# PHARMACOLOGY II

## Menoufia University, Faculty of Pharmacy

## Course Specifications

| | |
|---|---|
| **Program on which the course is given** | **BSc in pharmaceutical sciences** |
| **Major or minor element of program** | **Major** |
| **Department offering the course** | **Pharmacology & toxicology** |
| **Academic Year / Level** | **Third year, Second semester** |

**A- Basic Information**

| | |
|---|---|
| **Title: pharmacology 1** | **Code: 4137** |
| **Credit Hours :4** | **Lecture: 3** |
| **Tutorial:** | **Practical: 2** |
| **Total contact hours:5** | |

**B- Professional Information**

## 1. Overall aims of the course

**Upon successful completion of this course, the students should be able to:**

- Understand the mechanism of action, uses and side effects of different drugs affecting central nervous system, respiratory system, gastrointestinal system and blood.
- Identify drugs affecting central nervous system in laboratory animals.

## 2. Intended learning outcomes of the course (ILOs)

**a- Knowledge and understanding:**

- a1- Describe the principles of drug affecting central nervous system, respiratory system, gastrointestinal system and blood.
- a2- Describe pharmacological action of drug affecting central nervous system, respiratory system, gastrointestinal system and blood.
- a3- List the therapeutic uses, adverse effects and dosage of drugs from different pharmacological classes.
- a4- Describe disease state and management of it.
- a5- Describe action of medicine within living system.

# PHARMACOLOGY II

**Upon successful completion of this course, the student should be able to efficiently demonstrate the essential knowledge and understanding of:**

**b- Intellectual skills**

- b1- Recognize the mechanism of action of different drugs.
- b2- comprehend drug affects at all levels of biological organization
  - b3- Apply the basics of pharmacology and therapeutics to prepare a list of therapeutic drugs for the treatment of patients**.**
  - b4- predict all possible drug interaction.
  - b5- Assess any adverse reaction and contra-indication of different drugs.

**c- Professional and practical skills**

- c1- Use therapeutic agents in a rational & responsible manner in treatment of patients.
- c2- Identify different drug classes.
- c3- Select the drug of choice in different diseases.
- c4- Assess the mechanism and pharmacological actions of drugs
- c5- Advise the patient about dosage, food regimen, side effects of the drugs and drug interaction.
- c6- Design the dosing regimen for patients based on the conditions of each individual patient.
- C7- Employ library search, retrieval of information, and interpretation of experimental results.

**d- General and transferable skills**

- d1- Communicate in the health care team to avoid the adverse effects and interactions due to the use of drugs.
- d2- Use information to recognize the basic pharmacokinetic and pharmacodynamic principles of drugs.
- d3- Develop skills needed to acquire and evaluate therapeutically relevant details of pharmacological agents in medical & pharmacy practice.
- d 4- Retrieve information from a variety of sources, including libraries, databases and internet.
- d 5- work independently or as a part of team in different pharmaceutical fields.
- d6- Demonstrate oral and written communication skills.
- d7- demonstrate creativity and time management skills.
- d 8- Implementing presentation, writing reports and interviewing skills.

# PHARMACOLOGY II

## 3. Contents

| Week | Topic | Total contact hours | Lecture | practical |
|---|---|---|---|---|
| **1** | Central neurotransmitters | **4** | **2** | **2** |
| **2** | Pharmacological actions of drugs acting on central nervous system | **4** | **2** | **2** |
| **3** | Pharmacological actions of drugs acting on central nervous system(cont.) | **4** | **2** | **2** |
| **4** | Pharmacological actions of drugs acting on central nervous system (cont.) | **4** | **2** | **2** |
| **5** | Pharmacological actions of drugs acting on central nervous system(cont.) | **4** | **2** | **2** |
| **6** | Pharmacological actions of drugs acting on central nervous system (cont.) | **4** | **2** | **2** |
| **7** | **Mid-term exam** | | | |
| **8** | Pharmacological actions of drugs acting on central nervous system (cont.) | **4** | **2** | **2** |
| **9** | Pharmacological actions of drugs acting on central nervous system (cont.) | **4** | **2** | **2** |
| **10** | Autacoids | **4** | **2** | **2** |
| **11** | Pharmacological actions of drugs acting on non- steroidal anti- inflammatory drugs | **4** | **2** | **2** |
| **12** | Pharmacological actions of drugs acting on gastrointestinal system | **4** | **2** | **2** |
| **13** | Pharmacological actions of drugs acting on gastrointestinal system (cont.) | **4** | **2** | **2** |
| **14** | Pharmacological actions of drugs acting on respiratory system. | **2** | **2** | Practical exam |
| **15** | Pharmacological actions of drugs acting on blood disorders. | **2** | **2** | Practical exam |

# PHARMACOLOGY II

## Teaching and learning methods

| | |
|---|---|
| **a. Lectures** | **(√ )** |
| **b. Practical training / laboratory** | **(√ )** |
| **c. Seminar / Workshop** | **(√ )** |
| **d. Class Activity** | **(√ )** |

## Student assessment methods

| | | |
|---|---|---|
| **Written mid-term exam** | **To assess** | **The ability of students to follow-up the course subjects.** |
| **Practical exam** | **To assess** | **The gained experience in laboratory methods and techniques.** |
| **Oral exam** | **To assess** | **The ability of students in expressing and presenting their knowledge clearly and in systematic approach.** |
| **Written final exam** | **To assess** | **The overall outcomes.** |

## Assessment schedule

| | | | |
|---|---|---|---|
| **Assessment 1** | **Mid-term exam** | **Week** | **7** |
| **Assessment 2** | **Practical exam** | **Week** | **14,15** |
| **Assessment 3** | **Final exam** | **Week** | **16,17** |
| **Assessment 4** | **Oral** | **Week** | **16,17** |

## Weighting or assessments

| | | |
|---|---|---|
| **Mid-Term Examination** | **10** | **%** |
| **Final-Term Examination** | **50** | **%** |
| **Oral Examination** | **20** | **%** |
| **Practical Examination** | **15** | **%** |
| **Semester Work** | **5** | **%** |
| **Other types of assessment** | | **%** |
| **Total** | **100** | **%** |

## List of references

**Course notes**

- Notes on pharmacology 3 rd year students.

- Practical notes on pharmacology 3 rd year students.

**Essential books (text books)**

-The Pharmacological Basis of Therapeutics (2008). Goodman & Gilman's. 12 th edition. The McGraw-Hill Companies

**Recommended books**

- Basic & clinical pharmacology (2018). G. Katzung. 14th ed. Lavoisier S.A.S.

-A. Harvey and, C.Champe-Lippincott Modern Pharmacology (2019).(illustrated pharmacology Review).7 th ed. Lippincott Denise R.Williams & Wilkins.

**Websites**

www. Medscape.com

www. pubmed.com

## Facilities required for teaching and learning

**-Class rooms.**

**-Laboratory facilities. –Library.**

**- Projectors (Overhead, video projector)**

**-Computers. –Internet.**

## Course coordinator:

**Prof. Ahmed Mansour, ph.D.**

**Dr. Shady N. Allam, ph.D.**

**Dr. Marwa M. Mafouz, ph.D.**

**Date: 8 / 2 /2020**

# Neurotransmission in the CNS

The basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS) described in first term. For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic cleft to bind to specific receptors on the postsynaptic neuron.

**several major differences exist between neurons in the peripheral ANS and those in the CNS:**

- The circuitry of the CNS is more complex than that of the ANS.
- The number of synapses in the CNS is far greater.
- The CNS, unlike the peripheral ANS, contains networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission.
- The CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

**Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit.**

## Excitatory pathways

Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following:

1) Stimulation of an excitatory neuron causes the release of neurotransmitters, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium ($Na^+$) ions.

2) The influx of $Na^+$ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing.
3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. generating an all-or-none action potential.

## Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following:

1) Stimulation of inhibitory neurons releases neurotransmitters, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium ($K^+$) and chloride ($Cl^-$).

2) The influx of $Cl^-$ and efflux of $K^+$ cause a weak hyperpolarization, or IPSP, that diminishes the generation of action potentials.

Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons.

# PHARMACOLOGY II

**Summary of neurotransmitter pharmacology in the central nervous system.**

| **Transmitter** | **receptor** | **agonist** | **antagonist** | **mechanism** |
|---|---|---|---|---|
| Acetylcholine | Muscarinic (M)<br>Nicotinic (N) | pilocarpine | Atropine | Inhibitory<br>Excitatory |
| Dopamine | Dopaminergic $D_1$ - $D_2$ | Bromocriptine | Metoclopramide | Inhibitory |
| GABA | $GABA_A$ - $GABA_B$ | baclofen | picrotoxin | Inhibitory |
| Glutamate | N-Methyl-d-aspartate (NMDA) | NMDA | dizocilpine | Excitatory |
| Glycine | Taurine | β-alanine | Strychnine | Inhibitory |
| Serotonin | 5-Hydroxytryptamine (5-HT) | LSD | ondansetron | Inhibitory<br>Excitatory |
| Norepinephrine | $\alpha_1$- $\alpha_2$ – $\beta_1$ - $\beta_2$ | phenylephrine | Prazosin | Excitatory<br>Inhibitory |
| Histamine | H1 - H2 - H3 | histamine | Ranitidine | Excitatory<br>Inhibitory |
| Opioid | Mu – delta – kappa | enkephalin | Naloxone | Inhibitory |
| Endocannabinoids | CB1 cannabinoid | anandamide | Rimonabant | Inhibitory |

# Functional aspects of neurotransmitters:

## Dopamine:

1- Deficiency of dopamine lead to parkinsonism's disease.
2- Dopaminergic hyperactivity associated with schizophrenia.
3- Inhibition of dopamine associated with increase in prolactin secretion.
4- Dopamine antagonists have anti-emetic activity.

## Serotonin:

1- 5-HT pathways are involved in hallucinations.
2- 5-HT pathways are involved in control of mood, anxiety and wakefulness.
3- 5-HT2A antagonist used in treatment of schizophrenia.
4- 5-HT3 antagonist used as antiemetic especially in chemotherapy.

## Gamma- Aminobutyric Acid (GABA):

1- Potentiate effect of GABA producing sedative effects as benzodiazepines.
2- Non-competitive GABA antagonist as picrotoxin which acts as a stimulant and convulsant.

## Glycine:

1- Glycine blockers as Strychnine, which is a potent spinal cord convulsant and has been used in some rat poisons.

## Glutamate:

1- Glutamate is thought to play role in learning and memory.

## Acetylcholine:

1- Cholinergic pathways are related to learning and motor control.
2- Involvement of cholinergic neurons in neurodegenerative disorders as parkinsonism and dementia as (Alzheimer's disease).

# Neurodegenerative Diseases

Neurodegenerative diseases of the CNS include Parkinson disease, Alzheimer's disease and MS. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

# Parkinsonism

It is a progressive neurodegenerative disease characterized by muscular rigidity, bradykinesia, dyskinesia, tremor, mask like facies postural and gait abnormalities.

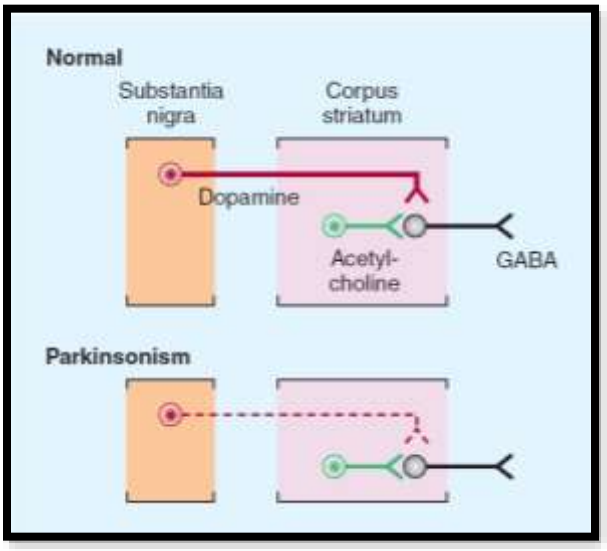
Idiopathic Parkinsonism is known as Parkinson's disease. Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.

## Etiology

In basal ganglia, the output neurons are controlled by dopamine and acetylcholine. Due to their opposite action, a balance is required between these two neurotransmitters for proper functioning of basal ganglia.

The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the neostriatum. The dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

The neostriatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini. In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of both areas.




Major pathology in Parkinsonism is decrease in nigrostriatal dopaminergic neurons, (with appearance of **Lewy bodies**) thus the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction, or a relative overactivity, of acetylcholine by the stimulatory neurons. consequently, cholinergic activity becomes dominant. This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.

**Note:**

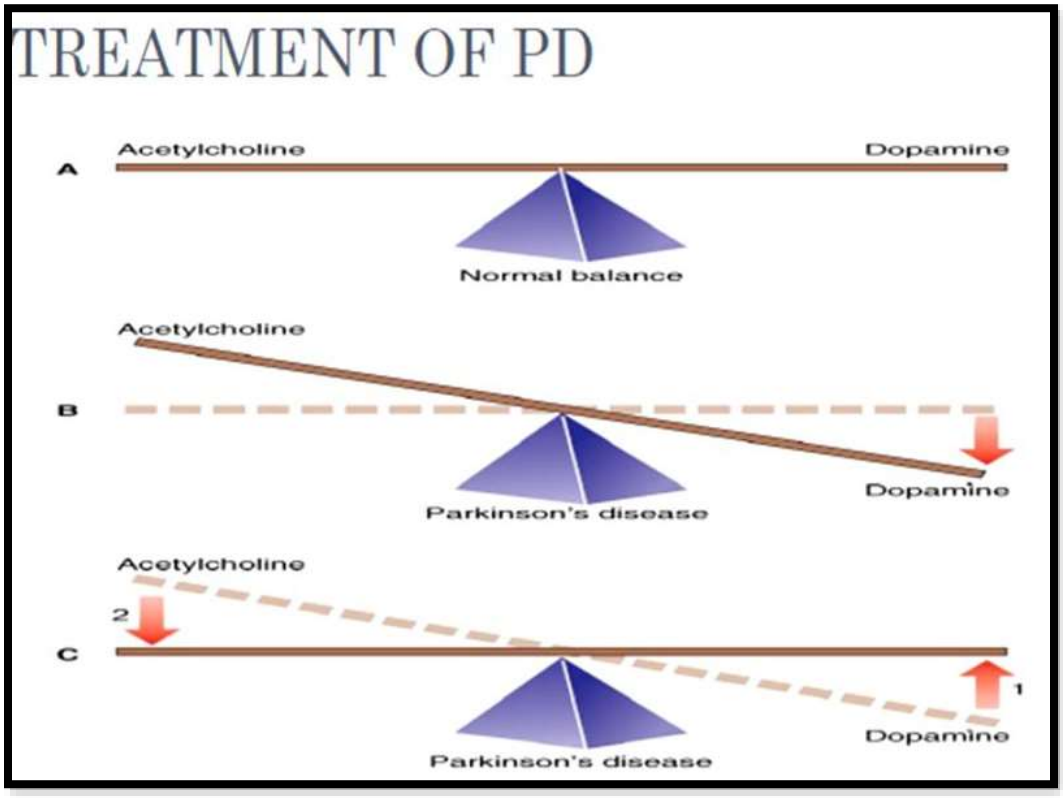
Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (pseudoparkinsonism). These drugs should be used with caution in patients with Parkinson disease.

**Treatment Strategy**

Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing

the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

Thus, **two major strategies** for the treatment of Parkinsonism are to increase brain dopaminergic activity or to decrease central cholinergic activity.




## 1- Drugs Increasing Brain Dopaminergic Activity

Brain dopaminergic activity can be increased by precursors of dopamine, inhibitors of dopamine metabolism, dopamine receptor agonists and drugs increasing presynaptic release of dopamine.

### A. Dopamine Precursors

Dopamine itself cannot cross blood brain barrier (BBB) but its precursor levo-dopa can cross BBB. Levo-dopa is metabolized by **dopa decarboxylase**. This conversion occurs

both in periphery as well as in the brain. Peripheral conversion is undesirable due to two reasons:

• It forms dopamine peripherally that cannot cross BBB, therefore only about 1-3% of l-dopa can reach its target site (brain).

• Peripherally formed dopamine will result in adverse effects like postural hypotension.

**Therefore**, levo-dopa is always given in combination with peripheral dopa decarboxylase inhibitors like carbidopa or benserazide.

**N.B.**

- levodopa–carbidopa substantially reduces the severity of symptoms for the first few years of treatment. Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.
- Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS.

