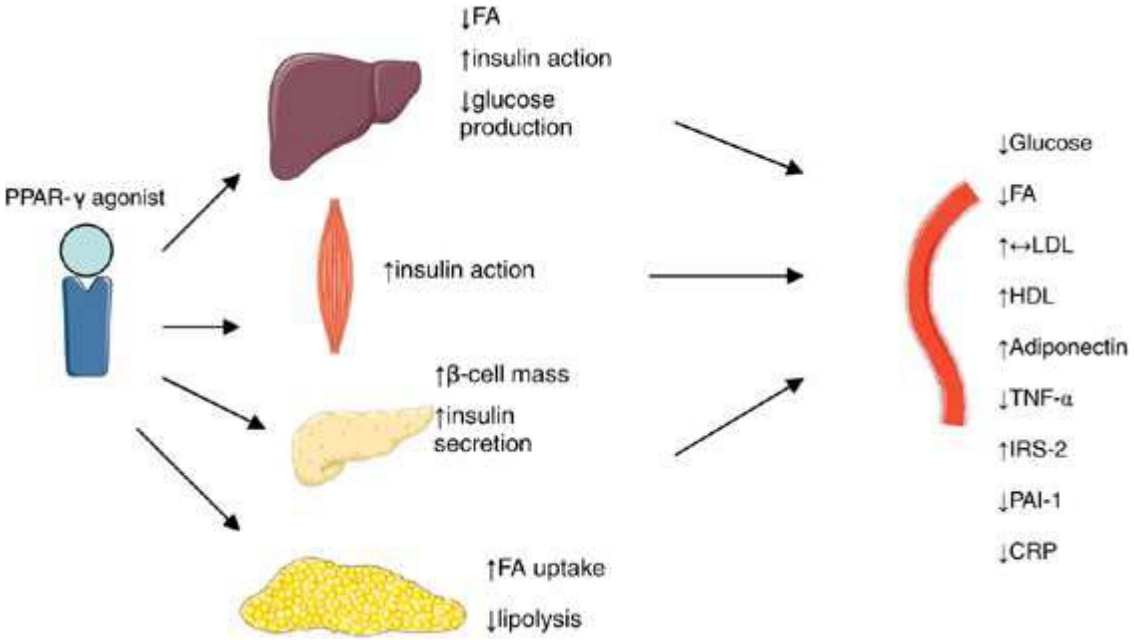
Metabolized with a long half life

Partial mimics of insulin actions, may bind insulin receptor or act through the peroxisomal proliferator activated receptor γ Ligands for PPAR-γ regulate adipocyte production,

secretion of fatty acids and glucose metabolism. Agents binding to PPAR-γ result in increased insulinsensitivity is adipocytes, hepatocytes and skeletalmuscle.

**Glitazones-insulin sensitizers**

Hyperglycemia, hypertriglyceridemia and elevated HbA1c are all improved. HDL levels are also elevated. Accumulation of subcutaneous fat occurs with these agents.




**Pharmacokinetics:** Both are extensively bound to albumin. Both undergo extensive P450 metabolism; metabolites are excreted in the urine the primary compound is excrete unchanged in the bile.

**Adverse Effects:**

Fatal hepatotoxicity has occurred with these agents; hepatic function must be monitored.

**Drug interaction:**

Oral contraceptives levels are decreased with concomitant administration These agents act as secretogogues.

**Mechanism:** These agents bind to ATP sensitive K+channels like sulfonylureas acting in a similar fashion to promote insulin secretion however their onset and duration of action are much shorter.

When used in combination with other oral agents they produce better control than any monotherapy.

**Pharmacokinetics:** These agents reach effective plasma levels when taken 10-30 minutes before meals.

These agents are metabolized to inactive products by CYP3A4 and excreted in bile.

Hypoglycemia is a great risk if meal is delayed

Very rapid onset of action and short duration

(TMAX = 1 hour, metabolized by liver T1/2 = 70 minutes)

No hypoglycemic metabolites. Less hypoglycemia than sulfonylureas

Improves postprandial glycemia (nateglinide)

Less effective in decreasing fasting blood glucose levels and HbA1C

**Demerits**

Fails to provides a stable 24 hours blood glucose control

Complicated dosage style (3-8 tablets/daily)

Headache, dyspepsia, arthralgia and weight gain

Repaglinide avoided in liver disease

**Drug interaction-**Drugs that inhibit CYP3A4 (ketoconazole, fluconazole, erythromycin, etc.) prolong their duration of effect.