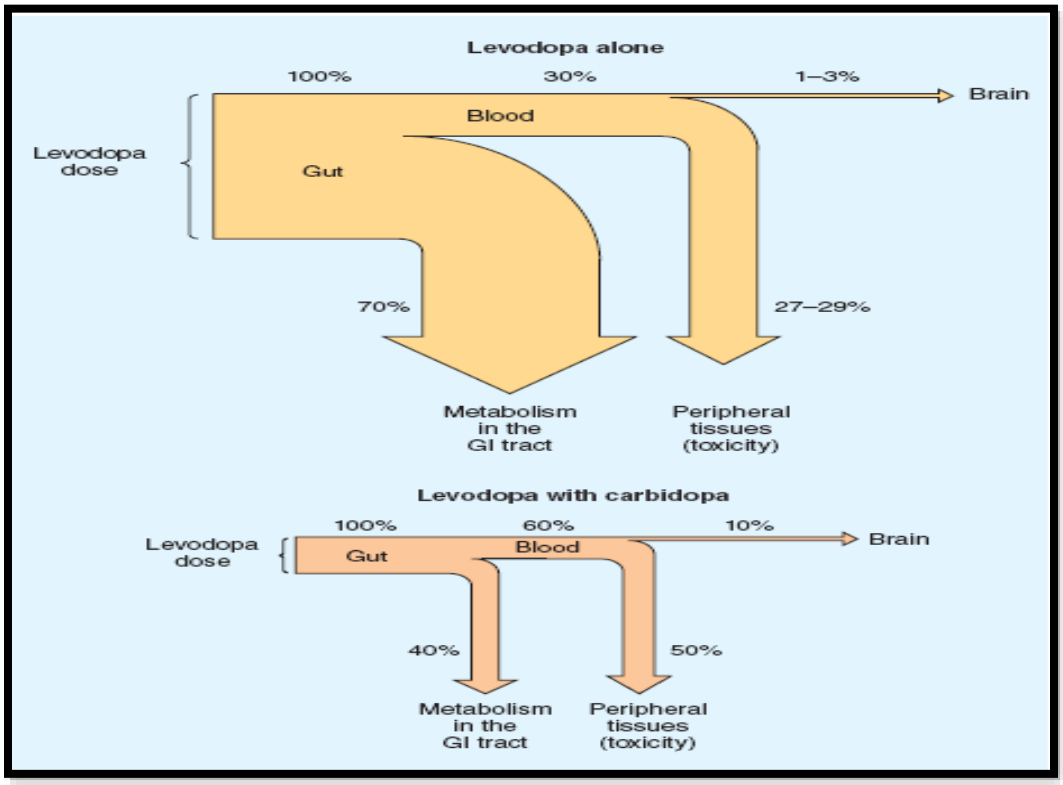
**Thus,** levodopa should be taken on an empty stomach, typically 30 minutes before a meal.

**Remember:**

**Addition of carbidopa to I-dopa therapy**
• Increase entry of L-dopa in brain.
• Decrease adverse effects due to peripherally formed dopamine

**Adverse Effects**

- Peripherally formed dopamine can lead to **postural hypotension** and **arrhythmias**.
- **Nausea and vomiting** occur commonly due to CTZ stimulation by dopamine (Domperidone but not metoclopramide can be used for the treatment of this vomiting).




On long term use "**wearing off**" effect or "**on-off phenomenon"** can result.

**'On'** means patient is having no symptoms of Parkinsonism (but abnormal movements are present) and **'off'** means patient has full symptoms of Parkinsonism (like no treatment is given). This effect is **due to short half life** (1-2 hrs.) of l-dopa and is reduced by carbidopa. **Long acting dopamine agonists show little tendency to cause on-off phenomenon**.

L-dopa especially in elderly can result in **hallucinations, vivid dreams, sleep disturbances** and even **psychosis *(thus C/I in psychosis).*** These behavioral disturbances are not prevented by carbidopa. Antipsychotic drugs are generally contraindicated in Parkinson disease, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics, such as quetiapine or clozapine, are sometimes used to treat levodopa-induced psychotic symptoms.

• It may even cause **mydriasis** ***(So, it is C/I in…….).***

• Vitamin complexes containing **pyridoxine decrease the effectiveness** of levodopa (pyridoxine is a cofactor of dopa decarboxylase and increases the formation of dopamine in the periphery. This results in decrease in l-dopa's central penetration).

• Abrupt withdrawal of levodopa may precipitate neurolept malignant syndrome.

• Levo-dopa should be given **carefully** in patients with **active peptic ulcer** (increased risk of bleeding) and **malignant melanoma** (levo-dopa is a precursor of melanin) so, saliva and urine may turn brownish color.

Concomitant administration of levodopa and nonselective monoamine oxidase inhibitors (MAOIs), such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production.

**Conclusion**

| **Adverse Effect** | **Mechanism** | **Remarks** |
|---|---|---|
| Nausea, Vomiting | CTZ stimulation | Reduced by carbidopa |
| Postural hypotension | D1 stimulation | Reduced by carbidopa |
| Arrhythmias | B1 stimulation | Reduced by carbidopa |
| Hypertension | α1 stimulation | Reduced by carbidopa |
| Mydriasis | α1 stimulation | Reduced by carbidopa |
| Psychotic symptoms | ↑ Activity of DA in Brain | Not reduced by carbidopa |

## B. Drugs Inhibiting Metabolism of Dopamine

Dopamine is metabolized by MAO (mono amine oxidase) and COMT (catechol-o-methyl transferase).

### (i) COMT Inhibitors

Inhibition of dopa decarboxylase by carbidopa diverts the metabolism of l-dopa to methylation by COMT, this enzyme metabolizes dopamine as well as l-dopa to form 3-O-methyldopa.

- **Tolcapone and entacapone** act by inhibiting COMT leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.
- Both of these agents reduce the symptoms of **"wearing-off"** phenomena seen in patients on levodopa–carbidopa.
- **Tolcapone** inhibits COMT in periphery as well as brain whereas **entacapone** acts only in the periphery. **Tolcapone** is more potent and longer acting than entacapone but is not preferred because of **hepatotoxic** effects.

**To**xic to
**L**iver

**Tol**capone

### (ii) MAO -B Inhibitors

**Selegiline and rasagiline** are irreversible and **selective inhibitors of MAO-B**. These drugs can be given in combination with levo-dopa + carbidopa to decrease the dose of levo-dopa. At normal doses these inhibit only MAO-B and thus have no interaction with cheese or tricyclic antidepressants. However, at high doses, they also inhibit MAO-A and can lead to hypertensive crisis (**cheese reaction**) with tyramine containing foods and serotonin syndrome with TCAs. Rasagiline has ***five times the potency*** of selegiline, these drugs are thought to **reduce the disease progression**.

**N.B.**

Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon

**C. Dopamine Agonists**

These drugs directly activate $D_2$ receptors and can be used as monotherapy in Parkinsonism:

1- **Ergot derived** dopamine agonists include **bromocriptine and pergolide**. These drugs are **short acting** and can cause digital **vasosopasm** (leading to gangrene). These drugs can also result in pleural, peritoneal and cardiac fibrosis. Ergot alkaloids require slow upward titration of dose.

2- Newer **non-ergot dopamine agonists**; **pramipexole, ropinirole, Apomorphine** and **rotigotine** do not have these limitations (these are **long acting** and **do not cause gangrene**). All four drugs can cause confusion and hallucinations. These agents are now the **first-choice drugs for Parkinsonism** (preferred over levo-dopa).

- **Ropinirole** has also been approved for **restless leg syndrome** and metabolized by liver.

> **restless leg syndrome (RLS)**
> a long-term disorder that causes a strong urge to move

- **Pramipexole** is excreted mainly by kidney and dosage adjustments are needed in renal dysfunction.

**N.B:**

Rare but important adverse effect of these drugs is **excessive day time sleepiness**.

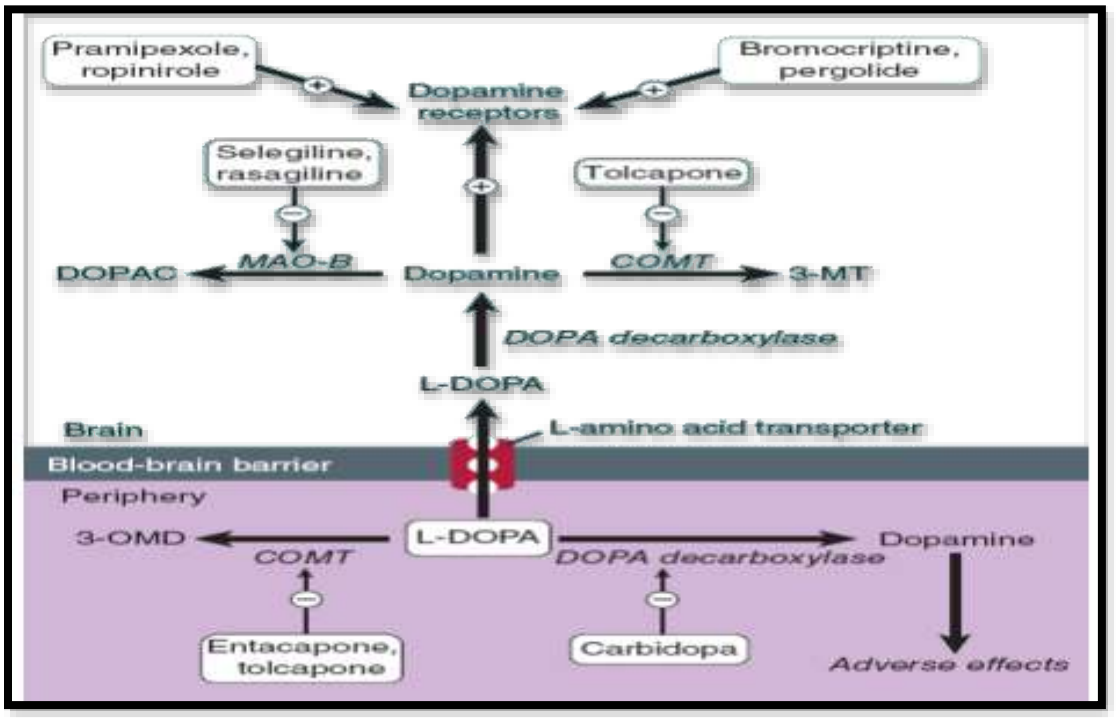
- **Apomorphine** can be given subcutaneously for temporary relief of off-periods that is used in severe and advanced stages of the disease.

- Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on levodopa.

- Dopamine agonists may delay the need to use levodopa in early Parkinson disease and may decrease the dose of levodopa in advanced Parkinson disease.

## D. Drugs Increasing Dopamine Level at Synapse

**Amantadine** is an **antiviral drug** that is also useful in Parkinsonism. It increases synaptic dopamine level by increasing presynaptic release and decreasing its reuptake. It also possesses anticholinergic and antiglutaminergic (NMDA blocking) activity.
It ameliorates dyskinesia associated with chronic levo-dopa therapy.



## 2- Drugs Inhibiting Brain Cholinergic Transmission (Antimuscarinic agents)

The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in anti-parkinsonism therapy.

Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity

**Central anticholinergic** drugs like **trihexiphenidyl (benzhexol), procyclidine, benztropine, orphenadrine** and **biperiden** are **the drugs of choice for drug induced Parkinsonism**.

**N.B:**

Drugs that act by blocking $D_2$ receptors in the brain (like antipsychotics, metoclopramide etc.) can cause Parkinsonism. In this condition, increasing dopamine level is not effective because the receptors on which it has to act ($D_2$) are already occupied, therefore anticholinergics are preferred.

**First generation antihistaminic** with high antimuscarinic activity like **promethazine** and **diphenhydramine** can also be used for this indication.

**Remember:**

Adverse effects of antimuscarinic drugs include urinary retention, blurred vision, dry mouth and constipation.

These drugs are contraindicated in patients with glaucoma and ……

# Assessment questions

Choose the correct answer:

**1- Drugs causing parkinsonism include:**

A. Bromocriptine
B. Phenothiazine
C. Haloperidol
D. Amantadine
E. Carbidopa

**2- Which antiparkinsonian drug may cause vasospasm?**

A. Amantadine
B. Bromocriptine
C. Entacapone
D. Ropinirole

**3- Entacapone may be useful in patients being treated with levodopa carbidopa combination because it:**

A. Activates COMT
B. Decreases formation of 3-OMD
C. Inhibits monoamine oxidase type B
D. Inhibits dopamine uptake

**4-Which of the following adverse effects of levodopa is not minimized even after combining it with carbidopa?**

A. Involuntary movements
B. Nausea and vomiting
C. Cardiac arrhythmia
D. 'On-off' effect

**5-Which of the following antiparkinsonian drugs directly activates dopaminergic $D_2$ receptors in the striatum?**

A. Pramipexole
B. Entacapone
C. Benserazide
D. Selegiline

# Alzheimer's Disease

Dementia of the Alzheimer's type has three distinguishing features:

1) accumulation of senile plaques (β-amyloid accumulations)

2) formation of numerous neurofibrillary tangles

3) loss of neurons, particularly cholinergic neurons.

**Symptoms:**

Alzheimer's disease was described by ***Alois Alzheimer*** in 1911 as a progressive brain disorder affecting regions of the brain that control memory and cognitive functions, gradually destroying a person's memory and ability to learn, to reason, to communicate, and to carry out the most basic activities of daily living. the memory loss that is a hallmark symptom of Alzheimer's disease which begin with a progressive decline in short-term memory.

Current therapies aim to either improve cholinergic transmission within the CNS or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.

Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit. None of the available therapeutic agents alter the underlying neurodegenerative process.

## Acetylcholinesterase inhibitors

Inhibition of acetylcholinesterase (AChE) within the CNS improves cholinergic transmission, at least at those neurons that are still functioning. The reversible AChE inhibitors approved for the treatment of Alzheimer's disease include donepezil,

galantamine and rivastigmine. These agents have some selectivity for AChE in the CNS, as compared to the periphery.

These compounds may provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients.

Rivastigmine is **the only** agent approved for the management of dementia associated with Parkinson disease (dementia that is associated with Parkinson's disease with deposition of Lewy bodies) and also **the only** AChE inhibitor available as a transdermal formulation.

Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps.

## NMDA receptor antagonist

Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories.
However, overstimulation of glutamate receptors, particularly of the NMDA type, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes.

Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows $Ca^{2+}$ to enter the neuron. Excess intracellular $Ca^{2+}$ can activate a number of processes that ultimately damage neurons and lead to apoptosis.

**Memantine** is an NMDA receptor antagonist indicated for moderate to severe Alzheimer disease. It acts by blocking the NMDA receptor and limiting $Ca^{2+}$ influx into the neuron, such that toxic intracellular levels are not achieved.

Memantine is well tolerated, with few dose-dependent adverse events. Expected adverse effects, such as confusion, agitation, and restlessness, are often indistinguishable from the symptoms of Alzheimer's disease.

memantine is often given in combination with an AChE inhibitor.

---

## Assessment questions

Choose the correct answer:

**Mechanism of action of donepezil is:**

A. Centrally acting reversible anticholinesterase
B. Centrally acting irreversible anticholinesterase
C. Irreversible cholinergic action
D. Reversible anticholinesterase

**Which drug is not used in Alzheimer Disease?**

A. Memantine
B. Galantamine
C. Ropinirole
D. Donepezil

**Case study:**

An 80-year-old male patient with moderate Alzheimer disease had a short trial of an oral medication for Alzheimer disease and experienced frequent nausea, along with difficulty swallowing the medication.