Drugs that promote CYP3A4(barbiturates, carbamazepine and rifampin) decrease

their effectiveness.

The combination of gemfibrozil and repaglinide has been reported to cause severe hypoglycemia.

**Meglitinides- Repaglinide, Nateglinide**

These agents act as secretogogues.

**Mechanism:** These agents bind to ATP sensitive K+channels like sulfonylureas acting in a similar fashion to promote insulin secretion however their onset and duration of action are much shorter.

When used in combination with other oral agents they produce better control than any monotherapy.

**Pharmacokinetics:** These agents reach effective plasma levels when taken 10-30 minutes before meals.

These agents are metabolized to inactive products by CYP3A4 and excreted in bile.

Hypoglycemia is a great risk if meal is delayed

Very rapid onset of action and short duration (TMAX = 1 hour, metabolized by liver T1/2 = 70 minutes)

No hypoglycemic metabolites. Less hypoglycemia than sulfonylureas

Improves postprandial glycemia (nateglinide)

Less effective in decreasing fasting blood glucose levels and HbA1C

**Demerits**

Fails to provides a stable 24 hours blood glucose control

Complicated dosage style (3-8 tablets/daily)

**Adverse effects**

Headache, dyspepsia, arthralgia and weight gain

Repaglinide avoided in liver disease

**Drug interaction-**Drugs that inhibit CYP3A4 (ketoconazole, fluconazole, erythromycin, etc.) prolong their duration of effect. Drugs that promote CYP3A4 (barbiturates, carbamazepine and rifampin) decrease their effectiveness.

The combination of gemfibrozil and repaglinide has been reported to cause severe hypoglycemia.

**Incretin mimetics**

Incretins are naturally occurring hormones that the gut releases throughout the day; the level of active incretins increases significantly when food isingested.

Endogenous incretins GLP-1 (glucagon-like peptide1) and GIP (glucose-dependent insulinotropic peptide) facilitate the response of the pancreas and liver to glucose fluctuations through their action on pancreatic β cells and α cells.

The combination of increased insulin production and decreased glucagon secretion reduces hepatic glucose production when plasma glucose is elevated.

The physiologic activity of incretins is limited by the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades active incretins after their release.

The Incretin Effect Is Diminished in Type 2 Diabetes

Levels of GLP-1 are decreased.

The insulinotropic response to GIP is diminished but not absent.

Defective GLP-1 release and diminished response to GIP may be important factors in glycemic dysregulationin type 2 diabetes.

**EXENATIDE**- is a long acting analogue as it is resistant to DPP-IV degradation obtained from

Potent agonist at GLP1 receptor(incretin mimetic)

It is orally inactive and given sc 5-10μg BD

GLP1 receptor agonist-stimulates insulin secretion from β-cells of pancreas -decrease glucagon release

Slows gastric emptying slows rate of nutrition absorption

Decrease appetite by acting at the level of hypothalamus(induces weight loss)

It is used along with metformin or sulfonylureas in DM2

Long acting synthetic GLP1 analog

Long half life

DM type 2 for once daily injectable therapy

0.6mg dose titrated

ADR- headache, dairrhoea, antibody formation,pancreatitis

**α-glucosidases**

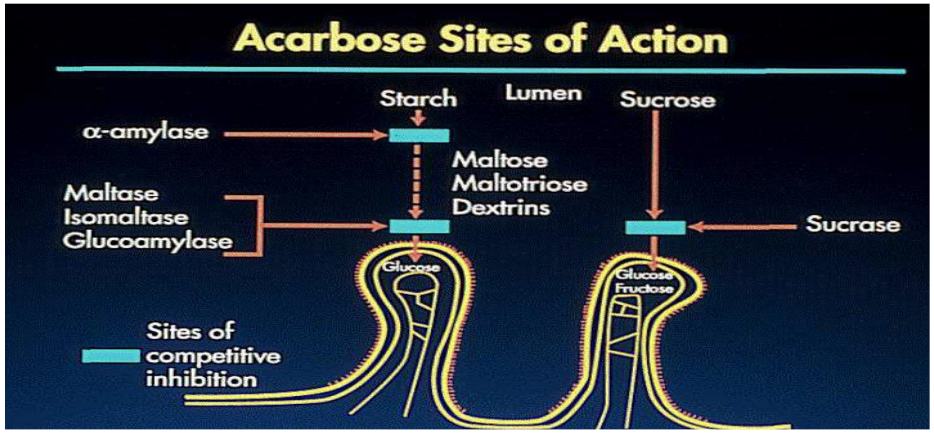
This enzyme hydrolyses oligosaccharides to monosaccharides which are then absorbed.