**What is best agent for management of Alzheimer disease in this patient?**

# Multiple Sclerosis

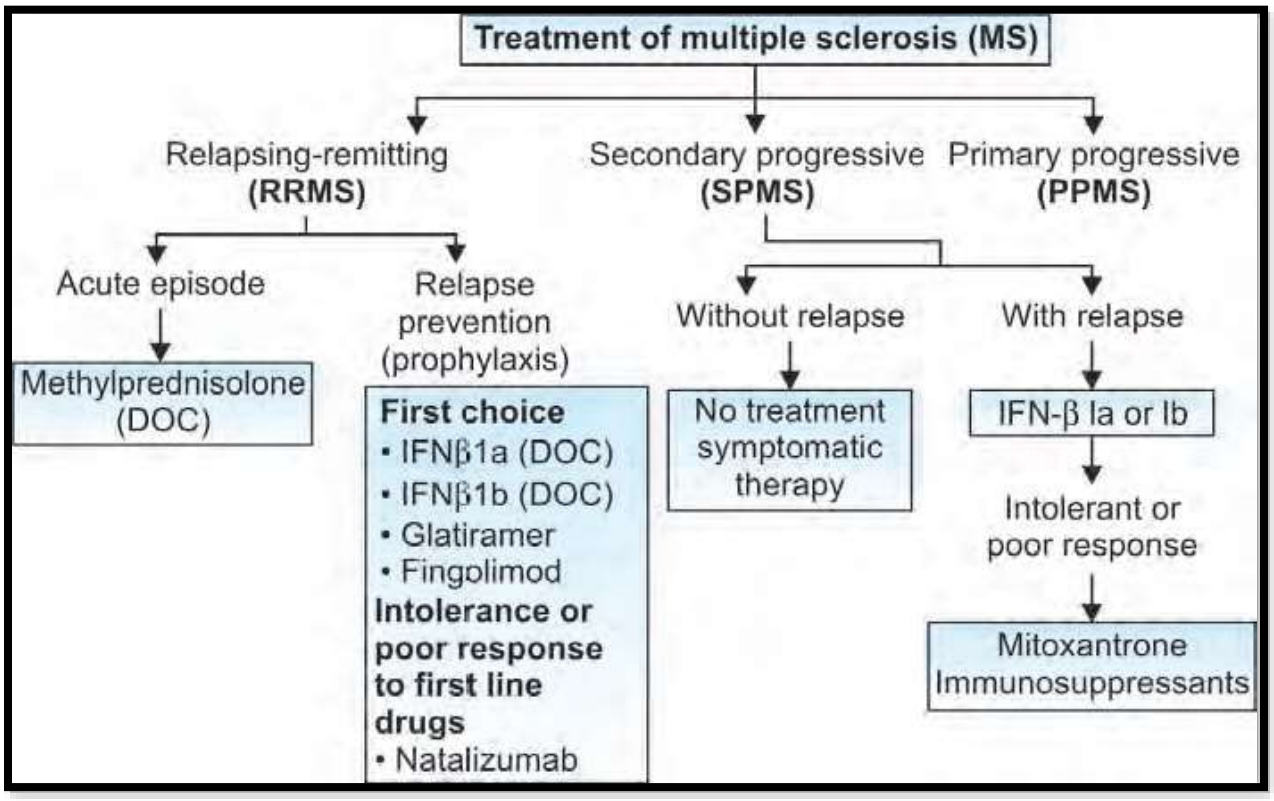
Multiple sclerosis (MS) is an autoimmune inflammatory multifocal demyelinating disease of the central nervous system. It is a chronic inflammatory with progressive neurodegeneration caused by an autoimmune response to self-antigens in a genetically susceptible individual that the body's immune system damages nerve pathways in the brain and the spinal cord.

**Symptoms of MS**

More than 30% of MS patients have moderate-to severe spasticity, mostly in the legs. Initial clinical findings in MS patients are often sensory disturbances as paresthesias (numbness and tingling), dysesthesias (burning, pins and needles), diplopia, optic neuritis, ataxia, vertigo, and bladder (urinary sphincter) disturbances. A common manifestation of MS is unilateral numbness affecting one leg that spreads to involve the other leg and rises to the pelvis, abdomen, or thorax. Sensory disturbances usually resolve but sometimes evolve into chronic neuropathic pain.

**Treatment strategy:**

- Drugs approved for MS are indicated to decrease relapse rates or to prevent accumulation of disability.
- The target of these medications is to modify the immune response by inhibition of white blood cell–mediated inflammatory processes that lead to myelin sheath damage and decreased axonal communication between cells.
- **corticosteroids** have been used to treat acute exacerbations of the disease used as iv infusion for 3-5 days.
- **Dalfampridine** is an oral K+ channel blocker indicated to improve walking in patients with multiple sclerosis.
- **Modafinil** is approved for improving fatigue in multiple sclerosis.




| Drug | Route | Frequency | Adverse Effects |
|---|---|---|---|
| **Interferon-β 1a**<br>**Interferon β 1b** | i.m.<br>S.C. | Once a Week<br>Thrice a week | Flu-like symptoms<br>• Altered LFT<br>• Injection site reaction on s.c. route<br>• Formation of neutralizing antibodies |
| **Glatiramer** | S.C. | Thrice a week | • Injection site reactions<br>• Flushing, Chest tightness, dyspnea, palpitations, anxiety<br>• Lipoatrophy |
| **Natalizumab**<br>(Monoclonal antibody | i.v. infusion | Once a month | • Progressive multifocal leucoencephalopathy if used for >2years |

| Drug | Route | Frequency | Adverse Effects |
|---|---|---|---|
| **Fingolimod** | Oral | Once a day | • Altered LFT<br>• First degree heart block<br>• Bradycardia |
| **Mitoxantrone** (Anthracycline anticancer drug) | i.v. | Once in 3 months | • Cardiotoxicity<br>• Acute leukemia |
| **Dimethyl fumarate** | Oral | Twice a day | Progressive multifocal leucoencephalopathy |
| **Teriflunomide** | Oral | Once a day | Hepatotoxicity |
| **Cladribine** (Purine analog anticancer drug) | Oral | Used for 2 weeks every year | Immunosuppression<br>• Secondary neoplasms<br>• Herpes zoster |
| **Dalfampridine** (4-Aminopyridine) | Oral | Once a day | Seizures |

---

# Assessment questions

Choose the correct answer:

**A 50-year-old male patient with secondary progressive multiple sclerosis reports continued difficulty walking and the distance that he can walk before being overcome by fatigue. Which agent may be beneficial to improve walking speed and disability in this patient?**

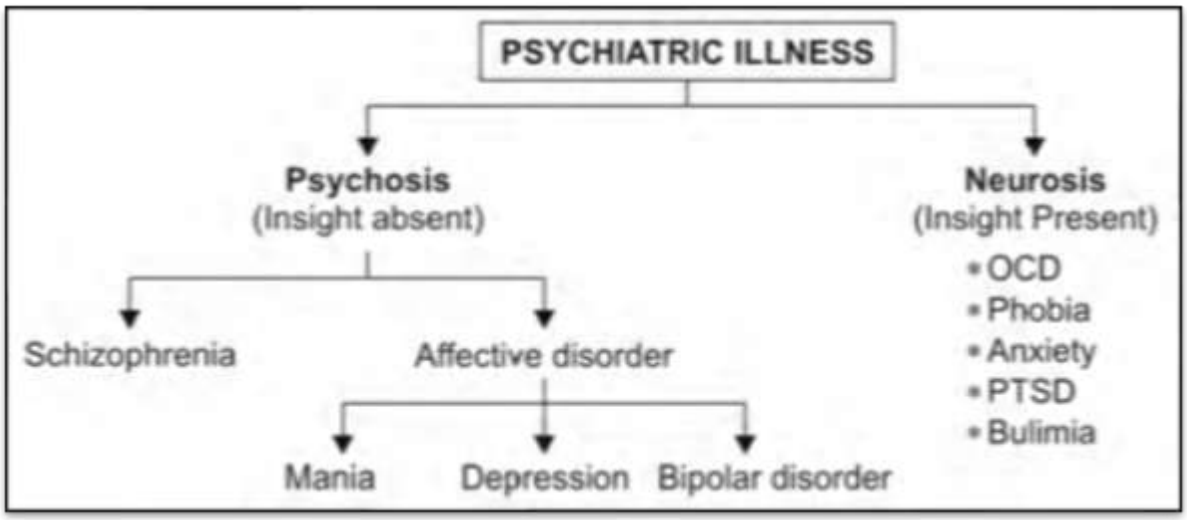
A. Dalfampridine
B. Donepezil
C. Riluzole
D. Bromocriptine

# Drugs for Psychiatric Illness

Two major types of psychiatric disorders are psychosis and neurosis.

**Psychosis**: Patient is not aware of his illness (insight is absent) and refuses to take treatment. It includes major psychosis like schizophrenia as well as mood disorders (like mania, depression and bipolar disorder).

**Neurosis**: It is less serious and insight is present. It includes anxiety, obsessive compulsive disorder (OCD), phobias, eating disorders and post-traumatic stress disorder (PTSD).




## Antipsychotic Drugs

Schizophrenia is a type of chronic psychosis characterized by positive symptoms appeared as delusions (disturbances in thought) and hallucinations often in the form of voice and vision (auditory visual hallucination) and negative symptoms appeared as social withdrawal. The onset of illness is often during late adolescence or early adulthood.

Schizophrenia is a severe psychiatric illness and is thought to be due to dopaminergic overactivity in the brain in mesolimbic region. Other neurotransmitters like 5-HT and NA also probably play a role in this disorder.

All drugs for schizophrenia have equal efficacy, these mainly differ in potency and can be classified as typical ($D_2$ blockers) and atypical (acting via other mechanisms by blocking of $D_2$, 5-HT receptors) antipsychotics.

Antipsychotic drugs are not curative and do not eliminate chronic thought disorders, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment.

## Typical Antipsychotics (first-generation)

**Chlorpromazine, Haloperidol**

Competitive blockade of dopamine $D_2$ receptors.

They are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors.

## Atypical Antipsychotics (second-generation)

**Risperidone, Paliperidone** (the active metabolite of risperidone), **Aripiprazole, Olanzapine, Quetiapine** and **Clozapine.**

The second-generation drugs owe their unique activity to blockade of both serotonin and dopamine receptors.

They have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic adverse effects, such as diabetes, hypercholesterolemia, and weight gain due to blocking effect of serotonin receptors.

There are long-acting injectable (LAI) formulations of antipsychotics. These formulations usually have a therapeutic duration of action of 2 to 4 weeks, with some having a duration of 6 to 12 weeks. Therefore, these LAI formulations are often used to treat outpatients and individuals who are nonadherent with oral medications.

**Note:**

Second-generation agents are generally used as first-line therapy for schizophrenia to minimize the risk of debilitating EPS associated with the first-generation drugs that act primarily at the dopamine $D_2$ receptor.

The clinical effects of antipsychotic drugs reflect a blockade at dopamine and/or serotonin receptors. However, many antipsychotic agents also block cholinergic, adrenergic, and histaminergic receptors.

## uses of antipsychotics

### 1- Antipsychotic effects

All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking $D_2$ receptors in the brain mostly resolved with (Typical antipsychotic drugs).

Also, reduce the “negative” symptoms by blocking 5-HT receptors in the brain mostly resolved with (Atypical antipsychotic drugs).

**2- Antiemetic effects**

The antipsychotic drugs have antiemetic effects that are mediated by blocking $D_2$ receptors of the chemoreceptor trigger zone of the medulla that are useful in the treatment of drug-induced nausea.

**3-** Chlorpromazine is used to treat intractable hiccups.

**4-** Risperidone and Haloperidol are also commonly prescribed for this tic disorder.

**5-** Risperidone and Aripiprazole are approved for the management of disruptive behavior and irritability secondary to autism.

**6-** Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder.

## Side effects of antipsychotics

**Extrapyramidal effects**

Blockade of dopamine receptors in the nigrostriatal pathway is believed to cause these unwanted movement symptoms (Parkinson-like syndrome) as Dystonia (sustained contraction of muscles), tremors, akathisia (motor restlessness), and tardive dyskinesia (repetitive involuntary movements).

**Neuroleptic malignant syndrome**

Fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status, unstable blood pressure, and myoglobinemia. It is must to stop treatment with the antipsychotic agent and supportive therapy. Administration of bromocriptine may be helpful.

**Autonomic disturbance**

- Mostly atypical antipsychotics produce anticholinergic effects Atropine like action as blurred vision, dry mouth, constipation and urinary retention.
- Blockade of α-adrenergic receptors causes orthostatic hypotension.
- The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment).
- Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor.

**Endocrine disturbance**

- In the pituitary, antipsychotics that block $D_2$ receptors may cause an increase in prolactin release resulting in galactorrhoea and amenorrhea.
- Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics (blockage of α receptors, increase of prolactin).
- Weight gain is also a common adverse effect of antipsychotics and is more significant with the second-generation agents.
- Chlorpromazine can cause cholestatic jaundice and cause liver damage.
- Clozapine affect Bone Marrow and can cause agranulocytosis.

# Assessment questions

Choose the correct answer:

**Which of the following antipsychotic agents is considered to be the most potent and thus have the highest risk of extrapyramidal symptoms?**
A. Thioridazine
B. Haloperidol
C. Quetiapine
D. Chlorpromazine

**Which antipsychotic agent is available in an LAI formulation that may be useful for patients with difficulty adhering to therapy?**
A. Fluoxetine
B. Chlorpromazine
C. Haloperidol
D. Aripiprazole

**Antipsychotic drug induced Parkinsonism is treated by:**
A. Anticholinergics
B. Levodopa
C. Selegiline
D. Amantadine

**Long-term antipsychotic use may cause:**
A. Depression
B. Mania
C. Schizophrenia
D. Tardive dyskinesia

**- Enumerate side effects of antipsychotic drugs.**

**- Explain prolong use of antipsychotic may lead to impotence.**

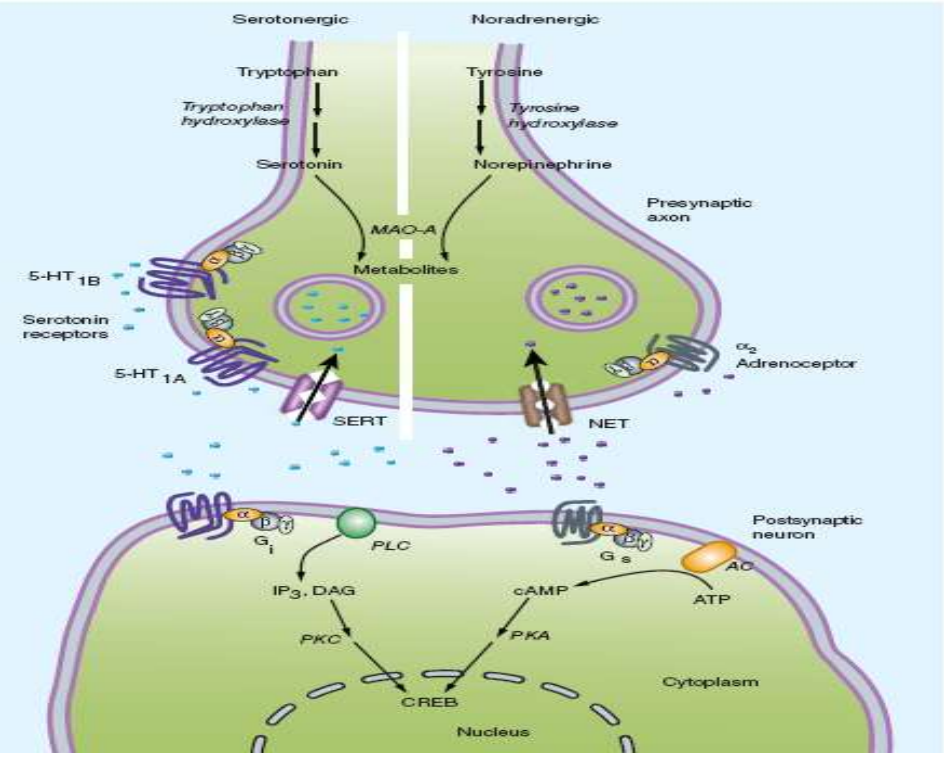
# Antidepressant Drugs

**Depression** is a disorder of mood rather than disturbance of thought and cognition. The symptoms of depression are feelings of sadness and hopelessness, as well as the inability to experience pleasure in usual activities, loss of interest, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

**Mania** is characterized by the opposite behavior: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

Most antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT) in the brain, as depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Therefore, drugs increasing their activity are called **typical anti-depressants**. Drugs acting by other mechanisms are called **atypical anti-depressants**.

**Conversely**, the theory proposes that mania is caused by an overproduction of these neurotransmitters.



**Depression is either:**

1- Unipolar depression (major depressive disorder)
   A. 67% of patient reactive (there is cause of depression)
   B. 25% of patients endogenous (there is no cause of depression).
2- Bipolar depression (manic depressive disorder) oscillating period of depression and mania

# Treatment of major depressive disorder

## Typical Antidepressants

Drugs may increase monoaminergic transmission by inhibiting the reuptake or metabolism of 5-HT or NA.

### 1. Tricyclic Antidepressants (TCA)

These drugs act by inhibiting the reuptake of **both serotonin and noradrenaline**. This results in increased concentration of these transmitters in the synaptic cleft.

Desensitization of receptors especially 5-HT $_{2A}$ occurs and enhanced transmission is seen. This explains the long latency (2-3 weeks) for the anti-depressant action of TCA and SSRIs despite immediate inhibition of reuptake process.

**Imipramine, Amitryptyline, Trimipramine and Clomipramine** inhibit the uptake of both 5-HT and NA.
**Desipramine and Nortriptyline** are predominantly NA reuptake inhibitors.

- TCAs block serotonergic, α-adrenergic, histaminic, and muscarinic receptors, actions at these receptors are likely responsible for many of their adverse effects.
- TCAs have long half-life and large VD so …….

**Remember:**

- Blockade of muscarinic receptors leads to blurred vision, xerostomia, urinary retention, constipation, and aggravation of glaucoma.

- Blockade of α-adrenergic receptors, causing orthostatic hypotension and reflex tachycardia.

- Blockade of histamine H1 receptors causing sedation. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction occurs in a minority of patients.

The TCAs improve mood, in 50% to 70% of individuals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer, these drugs are metabolized by the hepatic microsomal system with **low safety margin**.

**Note:**

- **Impiramine** are also indicated for nocturnal enuresis in children **(However, DOC is desmopressin)**.

- **Amitriptyline**, have been used to help prevent migraine headache and treat chronic pain syndromes (as neuropathic pain). Low doses of TCAs, can be used to treat insomnia.

**2. Selective Serotonin Reuptake Inhibitors (SSRI)**

These drugs inhibit the reuptake of **5-HT only** (not NA) and lack anticholinergic and α blocking properties leading to increased concentrations of the neurotransmitter in the synaptic cleft and decrease of many side effects.

Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

The SSRIs include **fluoxetine** (the prototypic drug), **citalopram**, **escitalopram (**pure S-enantiomer of citalopram), **fluvoxamine**, **paroxetine**, and **sertraline**.

**Note:**

• **Fluoxetine**: It is a prototype SSRI and is **longest acting** drug in this group. It is metabolized to nor-fluoxetine that retains the anti-depressant activity.

• Fluoxetine and paroxetine are potent **inhibitors** of a CYP450 isoenzyme (CYP**2D6**)

• **Fluvoxamine** is the **shortest acting** SSRI.

• **Escitalopram** is most **specific** SSRI.

• **Paroxetine** is most **teratogenic** among SSRIs.

SSRIs are now the **first-choice drugs** for depression, phobias, Obsessive–Compulsive Disorder (OCD), Post-Traumatic Stress Disorder (PTSD), Bulimia Nervosa, premenstrual tension syndrome and panic attacks because they offer several advantages over TCAs:

• No anticholinergic adverse effects

• No sedation or weight gain

• No propensity to cause seizures or arrhythmias

**Obsessive–compulsive disorder (OCD),** is an anxiety disorder in which time people have recurring, unwanted thoughts, ideas or sensations (obsessions) that make them feel driven to do something repetitively (compulsions).

**Bulimia Nervosa,** is an eating disorder characterized by binge eating (eating a large amount of food in a short amount of time) followed by purging (attempts to get rid of the food consumed)

**Post-Traumatic Stress Disorder (*PTSD),*** is a mental health condition that's triggered by a terrifying event, either experiencing it or witnessing it. Symptoms may include flashbacks, nightmares and severe anxiety and uncontrollable thoughts about the event.

SSRIs have fewer and less severe adverse effects than the TCAs and MAOIs, it includes headache, sweating, anxiety, agitation and Sexual dysfunction, which may include loss of libido, delayed ejaculation. SSRIs can cause akathisia.

**Akathisia,** is a movement disorder that makes it hard to stay still (urgent need to move) and feeling of restlessness.

The name comes from the Greek word "**akathemi**," which means to "**never sit down**."

Coadministration of SSRIs with MAO inhibitors or other highly serotonergic drug can result in **Serotonin Syndrome**, that include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs.

Because SSRIs affect platelet serotonin levels as Peripheral serotonin is important in platelet aggregation via blockade of serotonin reuptake in brain that lead to subsequent platelet dysfunction so, abnormal bleeding can occur. **Sertraline and citalopram** appear to be safest SSRIs to be used with **warfarin.**

**Discontinuation syndrome**

SSRIs have the potential to cause a discontinuation syndrome after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites.

Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

**SSRIs side effects:**

**S: S**exual dysfunction

**S: S**erotonin syndrome

**R: CR**amps

**I: I**rritability

**S: s**leep pattern

**N.B.**

**Fluoxetine** has the lowest risk of causing an SSRI discontinuation syndrome due to its longer half-life (**50 hours**) and active metabolite, **S-norfluoxetine** (**10 days**).

**Note:**

- fluoxetine and escitalopram are approved to treat childhood depression.
- Fluoxetine, sertraline, and fluvoxamine are approved for use in children to treat obsessive–compulsive disorder
- fluoxetine is the only approved SSRIs for bulimia nervosa.

## 3- Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

**Venlafaxine, desvenlafaxine and duloxetine** inhibit the reuptake of both serotonin and norepinephrine.

Depression is often accompanied by chronic pain, such as backache and muscle aches. This pain is modulated by serotonin and norepinephrine pathways in the central nervous system. With dual inhibition of serotonin and norepinephrine reuptake, both the SNRIs and the TCAs may be effective in relieving pain while, SSRIs are relatively ineffective.

These agents are also used in the treatment of pain syndromes, such as diabetic peripheral neuropathy, neuralgia, fibromyalgia, and low back pain.

**Fibromyalgia,** is a chronic disorder characterized by widespread musculoskeletal pain accompanied by fatigue (feeling tired), sleep, memory and mood issues. Fibromyalgia amplifies painful sensations by affecting the way the brain processes pain signals.

The SNRIs, unlike the TCAs, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer receptor mediated adverse effects than the TCAs. The SNRIs may precipitate a **discontinuation syndrome** if treatment is abruptly stopped. SNRIs may increase blood pressure and heart rate.

**N.B.**

- **Desvenlafaxine** is the active metabolite of venlafaxine.
- **Duloxetine** should be avoided in patients with liver dysfunction.
- **Duloxetine** is a moderate inhibitor of CYP**2D6** isoenzymes.

4- **Monoamine Oxidase Inhibitors**

Two types of monoamine oxidase enzymes (MAO-A and MAO-B) are involved in the metabolism of monoamines.

monoamine oxidase inhibitors permitting neurotransmitters to escape degradation and accumulate within the presynaptic neuron and leak into the synaptic space.

• **MAO-A** predominantly metabolizes **NA, 5-HT and DA** and is present in the intestine, peripheral nerve endings and liver.

• **MAO-B** preferentially metabolizes **dopamine** and is present in the brain, platelets and liver.

**i) Non- selective MAO inhibitors**

**Tranylcypromine, isocarboxazid and phenelzine** inhibits both isoforms of MAO irreversibly. Their anti-depressant effect takes 3-4 weeks to develop. These drugs exhibit a large number of drug and food interactions. The important ones are:

**A- Cheese reaction**:

These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyze tyramine, which is found in certain foods: aged cheeses, pickled or smoked fish, beer and red wine (indirectly acting sympathomimetic).

Normally it is metabolized by MAO-A present in the intestine and is not absorbed. In persons taking non-selective MAO inhibitors, tyramine escapes degradation and can lead to **hypertensive crisis** with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. It is known as **cheese reaction**. So, cheese etc. should not be given to patients on long term non-selective MAO inhibitor therapy. **Phentolamine** is the drug of choice for cheese reaction.

**B- Serotonin syndrome**:

If given along with or just after discontinuation of MAO inhibitors, **SSRIs** can result in serotonin syndrome. To avoid this fatal condition, SSRIs should be started at least 14 days after discontinuation of MAO inhibitors. It allows sufficient time for regeneration of MAO.

**N.B.**

Both SSRIs and MAOIs require a washout period of at least 2 weeks before the other type is administered, with the exception of fluoxetine, which should be discontinued at least 6 weeks before an MAOI is initiated, this is because…….

**C- increase the risk of seizures** if given along with **pethidine** due to enhanced generation of excitatory metabolite nor-meperidine.

**ii) Selective MAO -B inhibitors**

**Selegiline** inhibits only MAO-B and is useful in **Parkinsonism**. It is available as a transdermal patch for treatment of depression.

**Note:**

- Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks.
- Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia.
- The MAOIs are indicated for depressed patients who are unresponsive or intolerant of other antidepressants.

**Serotonin–Dopamine Antagonists**

While 60% to 80% of patients respond favorably to antidepressants, 20% to 40% experience a partial or poor response to monotherapy. The serotonin–dopamine antagonists (SDAs), or atypical antipsychotics, are occasionally used as adjunctive treatments to antidepressants in partial responders. Aripiprazole, quetiapine, and the combination of fluoxetine and olanzapine are approved for use as adjuncts in major depressive disorder (MDD).

## Atypical Antidepressants

The atypical antidepressants are a mixed group of agents that have actions at several different sites.

**1- Bupropion:**

Bupropion inhibits the uptake of NA and DA. It is metabolized to amphetamine like compound and possesses excitatory property. It is **used for smoking cessation** as sustained release formulation. It can precipitate **seizures** at high dose.

**2. Mirtazapine**

Mirtazapine enhances serotonin and norepinephrine neurotransmission by antagonism at $\alpha_2$ and 5-$HT_{2A}$ receptors. It is sedating because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs or interfere with sexual function like the SSRIs. **Increased appetite, and weight gain** frequently occur

**3- Nefazodone and trazodone**

- It blocks serotonin reuptake and antagonizes 5-$HT_2$A receptors.
- Trazodone is commonly used off-label for the management of insomnia due to potent histamine H1-blocking activity.
- Trazodone has been associated with priapism (prolonged and painful erection)
- nefazodone has been associated with a risk for hepatotoxicity.

**4- Vilazodone**

vilazodone is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.

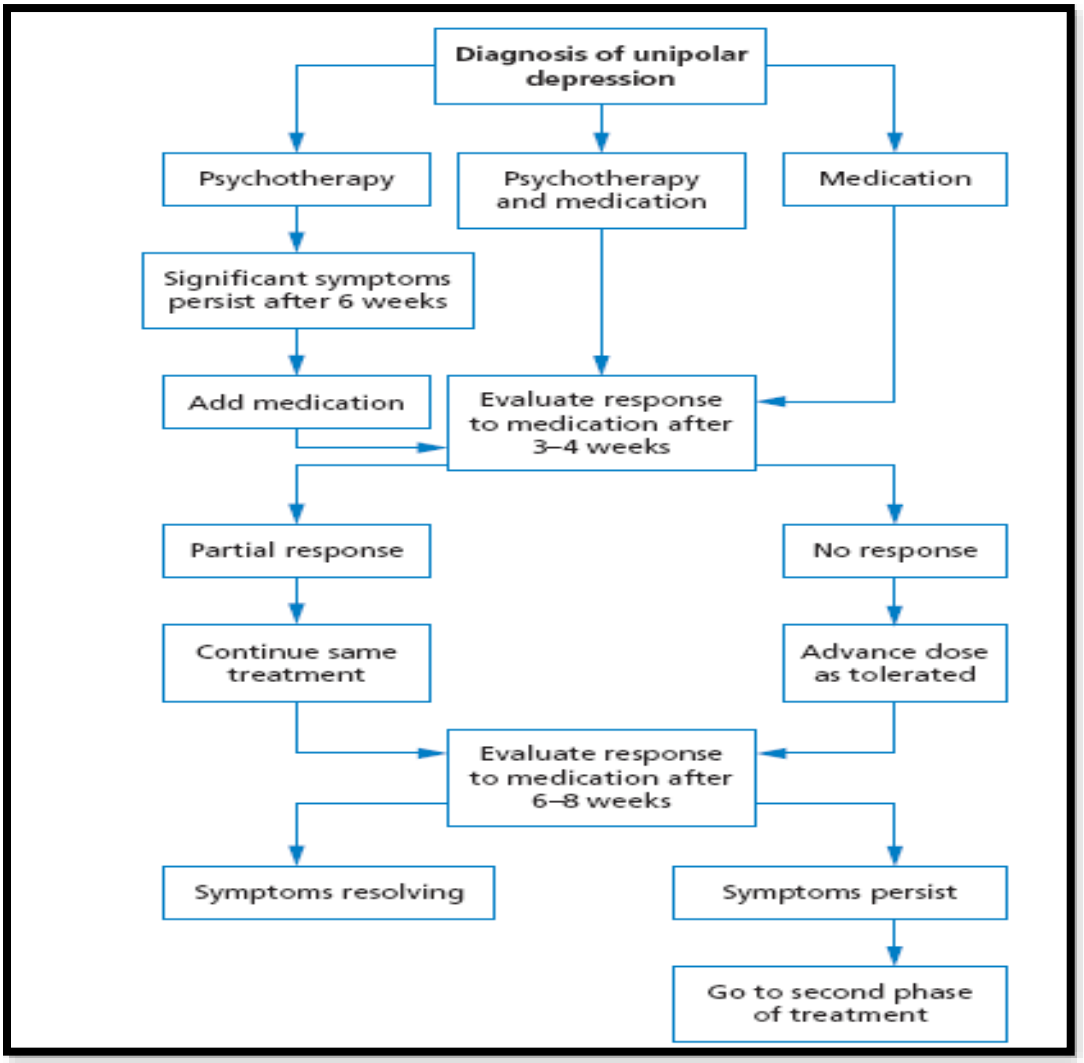
**5- Vortioxetine**

**6- Atomoxetine**

It is a selective inhibitor of NA reuptake and is useful for Attention Deficit Hyperkinetic Disorder.

**N.B:** Fluoxetine is longest acting and nefazodone is shortest acting antidepressant.

**Uses of anti-depressants**
**D** - **D**epression
**E** - **E**nuresis (Imipramine)
**P** - **P**hobia
**R** - **R**ecurrent panic attacks
**E** - **E**ating disorders (Bulimia)
**S** - **S**moking cessation (Bupropion)
**S** - **S**tress disorder (Post traumatic)
**I** - **I**mpulse disorder (Kleptomania)
**O** - **O**bsessive compulsive disorder
**N** - **N**europathic pain



# Treatment of mania and Bipolar Disorder

## Lithium carbonate

Lithium carbonate does not produce any acute effect but on prolonged use, acts as a mood stabilizer. It has no psychotropic effect in normal persons.

• It has **narrow margin of safety** (low therapeutic index) and therapeutic drug monitoring (TDM) is essential.

• It takes 1-2 weeks to exert its maximum effect. It is the **drug of choice for the prophylaxis of bipolar disorder. Its $t_{1/2}$ is 24 hours.**

• Plasma concentration of lithium should be **0.5-0.8 mEq/L for maintenance therapy** of bipolar disorder and **0.8-1.2 mEq/L for acute mania.** Toxic symptoms are seen if plasma concentration exceeds 1.5mEq/L.

**Other effects of lithium are**

**L** – **Leucocytes** are Useful in the treatment of cancer chemotherapy induced leucopenia

**I** – **Increased**

**T** – **Tremors** (Most common side effect)

**H** – **Hypothyroidism**

**I** – **Increased**

**U** – **Urine**

**M** should be avoided in expectant **Mothers** as it causes Ebstein's anomaly

**Ebstein's anomaly,**
is a rare heart defect that's present at birth (congenital)

**Lithium Toxicity**

Acute intoxication is characterized by ataxia, coma and convulsions, cardiac arrhythmias and hypotension.

• There is **no specific antidote** for lithium. **Dialysis** is most effective means of removing Li from body.

**Alternatives to Lithium**

• **Carbamazepine and valproate** are useful in manic depressive psychosis (bipolar disorder). These can also be used for acute mania. **Valproic acid is the drug of choice for treatment of rapid cycles** (> 4 cycles/year).

• **Benzodiazepines like lorazepam** are the **drugs of choice for acute mania** when combined with lithium (due to slow action of Li). Olanzapine and other atypical antipsychotics show efficacy in bipolar disorder as well as acute mania.

• **Lamotrigine is specifically useful for depressive phase of bipolar disorder.** It is the first agent to be approved by FDA for bipolar disorder without an indication for acute mania.

# Assessment questions

Choose the correct answer:

**A person taking tricyclic antidepressants presents with blurred vision and dry mouth. These adverse effects result due to blockade of:**

(a) $M_3$ muscarinic receptors
(b) GABAA receptors
(c) H1 histamine receptors
(d) $5HT_2$ receptors

**A patient of depression is stabilized on selective serotonin reuptake inhibitor (SSRI). This group of drugs produced withdrawal symptoms when stopped Which of the following drugs has minimum risk of causing drug discontinuation symptoms?**

(a) Paroxetine
(b) Fluoxetine
(c) Sertraline
(d) Fluvoxamine

**A woman treated with lithium during pregnancy, the fetus should be tested for:**

(a) Neural tube defects
(b) Cardiac malformations
(c) Urogenital abnormalities
(d) Scalp defects

**What is the drug of choice for Obsessive Compulsive Disorder?**

(a) Imipramine
(b) Fluoxetine
(c) Benzodiazepines
(d) Alprazolam

**Which of the following is not a mood stabilizer?**

(a) Lithium
(b) Valproate
(c) Carbamazepine
(d) Fluoxetine

# Analgesics

Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems.