Acarbose also inhibits pancreatic amylase.

The normal post-prandial glucose rise is blunted, glucose levels rise modestly and remain slightly elevated for a prolonged period, less of an insulin response is required and hypoglycemia is avoided;

Use with other agents may result in hypoglycemia.

Sucrase is also inhibited by these drugs.




**α-glucosidase inhibitors**

Acarbose, Voglibose and miglitol

**Mechanism of action:**

These agents are taken at the beginning of a meal delay carbohydrate digestion by competitively

inhibiting α-glucosidase, a membrane bound enzyme of the intestinal brush border.

Lowers HbA1c levels, lowers body weight

Lowers Serum triglycerides

Meglitol can block isomaltase and β-glucosidases

**Pharmacokinetics:** Acarbose is poorly absorbed. Migitol is absorbed and excreted by the kidney. Both agents exert their effect in the intestinal lumen.

**Adverse Effects:**

Flatulence, diarrhea, cramping.Can cause hypoglycemia when used with sulfonylureas

Metformin bioavailability is severely decreased when used concomitantly. These agents should not be used in diabetics with intestinal pathology.

**Contraindication**

Inflammatory bowel disease and intestinal obstruction

**DPP-4 (Dipeptidyl peptidase inhibitors)**

Sitagliptin, Vildagliptin

Orally active selective inhibitors of DPP-4 enzyme that inactivates GLP-1

Results in increase of GLP-1 activity and prolonged action

Once daily dosage is effective

**MOA**-Increased insulin secretion

Decrease glucagon release

Delay gastric emptying

Suppress appetiteThey can be used along with metformin and sulfonylureas

**Adverse effects** – nasopharyngitis,concentration of substance P can increase GIT distress, diarrhoea, Sitagliptin therapy requires adequate levels of GLP-1, which may not be feasible in patients taking carbohydrate free diet

**Amylin mimetics**

Amylin is a neuroendocrine hormone peptide hormone co-secreted with insulin from pancreatic Bcells.

It inhibits glucagon secretion

Delays gastric emptying

Suppress appetite

**Pramlintide** is a modified amylin peptide which is

agonist at amylin receptor(GPCR)

It is used 15-60µg sc before meals adjunct to insulinin DM1

ADR- nausea, diarrhoea, headache

**SGLT2 inhibitors**

**Dapoglifozin, Serglifozin, Remoglifozin**

Inhibiting SGLT2 decrease the amount of glucose reabsorption from the proximal tubule and increases its excretion in urine

SGLT2 is exclusively distributed on the proximal tubule

of the kidney

SGLT2 inhibitors can cause weight loss, no hypoglycemia as they are excreting only the excess

glucose from the blood

Improve insulin resistance

Beneficial in patients having hypertension with diabetes

**Disadvantages**

Polyurea can cause polydipsia

Increased risk of urinary infection in glycosuria

Risk of Na+ loss, as sodium-glucose co-transporter has been inhibited

**Bile acid sequestrant**

**Cholesevelam hydrochloride**

Bile acid sequestrant and cholesterol lowering drug

Treatment of type 2 DM

Enterohepatic circulation decrease in FXR farsinoid X receptor, nuclear receptor with multiple effects on cholesterol, glucose, and bile acid metabolism

Lowers HbA1c levels

Side effects- GI complaints, constipation, flatulance

Drug interactions- impairs glyburide, fat soluble vitamins.

# SEX HORMONES AND ORAL CONTRACEPTIVES

**Female sex hormones**

The ovaries of sexually-mature females secrete:-a mixture of estrogens of which 17β-estradiol
is the most abundant (and most potent) andprogesterone.