**Alleviation of pain depends on the specific type of pain:**

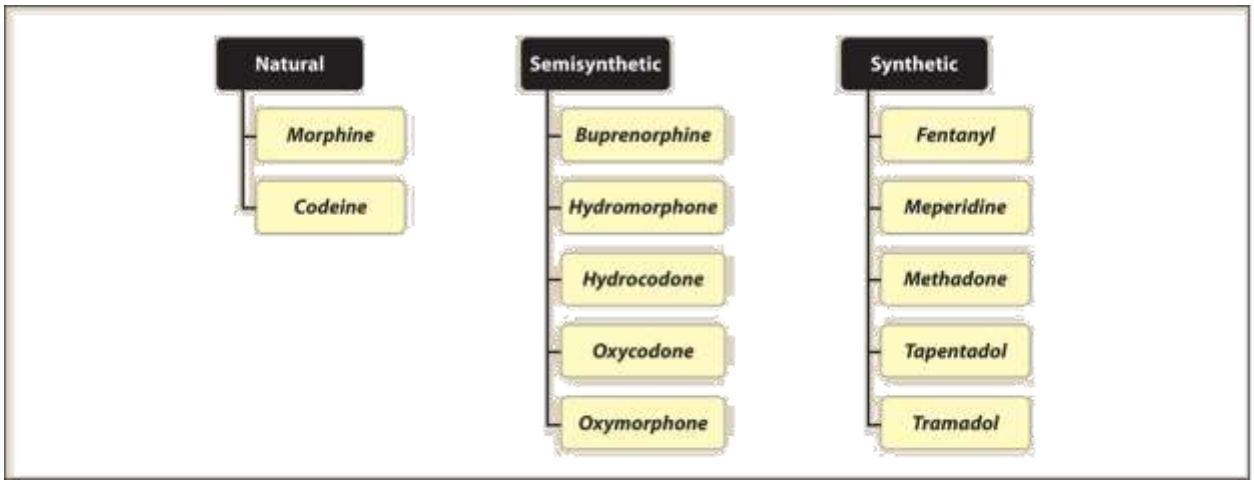
- mild to moderate arthritic pain (nociceptive pain), nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) are often effective.
- Neuropathic pain responds best to anticonvulsants, tricyclic antidepressants, or serotonin/norepinephrine reuptake inhibitors.
- for severe acute pain or chronic malignant or nonmalignant pain, opioids can be considered as part of the treatment plan in select patients.

## Opioids

Opioids are natural, semisynthetic, or synthetic compounds that produce morphine-like effects

**Note:**

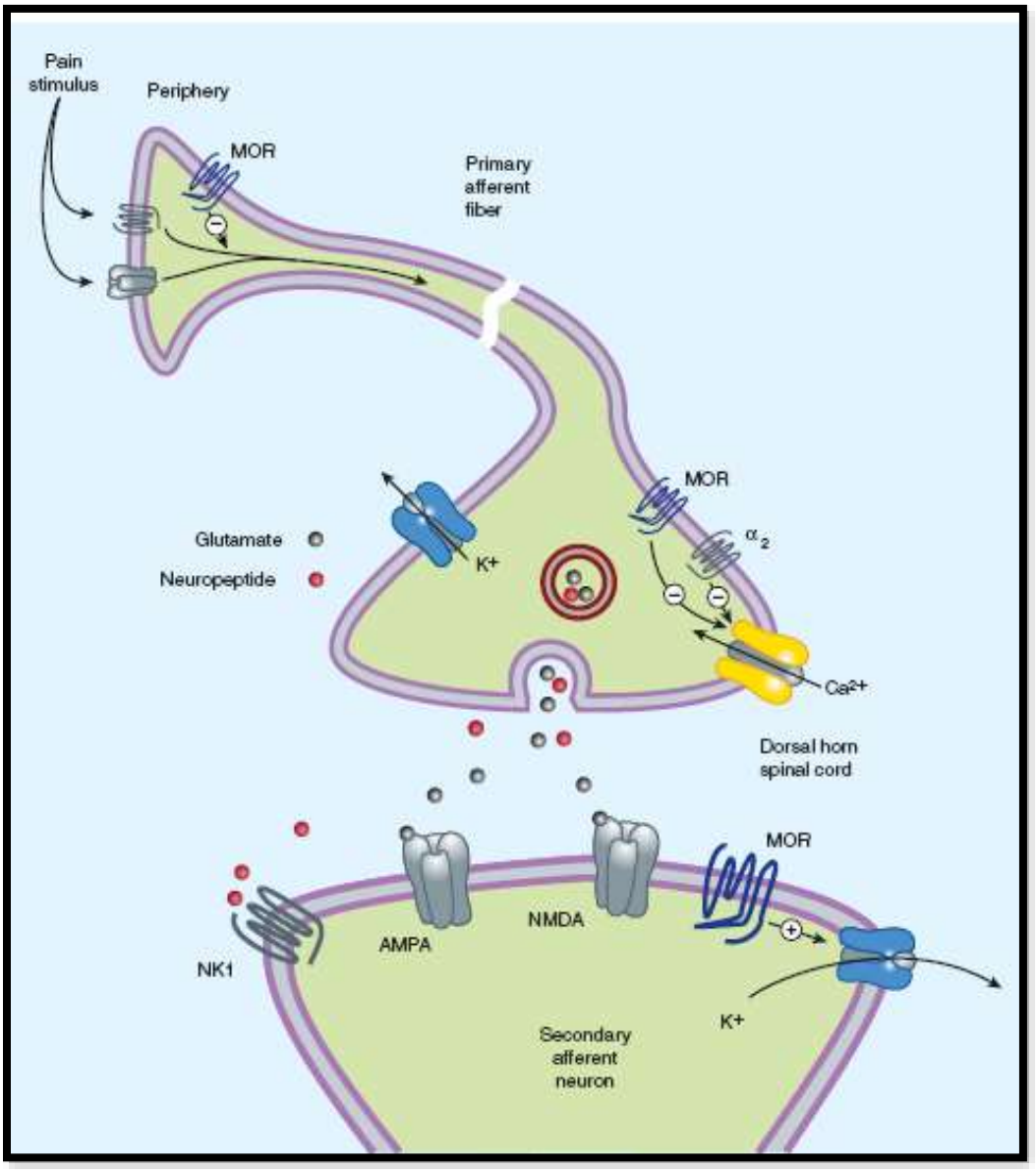
The term **opiate** specifically describes the naturally occurring alkaloids as morphine, codeine. In contrast, **narcotic** was originally used to describe sleep-inducing medications




All opioids act by binding to specific opioid receptors in the CNS μ {(mu, MOR), κ (kappa, KOR), and δ (delta, DOR)} to produce effects that mimic the action of endogenous peptide neurotransmitters as (endorphins, dynorphins, enkephalins).

| **Receptor Subtype** | **Functions** | **Endogenous Opioid Peptide Affinity** |
|---|---|---|
| μ (mu) | Supraspinal and spinal analgesia; sedation; constipation; respiratory depression; euphoria; miosis | Endorphins > enkephalins > dynorphins |
| δ (delta) | Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release | Enkephalins > endorphins and dynorphins |
| κ (kappa) | Supraspinal and spinal analgesia; psychotomimetic effects: dysphoria unpleasant state characterized by restlessness and malaise) slowed gastrointestinal transit (constipation) | Dynorphins > > endorphins and enkephalins |

All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase. They are also associated with ion channels, increasing postsynaptic $K^+$ efflux (hyperpolarization) or reducing presynaptic $Ca^{2+}$ influx.




## Morphine

Morphine, the prototypic opioid agonist, has long been known to relieve acute severe pain with remarkable efficacy.

- Morphine is somewhat selective to the μ opioid receptor but has some affinity for the κ and δ receptors. Morphine also inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.

- Morphine and other opioids relieve pain by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain.

- Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons.

- Morphine causes respiratory depression by reduction of the responsiveness of respiratory center neurons to carbon dioxide. This can occur with ordinary doses of morphine in patients who are opioid naïve. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect develops with repeated dosing, which allows for the safer use of morphine for the treatment of pain when the dose is correctly titrated.

- Both morphine and codeine have antitussive properties via depression of cough reflex.

- Morphine directly stimulates the chemoreceptor trigger zone that causes vomiting.

- Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscle. Morphine and other opioids produce constipation and considered the most common adverse effect {Opioid-induced constipation (OIC)}.

- Morphine has no major effects on blood pressure or heart rate at lower dosages, but hypotension and bradycardia may occur at higher doses.

- Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure (intracranial tension) so Morphine is usually contraindicated in individuals with head trauma or severe brain injury.

- Morphine releases histamine from mast cells causing urticaria **intense pruritus** over lips., sweating, and vasodilation.

- Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.

- Prolonged use of morphine may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic–pituitary–gonadal axis (HPA). This results in decreased production of sex hormones, especially testosterone, resulting in sexual dysfunction. Possible infertility,

- Morphine may prolong the labor by decreasing the strength, duration, and frequency of uterine contractions so, It should not be used for analgesia during labor.

- Because significant first-pass metabolism of morphine occurs in the liver, subcutaneous and intravenous (IV) injections produce the most reliable response. nasal insufflation of certain opioids can rapidly result in therapeutic blood levels.

- Only a small percentage of morphine crosses the blood–brain barrier, because morphine is the least lipophilic of the common opioids. By contrast, the more lipid-soluble opioids, such as fentanyl and methadone, readily penetrate the CNS.

- The duration of action of morphine is 4 to 5 hours when administered systemically to opioid-naïve individuals but considerably longer when injected epidurally because the low lipophilicity prevents redistribution from the epidural space.

**Codeine**

Codeine is a naturally occurring opioid and a weak analgesic compared to morphine. It is used for mild to moderate pain. The analgesic actions of codeine are derived from its conversion to morphine by the CYP2D6 enzyme. The drug exhibits good antitussive activity at doses that do not cause analgesia.

**Hydromorphone and hydrocodone**

Oral hydromorphone is approximately 4 to 7 times more potent than oral morphine. It is preferred over morphine in patients with renal dysfunction due to less accumulation of active metabolites.

**Oxycodone and oxymorphone**

Oxymorphone given parenterally is approximately ten times more potent than Morphine. Oxycodone is approximately two times more potent than morphine

**Fentanyl**

Fentanyl is a synthetic opioid chemically related to meperidine. Fentanyl has 100-fold the analgesic potency of morphine and is used for anesthesia and acute pain management. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually administered IV, epidurally, or intrathecally. Fentanyl is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain. **Fentanyl** can be applied as **transdermal patch** or can be administered by **buccal transmucosal** route.

**Meperidine (pethidine)**

Meperidine is a lower-potency synthetic opioid. Meperidine is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium compared with

other opioids. Meperidine has an active metabolite (normeperidine), which is potentially neurotoxic. accumulation of the metabolite may lead to delirium and seizures. Normeperidine is renally excreted so meperidine should not be used in elderly patients or those with renal insufficiency, hepatic insufficiency.

**Pethidine** is used to reduce shivering after anaesthesia [by its action on $\alpha_2$ receptor].

**Methadone**

Methadone is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of morphine. Methadone may be used for opioid withdrawal and maintenance therapy in the setting of prescription opioid and heroin abuse. The withdrawal syndrome with methadone is milder but more protracted (days to weeks) than that with other opioids. Methadone induces less euphoria and has a longer duration of action than morphine.

**Buprenorphine**

Buprenorphine acts as a potent partial agonist at the μ receptor and an antagonist at the κ receptors. Buprenorphine is very lipophilic and has a longer duration of action due to its high affinity for the opioid receptors when compared to morphine. Due to high affinity for the mu receptor, buprenorphine can displace full μ agonists, leading to withdrawal symptoms in an opioid-dependent patient. Because of the partial μ agonist activity, buprenorphine provides a "**ceiling effect**" causing less euphoric effects and a lower abuse potential than that of full agonists.

In contrast to methadone, which is available only at specialized clinics when used for opioid detoxification or maintenance, buprenorphine is approved for office-based treatment of opioid dependence. It has been shown to have shorter and less severe withdrawal symptoms compared to methadone.

**Tramadol**

Tramadol is a centrally acting analgesic that binds to the μ opioid receptor. It undergoes extensive metabolism via CYP2D6, leading to an active metabolite, which has a much higher affinity for the mu receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to severe pain.

**Note:**

Tramadol has less respiratory-depressant activity compared to morphine.

Administration of naloxone can only partially reverse tramadol toxicity and has been associated with an increased risk of seizures. Anaphylactoid reactions have been reported. Overdose or drug–drug interactions with SSRIs, MAOIs, and tricyclic antidepressants can lead to toxicity manifested by CNS excitation and seizures.

Tramadol should be used with caution in patients with a history of seizures. As with other agents that bind the μ opioid receptor, tramadol has been associated with misuse and abuse.

## Assessment questions

Choose the correct answer:

**Which of the following statements regarding adverse effects of opioid therapy is correct?**

A. The risk of respiratory depression is highest during an initial opioid initiation or following a dose increase.
B. Opioid-induced constipation is only seen with the initiation of opioid therapy.
C. The incidence of nausea and sedation increases with long-term use of opioid therapy.
D. Decreased testosterone levels are commonly seen with short-term use of opioid therapy.

**Case study:** A 76-year-old female with renal insufficiency has severe pain secondary to a compression fracture in the lumbar spine. She reports that the pain has been uncontrolled with tramadol, and it is decided to start treatment with an opioid. Which is the best opioid for this patient?

# Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

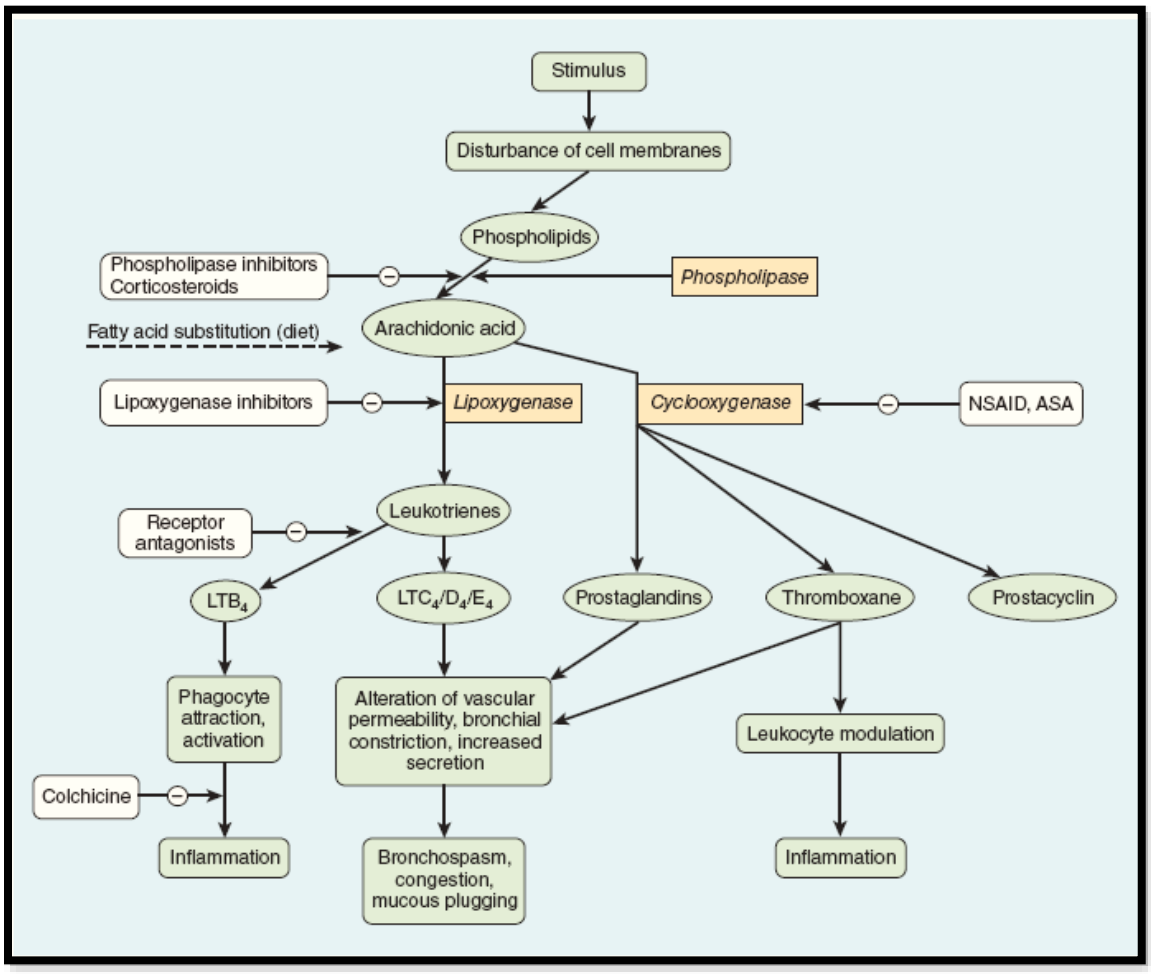
Inflammation plays a major role in the pathophysiology of a wide spectrum of diseases. It is primarily a protective response, but if excessive or inappropriately prolonged can contribute adversely to the disease process.

**Inflammatory cells:** many different cells are involved in different stages of different kinds of inflammatory response, including:

- neutrophils (in acute bacterial infections)
- eosinophils, mast cells and lymphocytes (in asthma)
- monocytes, macrophages and lymphocytes (in autoimmune disease as rheumatoid arthritis)

**Inflammatory mediators:** include prostaglandins and cytokines (for example, interleukins and tumour necrosis factor (TNF)). The mediators orchestrate and amplify the inflammatory cell responses.

Anti-inflammatory drugs work on different aspects of the inflammatory cascade including the synthesis and action of mediators, and in the case of immunosuppressants on the amplification of the response




Arachidonic acid is the primary precursor of the prostaglandins. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase $A_2$. There are two major pathways from arachidonic acid: lipoxygenase and cyclooxygenase pathways.

**Lipoxygenase pathway**

lipoxygenases can act on arachidonic acid to form leukotrienes. Antileukotriene drugs, such as zafirlukast, and montelukast, are treatment options for asthma.

**Action of LT s can be inhibited by:**

• Corticosteroids (decrease the production of LTs by inhibiting phospholipase $A_2$)

• Lipoxygenase inhibitors (zileuton).

• LT receptor antagonists (zafirlukast, montelukast, iralukast)

**Cyclooxygenase pathway**

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin biosynthesis by inhibiting cyclo-oxygenase (COX). COX is a key enzyme in the synthesis of prostaglandins and thromboxanes, important mediators of the erythema, oedema, pain and fever of inflammation. There are two main isoforms of the enzyme:

1- **A constitutive form (COX-1),** that is present in platelets, stomach, kidneys and other tissues.

2- **An inducible form (COX-2),** that is expressed in inflamed tissues as a result of stimulation by cytokines and is also present to a lesser extent in healthy organs, including the kidneys.

3- **A third form (COX-3)**, is a variant of COX-1 of uncertain importance in humans.

**Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

NSAIDs act by inhibiting COX enzyme and thus prostaglandin synthesis. Prostaglandins play a protective role in the stomach and non-selective COX inhibitors can cause GI toxicity (peptic ulcer) on long term use.

**NOTE:**

NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations.

The NSAIDs, have three major therapeutic actions: they reduce inflammation **(anti-inflammatory)**, pain **(analgesic effect)**, and fever **(antipyretic effect).**

**Classification**

• Non-selective COX inhibitors (inhibit both COX 1 and COX 2).

• Preferential COX 2 inhibitors (inhibitory activity on COX 2 is greater than COX 1).

• Selective COX 2 inhibitors.

**Note:**

Differences in safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for prevention of cardiovascular events and most adverse events. So selective inhibitors of COX-2 were developed with the potential of reduced gastric toxicity.

## Non-Selective Cox Inhibitors

### 1- Paracetamol (Acetaminophen)

It **does not possess anti-inflammatory activity** because it is ineffective in the presence of peroxides generated at the site of inflammation. Other explanation offered is **selective COX 3 inhibition** in the brain. It produces **very little GI toxicity** and can be administered in patients intolerant to other NSAIDs.

**N.B.** Acetaminophen does not affect platelet function or increase bleeding time. It is not considered an NSAIDs.

### 2- Aspirin

- Aspirin is one of traditional NSAIDs, but it exhibits anti-inflammatory activity only at relatively high doses more than 4 g/day.
- Aspirin is used more frequently at lower doses **(75 to 162 mg—commonly 81 mg)** to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke and myocardial infarction (MI) as it possesses antiplatelets activity.
- Aspirin is often differentiated from other NSAIDs since it is an irreversible inhibitor of cyclooxygenase activity, thus decreasing the synthesis of TXA2 (platelet aggregator). However, it also inhibits PGI2 (anti-aggregatory) synthesis.

Platelet aggregation is the first step in thrombus formation, and the antiplatelet effect of aspirin results in a prolonged bleeding time. For this reason, aspirin is often withheld for at least 1 week prior to surgery.

**Note:**

The antiplatelet effects persist for the life of the platelets (3 to 7 days) and chronic use of aspirin allows for continued inhibition as new platelets are generated

Aspirin should be avoided in patients less than 19 years old to prevent Reye syndrome.

**Reye syndrome**, a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death

- Salicylate is secreted into the urine and can decrease uric acid excretion lead to hyperuricemia. So, aspirin should be avoided in gout.
- Aspirin decreases the uricosuric action of probenecid.

- Concomitant use of NSAIDs and aspirin can prevent aspirin from binding to cyclooxygenase. Patients who take aspirin for cardio protection should avoid concomitant NSAIDs use if possible or take aspirin at least 30 minutes prior to other NSAIDs.
- Salicylate is 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in increased concentration of free salicylate. Alternatively, aspirin can displace other highly protein-bound drugs, as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of these agents.

**3- Other Non-selective COX Inhibitors**

**Indomethacin, Ibuprofen, Ketoprofen, Flurbiprofen, Naproxen, Mefenamic acid, Ketorolac, Piroxicam, Tenoxicam.**

- **Indomethacin** possesses immunosuppressive properties and it causes more GI upset than other NSAIDs.
- **Ketorolac** is the only NSAIDs that can be used i.v and can be used for more severe pain. It is also available as eye drops. Course longer than 5 days is not recommended.
- **Piroxicam and tenoxicam** are longest acting NSAIDs due to enterohepatic cycling.

## Preferential COX -2 inhibitors

These drugs have more inhibitory action on COX-2 than COX-1. Drugs included in this group are: **meloxicam, etodolac and diclofenac**.

Relatively less GI toxicity is experienced with the use of these drugs.

## Selective COX -2 inhibitors

These drugs have advantage of **very little GI toxicity**. However renal toxicity is similar and **chances of thrombosis** (acute MI and stroke) are **increased on prolonged use**.
Drugs included in this group are: **Etoricoxib, Lumiracoxib, Parecoxib, Celecoxib.**

- **Rofecoxib and valdecoxib** were withdrawn due to increased risk of thrombotic disorders like myocardial infarction.
- **Celecoxib** is sulfonamide derivatives, thus can cause rash and hypersensitivity.

**Therapeutic uses of NSAIDs**

NSAIDs are used in the treatment of osteoarthritis, gout, RA, and common conditions requiring analgesia (as headache, arthralgia, myalgia, and dysmenorrhea).

**Adverse effects of NSAIDs:**

Because of the adverse event profile, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

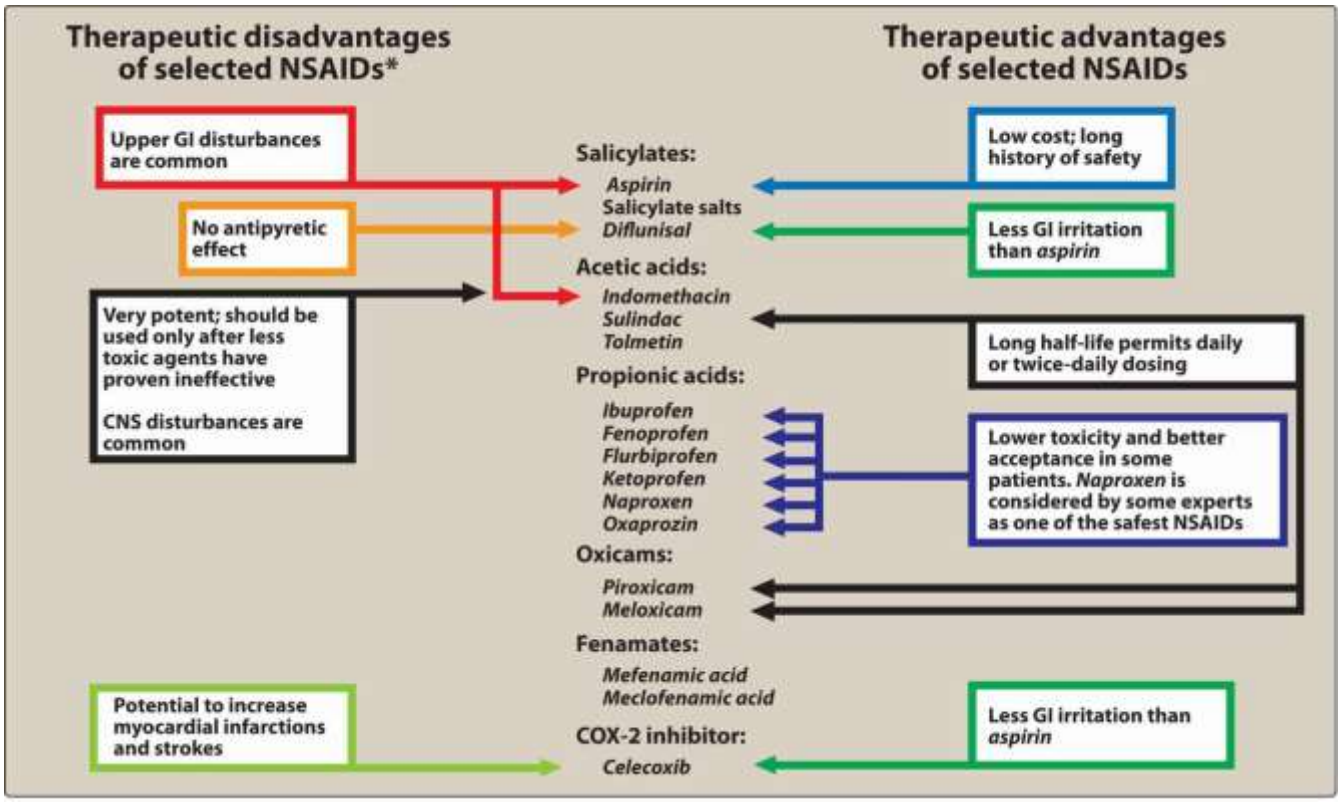
1- **Gastrointestinal effects** are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding due to …….

2- **Increase risk of bleeding** (antiplatelet effect) due to……..

**3- Renal effects,** NSAIDs prevent the synthesis of prostaglandins that are responsible for maintaining renal blood flow. Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema that may led to acute kidney injury.

4- **Increase the risk of asthma exacerbations** as NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotrienes production as LTs are the main Broncho constricting mediators in human asthma.

5- **Increase risk for cardiovascular events, including MI and stroke.** As agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI2 production mediated by COX-2 ,while NSAIDs with a very high degree of COX-1 selectivity at low doses, have a cardiovascular protective effect due to a reduction in the production of $TXA_2$.


Therapeutic disadvantages of selected NSAIDs*
Therapeutic advantages of selected NSAIDs
Upper GI disturbances are common
No antipyretic effect
Very potent; should be used only after less toxic agents have proven ineffective
CNS disturbances are common
Potential to increase myocardial infarctions and strokes
Salicylates:
Aspirin
Salicylate salts
Diflunisal
Acetic acids:
Indomethacin
Sulindac
Tolmetin
Propionic acids:
Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin
Oxicams:
Piroxicam
Meloxicam
Fenamates:
Mefenamic acid
Meclofenamic acid
COX-2 inhibitor:
Celecoxib
Low cost; long history of safety
Less GI irritation than aspirin
Long half-life permits daily or twice-daily dosing
Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs
Less GI irritation than aspirin

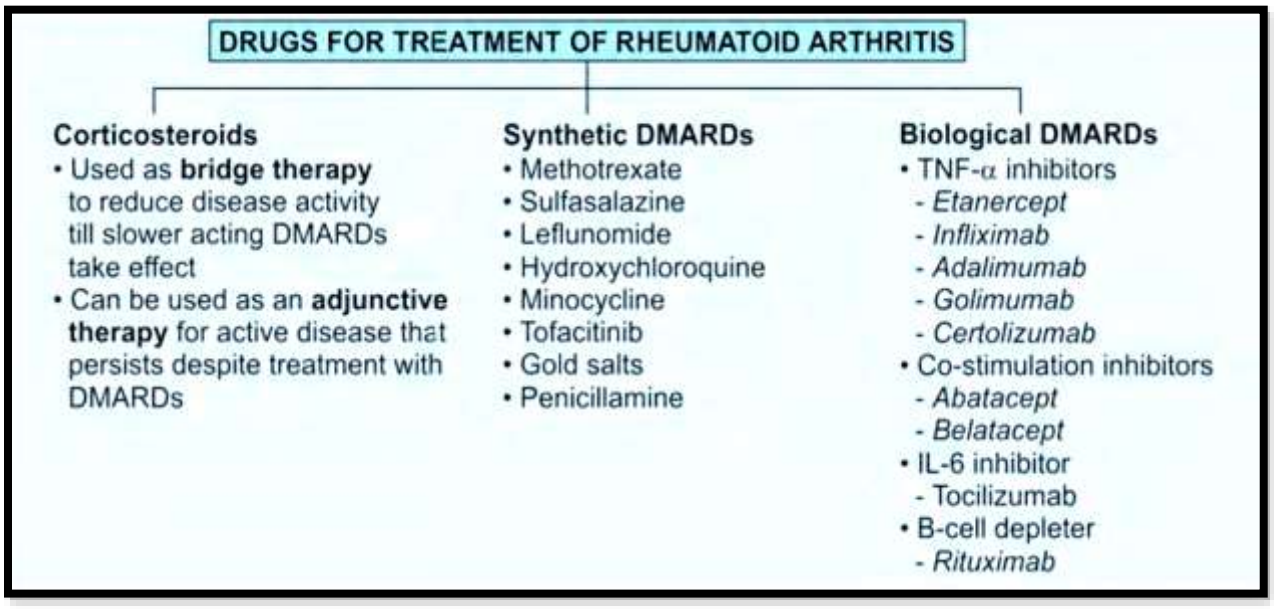
# Rheumatoid arthritis (RA)

inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA). Normally, the immune system can differentiate between self and nonself. In RA, white blood cells (WBCs) view the synovium as nonself and initiate an inflammatory attack. WBCs activation leads to stimulation of T lymphocytes, which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity, ultimately leading to joint destruction and other systemic abnormalities characteristic of RA. In addition to lymphocyte activation, B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation. These defensive reactions cause progressive tissue injury, resulting in joint damage and erosions, functional disability, pain, and reduced quality of life.

Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, induce remission and halting or slowing disease progression to prevent further destruction of the joints and involved tissues is called disease-modifying antirheumatic drugs (DMARDs).

**N.B.** nonsteroidal anti-inflammatory drugs (NSAIDs) are used to provide symptomatic relief but exert no effect on the progression of the disease.

Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease.




## Corticosteroids

- Corticosteroids are potent anti-inflammatory drugs can be used as a bridge therapy until DMARDs start to work (takes 6 weeks to 6 months) or as adjunctive therapy (with DMARDs) in rheumatoid arthritis.
- Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

## Synthetic DMARDs

### 1. Methotrexate

- It is **first choice DMARD** and is used at much lower doses (7.5 mg weekly) than required in cancer chemotherapy (30 mg daily). Methotrexate is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects.
- Response to methotrexate usually occurs within 3 to 6 weeks of starting treatment

**Adverse effects of methotrexate**

- Gastric irritation and stomatitis (most common)
- Pancytopenia
- Hepatotoxicity with fibrosis and cirrhosis
- Interstitial pneumonitis (Hypersensitivity reaction), pneumonia-like syndrome
- Teratogenicity
- Increased risk of B-cell lymphomas
- Amoxycillin and probenecid increase risk of methotrexate toxicity

**Note:** Supplementation with **folic acid** may improve tolerability of methotrexate and reduce GI and hepatic adverse effects.

2. **Sulfasalazine**

It is metabolized to ***sulfapyridine*** and ***5-aminosalicylic acid***, which is useful for ulcerative colitis. It is used in patients when methotrexate is contraindicated. The onset of activity is 1 to 3 months, and it is associated with leukopenia.

3. **Leflunomide Avara®- Arava®** 

- It is a **prodrug** (converted in the body to an active metabolite)
- It is faster acting (action is manifested in 4 weeks as compared to 3 months with other DMARDs)
- Common adverse effects include a flu-like syndrome, alopecia, hypokalemia and hepatotoxicity. Leflunomide is contraindicated in pregnancy.

**Remember:**

**Teriflunomide** is indicated for relapsing-remitting multiple sclerosis.

### 4. Chloroquine and hydroxychloroquine

These antimalarial drugs are also useful as DMARDs. onset of effects takes 6 weeks to 6 months. They may cause ocular toxicity including irreversible retinal damage.