**Estrogens**

Estrogen is a steroidal hormone most estrogen in the female is produced in the ovaries
by the theca interna and the granulosa cells of the follicles.
Estrogens include the natural hormones as well as semi-synthetic and synthetic agents
Estrogens are used as hormone-replacement therapy (menopause), in oncology and as contraceptives.
They antagonize the effects of the parathyroid hormone, minimizing the loss of calcium from bones and thus helping to keep bones strong.

**Natural estrogens**

**Estradiol** : It is rapidly oxidized in liver to *estrone*which is hydroxylated to form *estriol*. All three arefound in blood but estradiol is the most potent estrogen.– (transdermal: Climara, Alora, Vivelle, Vivelle-Dot,Estraderm, FemPatch) estrone:– Kestrone 5 (injectable only)

**Synthetic Estrogens- Ethinyl Estradiol, Mestranol**

Very commonly utilized in oral contraceptive products ethinyl estradiol is more potent than mestranol

**Estrogen receptors**

ERα and ERβ types are tissue-specific.
ERα (uterus, breast, hypothalamus and blood vessels)
ERβ (prostate gland in male, ovaries in females )

**ER Signalling Mechanisms**

1. Classical mechanism of ER action. Nuclear E2-ERs bind directly to EREs in target gene promoters.

2. ERE-independent genomic actions. Nuclear E2-ER complexes are tethered through protein-protein interactions to a transcription factor complex (TF) that contacts the target gene promoter.

3. Ligand-independent genomic actions. Growth factors (GF) activate protein-kinase cascades, leading to phosphorylation (P) and activation of nuclear ERs at EREs.

4. Nongenomic actions. Membrane E2-ER complexes activate protein-kinase cascades, leading to altered functions of proteins in the cytoplasm, *e.g.* activation of eNOS, or to regulation of gene expression through phosphorylation (P) and activation of a TF.

**Actions of estrogens**

• Development and maintenance of internal (fallopian tubes, uterus, vagina), and external genitalia

• Skin: increase in vascularization, developmentof soft, textured and smooth skin

• Bone: increase osteoblastic activity

• Electrolytes: retention of na+, cl- and water by the kidney

• Cholesterol: hypocholesterolemic effect

**ANTIESTROGEN AND SERMS**

Selective Estrogen Receptor Modulators (SERMs). Are mixed agonists/antagonists.

• Tamoxifen – an ER antagonist in breast, but a partial agonist in endometrium and bone.

• Raloxifene – ER agonist in bone, but an antagonist in both breast and endometrium.

• Clomifene – used to induce ovulation. Is an ER antagonist in hypothalamus and ant pit, but a partial agonist in ovaries.

**Progesterone**

Progesterone is also a steroid. A natural hormone secreted by the corpus luteum and the placenta.

Intestinal absorption is quite erratic; must be micronized for most effective absoption.

Important in menstrual cycle and pregnancy.

Used for hormonal contraception and for producing longterm ovarian suppression for other purposes (*e.g.*, dysmenorrhea, endometriosis, hirsutism and bleeding disorders) when estrogens are contra-indicated.

**PROGESTINS**

Drugs which mimic the action of progesterone complement the action of estrogen on primary and secondary sex characteristics many are used as oral contraceptives: norgestrel, levonorgestrel, norethindrone, norethindrone acetate, norethynodrel, ethynodiol diacetate, desogestrel and norgestimate

**Natural progestin**

Progesterone, a 21 carbon steroid is the naturalprogestin and derived from cholesterol.

It is secreted in the later half of menstrual cycle under the influence of LH.

**Synthetic progestin**

A number of synthetic progestin with high oral activity have been produced.

These are either progesterone derivatives or 19- nortestosterone derivatives.

Progesterone derivatives :- medroxyprogesterone acetate, megestrol acetate, dydrogesterone,

nomegestrol acetate.

19-nortestosterone derivatives:- norethindron, lynestrenol, allylestrenol, desogestrel, gestodene,

nordestimate.

**Action of progestin**

• Uterus:- progesterone bring about secratory changes in the estrogen primed endometrium and increased glandular secretion while epithelial proliferation is suppressed. It also decreases sensitivity of myometrium to oxytocin.

• Cervix:- progesterone converts the watery cervical secretion induced by estrogen to viscid, scanty and cellular secretion which is hostile to sperm penetration.