**Hydroxychloroquine** is the safest DMARD can be used in pregnancy.

### 5. Tofacitinib

- Tofacitinib is approved for severe RA refractory to methotrexate. It is effective orally. Hemoglobin concentrations must be greater than **9 g/dL** to start tofacitinib and must be monitored during therapy due to the risk for anemia, also lymphocyte and neutrophil counts should be checked.
- Tofacitinib treatment may also increase the risk for new primary malignancy and opportunistic infections. Like TNF-α inhibitors, screening of patients for latent TB must be done prior to receiving the drug

### 6. Old drugs

**Gold and d-penicillamine** are highly efficacious DMARDs but are rarely used now due to severe toxic reactions including kidney and liver damage, peripheral neuropathy, pulmonary fibrosis, encephalopathy and bone marrow depression.

## Biological DMARDs

IL-1 and TNF-α are proinflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption.

Biologic DMARDs include the TNF-α inhibitors, as well as the non-TNF biologic agents are generally used in RA after a patient has an inadequate response to traditional

DMARDs, and they may be used alone or in combination with traditional DMARDs. If a patient has failed monotherapy with one non-TNF biologic, a trial of another non-TNF biologic with or without **methotrexate** is warranted. Clinical response of DMARDs can be seen within 2 weeks of therapy.

Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis.

**N.B:**

- Reactivation of hepatitis B may occur with the use of these agents.
- Live vaccinations should not be administered to patients taking any of the biologic DMARDs.

**Note:**

❖ TNF-α inhibitors and non-TNF biologic agents should not be used together due to the risk of severe infections.

❖ TNF-α inhibitors find use in a number of disorders, such as ulcerative colitis and Crohn disease and psoriasis.

**1. TNF-α blocking agents**

| Generic name | Brand name ® | Route of administration | Frequency |
|---|---|---|---|
| Infliximab | Remicade® | Intravenous | 0,2,6,10,14 weeks, then every 8 weeks |
| Etanercept | Enbrel® | Subcutaneous | Weekly |
| Adalimumab | Humira® | Subcutaneous | Once in 2 weeks |
| Golimumab | Simponi® | Subcutaneous | Monthly |
| Certolizumab | Cimzia® | Subcutaneous | Every 2-4 weeks |

**NOTE:**

***Infliximab*** is not indicated for monotherapy, as this leads to the development of anti-*infliximab* antibodies and reduced efficacy. It should be administered with *methotrexate*. Infusion-related reactions, such as fever, chills, pruritus, and urticaria, may occur.

**2. Co-stimulation inhibitors (Abatacept**)

It is act by inhibiting CD80 and CD86 co-stimulatory molecules on antigen presenting cells. Interaction of these with CD 28 on T-cells is necessary for T-Cell activation. Abatacept is administered as IV infusion every 4 weeks.

**3. IL-6 inhibitors (Tocilizumab)**

It is a monoclonal antibody against IL-6. It is approved for RA in combination with methotrexate. A subcutaneous injection every 2 weeks. Tocilizumab may also be administered as an intravenous infusion every 4 weeks.

**4.B- cell depleter (Rituximab) Mab Thera®**

Administration of *rituximab* results in B-cell depletion. *Rituximab* is administered as an intravenous infusion every 16 to 24 weeks.

**NOTE:**

- To reduce infusion reactions: methylprednisolone, acetaminophen, and an antihistamine are administered prior to each infusion.
- Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

# Gout

Gout is a metabolic disorder characterized by high levels of serum uric acid (hyperuricemia). Uric acid has low water solubility lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals.

Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally.

Secondary hyperuricemia may result due to **excessive production** (breakdown of proteins and nucleic acids during cancer chemotherapy) or **decreased excretion** (due to the use of thiazides, loop diuretics, ethambutol, clofibrate etc.) of uric acid.

Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

**Treatment of acute gout**

- Acute gout attacks manifested as severe inflammation of joints, can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease.

- NSAIDs, corticosteroids, and colchicine are effective agents for the management of acute gouty arthritis. Indomethacin is considered the classic NSAIDs of choice, although all NSAIDs are likely to be effective in decreasing pain and inflammation. Aspirin is not used as it may cause hyperuricemia.

- Intra-articular administration of corticosteroids (when only one or two joints are affected) is also appropriate in the acute setting, or systemic corticosteroids for more widespread joint involvement.

• **Colchicine** is more effective and faster acting than NSAIDs but is used rarely due to its high toxicity. It acts by inhibiting granulocyte migration into the inflamed joint. Most common and dose limiting toxicity is diarrhea. It can also cause kidney damage, myopathy and bone marrow depression.

**Uses of Colchicine**

Prophylaxis of recurrent attacks of gouty arthritis and in acute **M**editerranean fever.

## Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout.

**Treatment strategies include the use of:**

- xanthine oxidase inhibitors to reduce the synthesis of uric acid.
- uricosuric drugs to increase excretion of uric acid.
- Increase metabolism of uric acid.

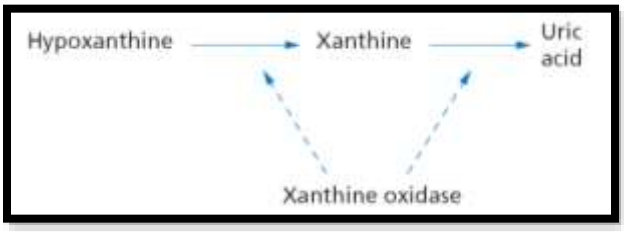
**N.B:** Medications for the prevention of an acute gout attack (low-dose colchicine, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.

## Drugs Decreasing Synthesis

Xanthine oxidase inhibitors are first-line urate lowering agents.

**Allopurinol, Febuxostat**

**Allopurinol (**a purine analog) and recently approved drug, **febuxostat** (a non-purine drug) decrease the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase.




- The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing.

- The drug and its active metabolite are excreted in the urine Allopurinol requires dose adjustment in renal failure whereas febuxostat can be administered without dose adjustment.

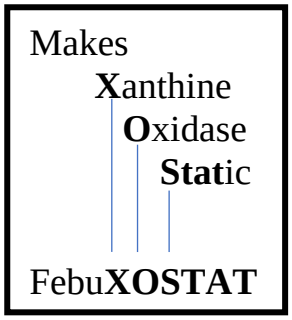
- Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions.

- These are indicated as **drug of choice for chronic gout** in the inter-critical period (between two acute attacks) and also with anticancer drugs (to decrease secondary hyperuricemia).

**N.B:**

- 6-Mercaptopurine and azathioprine are metabolized by xanthine oxidase; therefore, dose of these drugs should be decreased when given with allopurinol.

- **It is contra-indicated in acute gout** because uric acid has inhibitory effect on release of cytokines and allopurinol may aggravate the inflammation by reducing uric acid.



## Drugs Increasing Excretion (Uricosuric agents)

Uricosuric agents may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents.

**Probenecid, sulfinpyrazone** acts as competitive inhibitors of reabsorption of uric acid in proximal tubules. Plenty of fluids and urinary alkalinizers should be given concurrently to prevent precipitation of uric acid crystals in the kidney tubules.

These drugs are ineffective in the presence of renal damage. Probenecid is also used along with penicillins to decrease their renal excretion.

**Uricosuric drugs should not be used if**

- Creatinine clearance is <50ml/min.
- History of nephrolithiasis (uric acid or calcium stones)
- Evidence of overproduction of uric acid (> 800 mg of uric acid in a 24-hour urine collection).

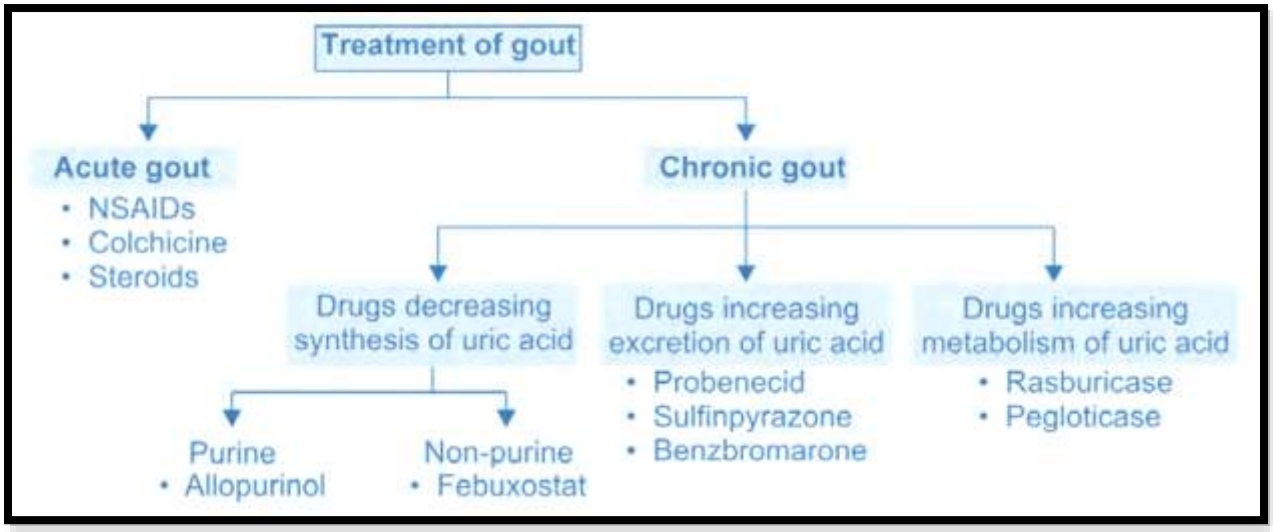
## Drugs Increasing Metabolism

**Rasburicase*, Pegloticase***

- Are recombinant form of the enzyme urate oxidase or uricase. As this enzyme is present in the birds and absent in humans. It acts by metabolizing insoluble uric acid to soluble allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys.

- It is administered as IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with pegloticase, and patients should be premedicated with antihistamines and corticosteroids.

**Summary:**




## Assessment questions

Choose the correct answer:

**Which statement correctly describes the proposed mechanism of cardioprotection from low-dose aspirin?**

A. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in thromboxane A2 levels.
B. Aspirin preferentially inhibits COX-1 to lead to a relative reduction in thromboxane A2 levels.
C. Aspirin preferentially inhibits COX-2 to lead to a relative reduction in prostacyclin levels.
D. Aspirin preferentially inhibits COX-1 to lead a relative reduction in prostacyclin levels.

**Which agent for RA competes with CD28 to prevent full T-cell activation?**

A. Sarilumab
B. Abatacept
C. Golimumab
D. Adalimumab

**A 64-year-old man presents with signs and symptoms of an acute gouty flare. Which strategy is the *least* likely to acutely improve his gout symptoms and pain?**

A. Naproxen
B. Colchicine
C. Probenecid
D. Prednisone

# CNS Stimulants

Psychomotor stimulants and hallucinogens are two groups of drugs that act primarily to stimulate the central nervous system (CNS). The psychomotor stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The hallucinogens produce profound changes in thought patterns and mood.

## Psychomotor Stimulants

### Methylxanthines

- The methylxanthines include theophylline, which is found in tea; theobromine, which is found in cocoa; and caffeine. Caffeine, the most widely consumed stimulant in the world.
- The caffeine contained in one to two cups of coffee (100 to 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2 to 5 g) of caffeine. Tolerance can rapidly develop to the stimulating properties of caffeine, and withdrawal consists of feelings of fatigue and sedation.
- A high dose of caffeine has positive inotropic and chronotropic effects on the heart, Increased contractility can be harmful to patients with angina pectoris.
- Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.
- Methylxanthines stimulate secretion of gastric acid, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines.

- Caffeine and its derivatives relax the smooth muscles of the bronchioles. Theophylline has been used for treatment of asthma.
- Moderate doses of caffeine cause insomnia, anxiety, and agitation. The lethal dose is 10 g of caffeine, which induces cardiac arrhythmias.

**Nicotine**

- Nicotine is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), nicotine remains important because it is second only to caffeine as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, nicotine represents a serious risk factor for lung and cardiovascular disease, and other illnesses.

- In low doses, nicotine causes ganglionic stimulation by depolarization. At high doses, nicotine causes ganglionic blockade.

- Nicotine is highly lipid soluble and crosses the blood–brain barrier. Cigarette smoking or administration of low doses of nicotine produces some degree of euphoria as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of nicotine result in central respiratory paralysis and severe hypotension. Nicotine is also an appetite suppressant.

- the average smoker takes in 1 to 2 mg of nicotine per cigarette. The acute lethal dose is 60 mg.

## Cocaine

Cocaine is a widely available and highly addictive drug. Because of its abuse potential, cocaine is classified as a Schedule II drug by the U.S. Drug Enforcement Agency.

The effect of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals. This potentiates and prolongs the CNS and peripheral actions of these monoamines that produces euphoria. Chronic intake of cocaine depletes dopamine. This depletion triggers craving for cocaine

## Amphetamine

Amphetamine shows neurologic and clinical effects similar to those of cocaine.
behavioral effects of amphetamine result from a combination of its dopamine and norepinephrine release–enhancing properties, this leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. Amphetamine used for the treatment of hyperactivity in children, narcolepsy, and obesity. At high doses, psychosis and convulsions may occur.

## Hallucinogens

A few drugs have the ability to induce altered perceptual states. Many of these altered states are accompanied by visions of bright, colorful changes in the environment. The individual under the influence of these drugs is incapable of normal decision-making because the drug interferes with rational thought. These compounds are known as hallucinogens, **lysergic acid diethylamide (LSD)** and **tetrahydrocannabinol (from marijuana)** are examples of agents in this class.

# Anxiolytic sedative and Hypnotic Drugs

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from a unknown source). Disorders involving anxiety are the most common mental disturbances. Anxiolytic sedative and Hypnotic Drugs include:

- **Barbiturates**
- **Benzodiazepines**
- **Miscellaneous agent**

## I. Barbiturates

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because Barbiturates induce tolerance and drug-metabolizing enzymes. In addition barbiturates are associated with very severe withdrawal symptoms.

**Mechanism of action:**

The sedative hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors. Barbiturates potentiate GABA action on chloride entry into the neuron by **prolonging the duration of the chloride-channel openings.** In addition, barbiturates can **block excitatory glutamate receptors.**

Anesthetic concentrations of *pentobarbital* also block **high-frequency sodium channels.** All of these molecular actions lead to decreased neuronal activity

**Classification of barbiturates**

Barbiturates are classified according to their duration of action For example:

**Thiopental** , acts within seconds and has a duration of action of about 30 minutes, is used in the IV induction of anesthesia.

**Phenobarbital** has a duration of action greater than a day, is useful in the treatment of seizures

**Pentobarbital, secobarbital and amobarbital** are short-acting barbiturates, which are effective as sedative and hypnotic agents.

**Pharmacological Actions**

**1. Depression of CNS:**

At low doses, the barbiturates produce sedation . At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Barbiturates do not cause analgesic antidepressant or antipsychotic action.

**2. Respiratory depression:**

Barbiturates suppress the hypoxia and chemoreceptor response to CO2, and over dosage is followed by respiratory depression and death.

**3. Enzyme induction:**

Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver.

4.**GIT:** Inhibit gut motility and secretion

5.**Kidney** : induce the release of antiduretic hormone causing oliguria and anuria

**Therapeutic uses**

**1. Anesthesia:** The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

**2. Anticonvulsant:** Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus. Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures. **However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.**

**3. Anxiety:** most have been replaced by the benzodiazepines

**Pharmacokinetics**

Barbiturates are absorbed orally and distributed widely throughout the body metabolized in the liver, and inactive metabolites are excreted in urine.

**Adverse effects**

**1. CNS:** Barbiturates cause drowsiness, impaired concentration, and physical sluggishness.

**2. Drug hangover.**

**Contraindication:** Barbiturates are contraindicated in Patient with liver disease , renal disease and bronchial asthma

1. **Mental and Physical dependence:** Abrupt withdrawal from barbiturates may cause Anxiety, Restlessness, Tremors, Weakness, Nausea, Vomiting, Seizures, Cardiac arrest and Delirium

Withdrawal is much more severe than that associated with opiates and can result in death.