• Proliferation of acini in mammary glands.

• CNS:- high circulating concentration of progesterone (during pregnancy) appears to have a sedative effect.

• Slight increase in body temp.

• Weak inhibitor of Gn secretion from pituitary.

**How estrogens and progesterone achieve their effects**

• Steroids like estrogens and progesterone are small, hydrophobic molecules that are transported in the blood bound to a serum globulin.

• In "target" cells, i.e., cells that change their gene expression in response to the hormone, they bind to receptor proteins located in the cytoplasm and/or nucleus.

• The hormone-receptor complex enters the nucleus (if it formed in the cytoplasm) and binds to specific sequences of DNA, called the estrogen (or progesterone) response elements.

Response elements are located in the promoters of genes.

• The hormone-receptor complex acts as a transcription factor which turns on (sometimes off) transcription of those genes.

• Gene expression in the cell produces the response. **Regulation of Estrogen and Progesterone**

• The synthesis and secretion of estrogens is stimulated by follicle-stimulating hormone (FSH), which is, in turn, controlled by the hypothalamic gonadotropin releasing hormone (GnRH).

• Hypothalamus → GnRH → Pituitary → FSH/LH →

Follicle/ Corpus luteum → Estrogens/ progesterone

**Antiprogestin**

**Mifepristone:-**

• It is 19-norsteroid with potent competitive antiprogesterone.

• Given during the follicular phase slowing of follicular development / failure of ovulation.

• During luteal phase prevent progesterone secretion.

• Orally active.

**Uses:-**

• Termination of pregnancy:- up to 7 weeks 600 mg single oral dose.

• Postcortical contraception:-within 72 hr of intercourse.

• Indication of labour:- by blocking relaxant action of progesterone on uterus of late pregnancy.

• Cushiong's syndrome:- due to glucocorticoid receptor blocking property.

# OXYTOCIN AND OTHER STIMULANTS AND RELAXANTS

**UTERINE STIMULANTS (Oxytocics, Abortifacients)**

Drugs Used For Induction and Augmentation of Labour

Posterior Pitutary Hormone: Oxytocin, Desaminooxytocin

Prostaglandins: PGE2, PGE1, PGF2α , 15-methyl

PGF2α(Carboprost), Misoprostol (Methyl ester of PGE1)

Ergot Alkaloids: Ergometrine, Methylergometrine

Miscellaneous: Ethacridine, Quinine

Anti Progestin: Mifepristone

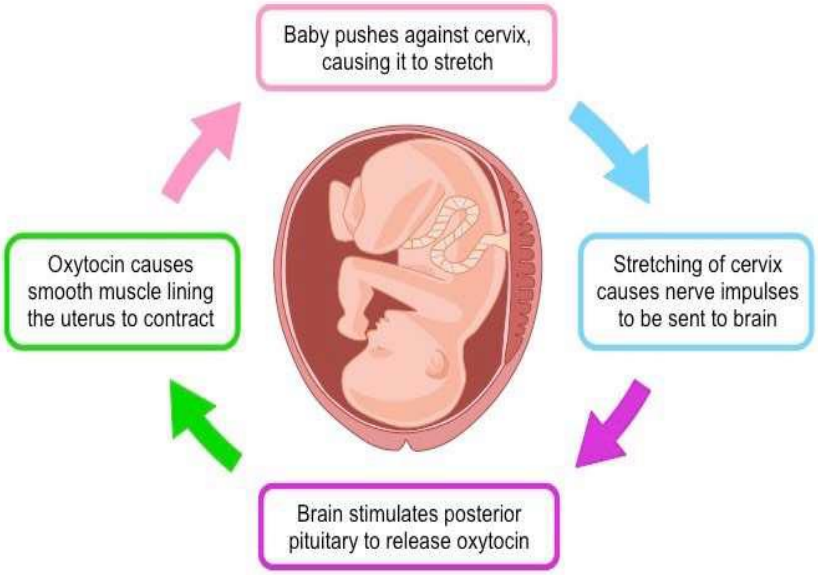
**OXYTOCIN**

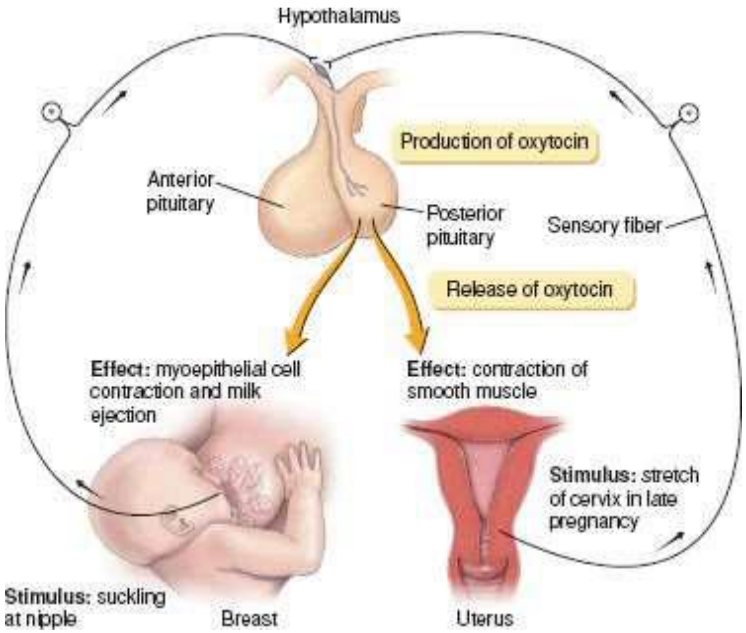
1. Effects on Uterus: Increases force and frequency of uterine contraction

2. Effects on Breast: Milk ejection

3. Cardiovascular System (CVS): fall in blood pressure, reflex tachycardia

4. Kidney: ADH like action at high doses





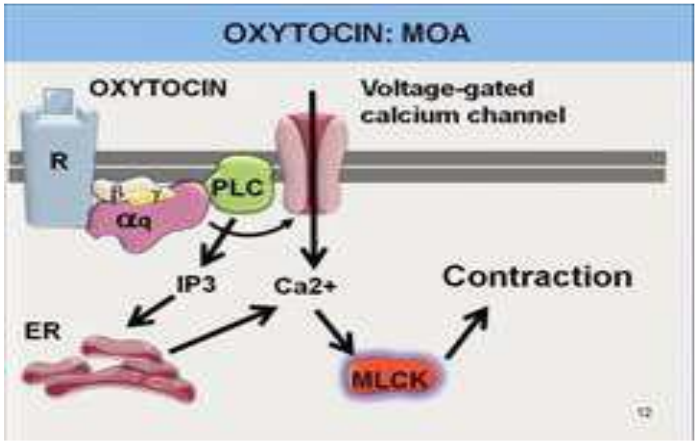

**Mechanism of Action**: Oxytocin action is mediated through specific G-protein coupled oxytocin receptors. When these receptors are activated, theymediate response through:

Depolarization of muscle fibres and influx of Ca++ ions (main mechanism)

Through phosphoinsitide hydrolysis and IP3mediated intracellular release of Ca++ ions.

Number of oxytocin receptors increases markedlyduring later part of pregnancy

Also increases Prostaglandin (PG) synthesis andrelease by the endometrium




**Uses:**

• Drug of Choice

• Induction of Labour (slow i.v. infusion 5IU in 500 mlglucose or NS; 10milli IU/mL: 0.2-2.0 mL/min)

• Uterine Inertia

• Postpartum Haemorrhage

• Breast Engorgement (inefficient milk ejection reflex; intra-nasally)

• Oxytocin Challenge Test (risky and rarely performed)

**Side Effects:**

• Injudicious use: maternal and foetal soft tissue injury, ruptured uterus, foetal asphyxia/death

• Water intoxication

**Prostaglandins**

• Local Hormones, derived from breakdown of membrane phospholipid (yielding arachidonic acid)

• **PGE2 and PGF2α**: commonly used clinically

• **Dinoprostone (PGE2):** cervical maturation/ripening  5 times potent than and less toxic than PGF2α; costly

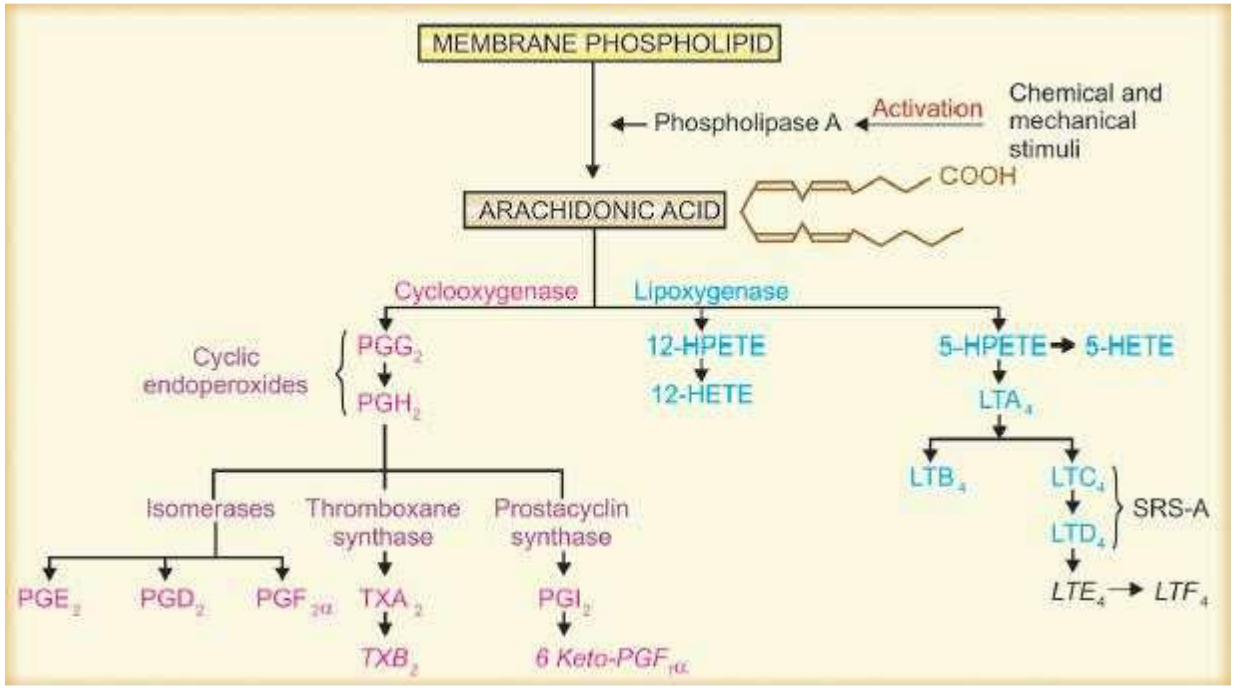
• **Dinoprost tromethammine (PGF2α):** myometrialcontractility

• **Promotes myometrial contraction irrespective of duration of gestation**

**Mechanism of Action:**

• Change in myometrial cell membrane permeability and alteration of membrane bound Ca++.

• Also sensitizes uterus to oxytocin




**Uses:**

• **Misoprostol/PGE1**: induction of abortion/labour; cervical ripening

• Induction of labour (poor pre-induction cervical score as in Intrauterine Fetal Death, shorter period of gestation, primigravida: PGE1)
• Acceleration of labour
• Cervical ripening for induction of labour/abortion
• Management of atonic postpartum haemorrhage
• Medical management of tubal ectopic pregnancy

**Side effects:**

• On systemic use:
• Nausea, vomiting, diarrhoea, pyrexia, bronchospasm
• Cervical laceration when used as an abortifacient
• Tachysystole of uterus during induction
• Foetal Distress
• Rupture of uterus: Rare
• Should not be used in patients with previous history of Caesarean Section

**Ergot Alkaloids**

**Ergometrine and Methylergometrine**

**Uterus**: Force, frequency and duration of uterine contraction increased

**Mechanism of action**: partial agonistic action on 5-HT2 and alpha adrenergic receptors

**CVS**: Weak vasoconstrictors, raise blood pressure

**Gastrointestinal Tract**: Increased peristalsis

**Uses:**

• Control and Prevent Postpartum Haemorrhage

• After Caesarean Section

• To ensure normal involution

**Side Effects:** Nausea, Vomiting, Rise in blood pressure,

Decrease milk secretion if used in high dose for many days

**Contraindication:**

• Vascular disease

• Presence of sepsis

• Liver and Kidney disease

## UTERINE RELAXANTS (TOCOLYTICS)

• These are drugs which decrease uterine motility.

• Delay or postpone labour

• Arrest threatened abortion

• Used in Dysmenorrhoea

## UTERINE RELAXANTS (TOCOLYTICS)

• Adrenergic (β2) agonist: **Ritodrine, Isoxsuprine, T Terbutaline, Salbutamol**

• Calcium channel blockers: **Nifedipine**

• Oxytocin Antagonist: **Atosiban, Magnesium sulfate (MgSO4)**

• Miscellaneous: **Ethyl alcohol, nitrates**, **progesterone, general anaesthetics, indomethacin, Halothane,Ritodrine**

**Mechanism of action**: Ritodrine acts as selective β2 agonist on uterus & causes uterine relaxation.

**Use:**

Supress premature labour

Delay delivery

Started as 50 μg/min i.v. infusion, increased gradually

**Side Effects:** hypotension, tachycardia, arrhythmia, pulmonary edema, metabolic complications (hyperglycaemia, hyperinsulinemia, hypokalemia), anexiety, restlessness, headache, foetal pulmonary edema

**Contraindication:** Mother having diabetes or heart disease, or receiving β blockers or steroids

**Salbutamol** and **Terbutaline** are alternatives to Ritodrine.

• **Isoxsuprine** is used to stop threatened abortion.

**Nifedipine**

**Mechanism of Action**: Nifedipine is L-type **Ca++** Channel Blocker. It Reduces the tone of myometrium and opposes contraction. It has prominent smooth muscle relaxant action.

**Uses**: Postpone labour

Oral nifedipine 10 mg repeated once or twice after 20–30 min, followed by 10 mg 6 hourly has been used.

**Side Effects:**

• Maternal - Tachycardia, Hypotension

• Foetal – Foetal Hypoxia due to placental perfusion

**Other Tocolytics**

**Atosiban**

Mechanism of Action: Atosiban acts as antagonist at the oxytocin receptors.

**Magnesium sulfate**

Mechanism of Action: Acts as tocolytics by competiting with Ca++ ions for entry into myometrium through both voltage gated and ligand gated Ca++ channels.

A/E: may increase perinatal mortality

## PHARM D II YEARS PHARMACOLOGY-I (Uncovered Portion)

**SUBJECT CODE-2.4**

### PHARMACOLOGY OF DRUGS ACTING ON RESPIRATORY TRACT

The respiratory tract may be divided into upper and lower portions. The upper portion consists of the nose, sinuses, oropharynx, and larynx. The lower portion comprises the trachea and lungs with their associated airways. Disorders and drug therapy of the upper respiratory system differ from those of the lower respiratory tract.

Disorders of the upper respiratory tract are those associated with infections (most commonly uncomplicated viral rhinotracheitis) and seasonal allergies (allergic rhinoconjunctivitis and rhinotracheitis). For the most part, these dysfunctions are self-limiting, and the drug classes used to treat them may be obtained without a prescription (over-the-counter, OTC). Disorders of the lower respiratory tract may be broadly classified as parenchymal infections (e.g., pneumonia) and obstructive airway (bronchial) conditions. In general, the latter disorders limit expiratory airflow. They are divided into bronchial asthma, which is characterized by acute episodes, and chronic obstructive airway disorders. Chronic obstructive airway disorders are further subdivided into chronic bronchitis, emphysema, bronchiectasis, and cystic fibrosis. The treatment of infections in all parts of the respiratory tract.

Manifestations of upper respiratory tract dysfunctions include mucous and watery discharges and vasodilation, mediated in part through histamine and other substances released from mast cells. Mast cells are important “gate-keeper” cells that are concentrated in the skin and other tissues near external body surfaces.

Histamine is produced from the amino acid histidine and is stored in vesicles. The four histamine receptor subtypes characterized to date are designated $H_1$ to $H_4$. $H_1$ receptors mediate mucous discharge and vasodilation, $H_2$ receptors are important in gastric acid secretion $H_3$ receptors are found in the central nervous system (CNS), and $H_4$ receptors may modulate inflammatory reactions by chemotactic effects on eosinophils and mast cells. Secretion of histamine and other mast cell mediators causes vasodilation of the nasal vasculature, leading to the nasal congestion and “runny nose” commonly associated with seasonal allergies and viral