**No specific barbiturate antagonist is available.**

**The major drawbacks of barbiturates**

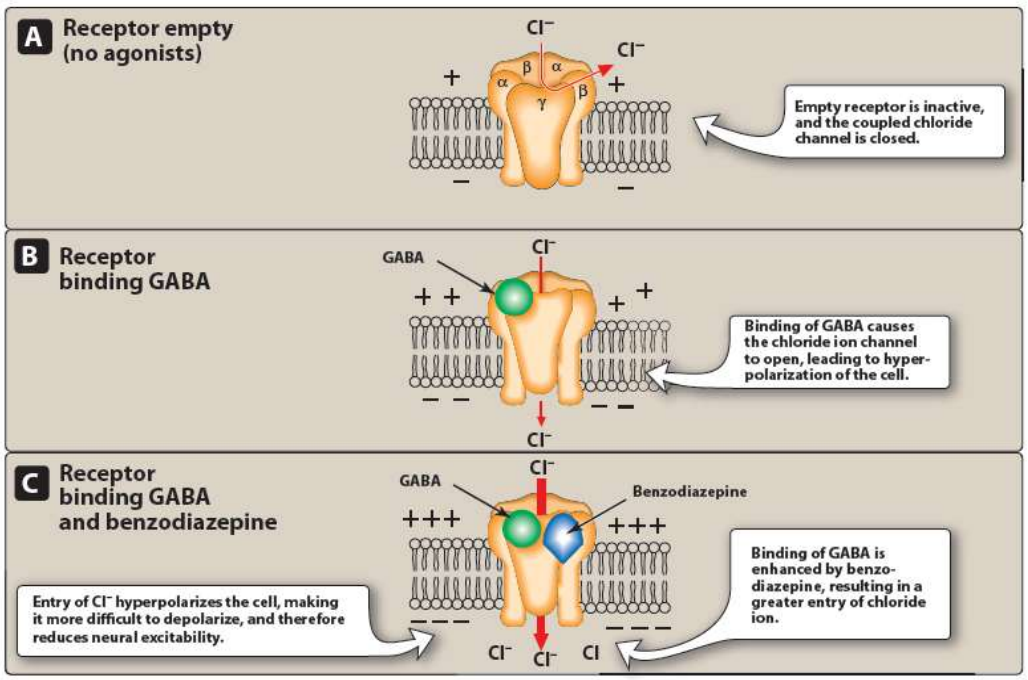
- Confusion
- Respiratory and circulatory depression
- Tolerance
- Physical dependence
- High risk of drug interaction

## II. Benzodiazepines

Benzodiazepines are the most widely used anxiolytic drugs. The targets for benzodiazepine actions are the $GABA_A$ receptors. Binding of GABA to its receptor triggers an opening of a chloride channel, which leads to an increase in chloride conductance.

Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and, thus, inhibits the formation of action potentials.

**Pharmacological action**




At low doses, the benzodiazepines are anxiolytic. All benzodiazepines have sedative properties, and some can produce hypnosis (artificially-induced sleep) at higher doses. Benzodiazepines may be associated with anterograde amnesia

Some benzodiazepines **have anticonvulsant.** At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord

| Long-acting | Intermediate acting | Short acting |
|---|---|---|
| **Clorazepate** | **Alprazolam** (Xanax®, Zolam®, Alprax®, Restolam®) | **Midozolam** (Dormicum®, Mediathetic®) |
| **Chlordiazepoxide** | **Temazepam** | **Oxazepam** |
| **Diazepam** (Valium®, Valpam®) | **Lorazepam** (Ativan®) | **Triazolam** |
| **Flurazepam** | | |

**Therapeutic uses:**

**Indication of BZ** The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another.

**Therapeutic uses of benzodiazepine**

**Anxiety disorders:** Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder and generalized anxiety disorder (GAD),

These drugs should not be used to alleviate the normal stress of everyday life. They should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential.

**Muscular disorders**: Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain.

**Induction of anesthesia**: **Midazolam** is used as preaneathetic medication

**Seizures: Clonazepam** is occasionally used in the treatment of certain types of epilepsy, whereas **diazepam and lorazepam** are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus

**Sleep disorders:** Not all benzodiazepines are useful as hypnotic. Agents used for sleep disorders include

- Long-acting **flurazepam**
- Intermediate-acting **temazepam**
- Short-acting **triazolam.**

**Benzodiazepines Pharmacokinetics**

benzodiazepines rapidly and completely absorbed after oral administration and distribute throughout the body metabolized by the hepatic microsomal system to compounds that are also active.

**Excretion**: The drugs' effects are terminated not only by excretion but also by redistribution.

**Dependence**

Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including: Confusion, Restlessness, Anxiety, Agitation, Insomnia, Tension.

**Tolerance:** Tolerance occurs when used for more than 1 to 2 weeks. Tolerance is associated with a decrease in GABA-receptor density.

**Adverse effects**

- Drowsiness and confusion
- Ataxia occurs at high doses
- Cognitive impairment (decreased long term recall and retention of new knowledge) can occur with use of benzodiazepines.

**Precautions:** Benzodiazepines should be used cautiously in treating patients with liver disease. These drugs should be avoided in patients with acute narrow- angle glaucoma.

**Benzodiazepine antagonist:** Flumazenil is a GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but duration is short, with a half life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine.

Flumazenil induces some side effects such as dizziness, nausea, vomiting, and agitation.

**Advantage of benzodiazepines**

- Safe with high therapeutic index
- Have specific antidote
- Produce less respiratory and circulatory depression
- Risk of dependence is low and withdrawal symptom is less intense.

## III. Other anxiolytic agents

**Antidepressants** Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders especially **Selective serotonin reuptake inhibitors**

**Antihistamines** : Some antihistamines with sedating properties, such as **diphenhydramine, hydroxyzine and doxylamine,** are effective in treating mild types of insomnia but they have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines

**Buspirone**

Buspirone is useful for the chronic treatment of GAD and has an efficacy comparable to that of the benzodiazepines. This agent is not effective for short-term or "as-needed" treatment of acute anxiety states.

Although many serotonin receptors are implicated, the main action is mediated by 5- $HT_{1A}$ receptor. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. Buspirone has the disadvantage of a slow onset of action.

**Ramelteon**

Ramelteon [ram-EL-tee-on] is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Stimulation of MT1 and MT2 receptors by melatonin is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep–wake cycle.

Normally, light stimulating the retina transmits a signal to hypothalamus then to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin.

*Ramelteon* is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The potential for abuse of *ramelteon* is believed to be minimal, and no evidence of dependence or withdrawal effects has been observed. Therefore *ramelteon* can be administered long term.

adverse effects of *ramelteon* include dizziness, fatigue, and somnolence and increased prolactin levels.

# Antiepileptic drugs

Epilepsy is a chronic neurological disorders characterized by seizure. Epilepsy is controlled but not cured

**Causes of epilepsy :**

- Idiopathic
- Neoplasm
- Asphaxia
- Birth truma
- Metabolic defect
- Congenital malformation
- Serious head injury Hereditary
- Metabolic (hypoglycemia)
- Infection (meningeitis)
- Medication (drug withdrawal )

**Classification of seizures**

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been classified into two broad groups:

1. Partial (or focal)
2. Generalized.

A. Partial seizures involve only a portion of the brain ( consciousness is usually preserved).

1. Simple partial: The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain

experiencing the electrical disturbance. The patient does not lose consciousness.

2. Complex partial: These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered.

Simple partial seizure activity may spread to become complex and then spread to a generalized convulsion.

Complex partial seizures may occur at any age.

B. Generalized

- Generalized seizures include abnormal electrical discharges throughout both hemispheres of the brain.
- 1. tonic -clonic seizures (Grand mal epilepsy) : unconsciousness, convulsion and muscle rigidity
- 2. Myoclonic seizures: sporadic jerks like electric shocks
- 3. Petite mal (absence of seizure ) brief loss of consciousness especially in children
- 4. Atonic seizure: loss of muscle tone

**Status epilepticus:** In status epilepticus, two or more seizures occur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment.

**Mechanism of action of antiepileptic drugs**

**1. Blocking voltage gated channels (Na+ or Ca2+):**

A) Block of Na channel, inhibition of action potential

- Phenytoin and carbamazepine

B) Block of Ca influx

- Ethouxamide and Na valproate

3. **Enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses**

A) Facilitate GABA mediated opening of Cl channel

- BZ and phenobarbitone

B) Inhibiting GABA transaminase : valproate, vigabatrin

C) Agonist at GABA a receptor : gabapentin

D) Inhibitinh GABA uptake into neuron tiagabine

3. **Interfering with excitatory glutamate transmission**

A) Antagonist at NMDA receptors: Felbamate

B) Inhibit gutamate release: Phenytoin and felbamate

Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined

**I: Blocking voltage gated channels (Na+ or Ca2+):**

**Phenytoin :**

Phenytoin blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. At very high concentrations, *phenytoin* can also block voltage dependent calcium

channels and interfere with the release of monoaminergic neurotransmitters.

Phenytoin is effective for treatment of partial seizures and generalized tonic-clonic seizures and in the treatment of status epilepticus

Side effect:

- Nystagmus and ataxia.
- Gingival hyperplasia may cause the gums to grow over the teeth
- Long-term use may lead to development of peripheral neuropathies and osteoporosis.

**Fosphenytoin**

It a is a prodrug and is rapidly converted to phenytoin in the blood, reaching high levels within minutes. Fosphenytoin may also be administered intramuscularly (IM). However, phenytoin sodium should never be given IM because it can cause tissue damage and necrosis.

**Carbamazepine**

Carbamazepine blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. Cbz is a drug of choice for partial siezure, used in treatment of neurogenic pain

Side effect: Diplopia , atexia, aplastic anemia, agranulocytosis

**Ethosuximide**

Ethosuximide reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. Ethosuximide also appears to inhibit the sodium-potassium ATPase system. **It is effective in**

**treating only absence seizures**

**Sodium valproate**

Valproic acid has been shown to block voltage- dependent sodium channels at therapeutically relevant concentrations. In several experimental studies, valproate caused an increase in brain GABA (Inhibiting GABA transaminase). There is evidence that valproate may also inhibit T-calcium channels and this may be important in its mechanism of action in patients with absence epilepsy. These varied mechanisms provide a broad spectrum of activity against seizures. This drug is effective for the treatment of partial and primary generalized epilepsies.

**II. Enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses**

**Benzodiazepines**

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. diazepam and lorazepam are most often used as an adjunctive therapy. *Lorazepam* has a shorter pharmacokinetic half-life but stays in the brain longer than *diazepam***.**

**Phenobarbital**

Phenobarbital enhances the inhibitory effects of GABA-mediated neurons. Phenobarbital in epilepsy should be used primarily in the treatment of status epilepticus.

**Vigabatrin :**

This drug acts as an irreversible inhibitor of γ-aminobutyric acid

transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA.

**Gabapentin**

Gabapentin was initially designed to be a rigid analogue of GABA. It augment GABA action Although it has not yet been possible to describe any definite mechanism to its antiepileptic activity.

**Tiagabine**

Tiagabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding, and therefore, to enhanced inhibitory activity. Tiagabine is effective in decreasing the number of seizures in patients with partial onset epilepsy.

**Felbamate**

Felbamate has a broad spectrum of anticonvulsant action. The drug has multiple proposed mechanisms including

- Blocking voltage-dependent sodium channels,
- Competing with the glycine- coagonist binding site on the n-methyl-d-aspartate (NMDA) glutamate receptor
- Blocking calcium channels
- Potentiating the action of GABA.

**Other new antiepileptic**

- Lacosamide
- Levetiracetam
- Rufinamid
- Zonisamide
- Lamotrigine
- Pregabalin
- Topiramate

# General anesthesia

General anesthesia is a reversible state of central nervous system (CNS) depression, resulting in loss of response to and perception of external stimuli.

Anesthesia provides these five important benefits:

1. Sedation and reduction of anxiety
2. Lack of awareness and amnesia
3. Skeletal muscle relaxation
4. Suppression of undesirable reflexes
5. Analgesia

**Preanesthetic medications**: The role of preanesthetic medications is Calm the patient, relieve pain , Minimize the undesirable side effects associated with some of the anesthetic agents and reducing the requirement for high anesthetic doses in addition Reducing the volume and acidity of gastric contents

Skeletal muscle relaxants facilitate intubation of the trachea and suppress muscle tone to the degree required for surgery.

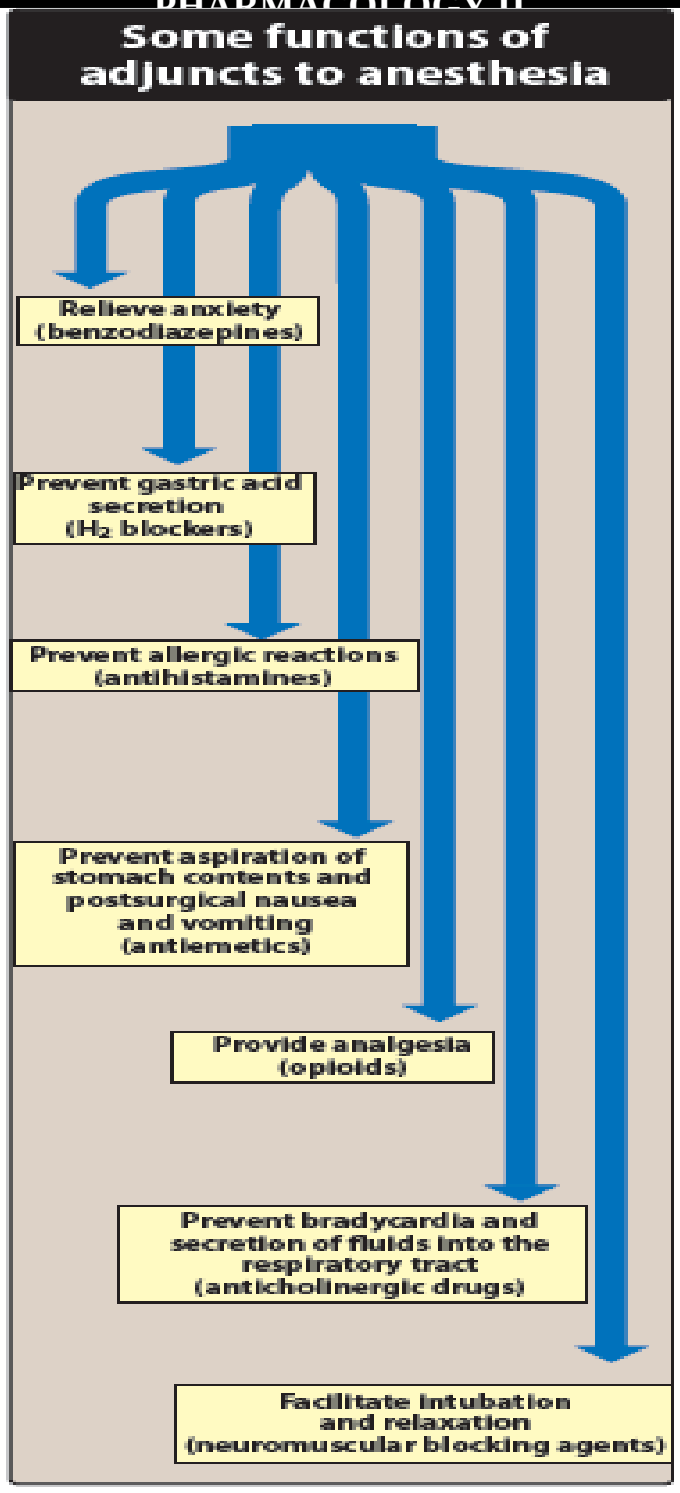
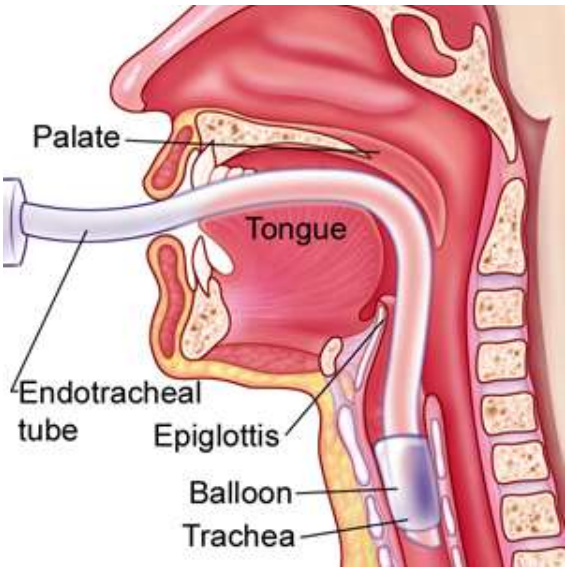



**Figure 11.2**
Components of balanced anesthesia.

During a general anesthetic, the airway is protected by the insertion of a tube (endotracheal tube) through the mouth and into the trachea (windpipe). A low pressure balloon is inflated between the tube and trachea wall to prevent secretions or stomach contents from getting into the trachea.




General anesthesia can be divided into three stages:

**Induction Maintenance** and **Recovery.**

**Induction :**Induction is defined as the period of time from the onset of administration of the potent anesthetic to the development of effective surgical anesthesia in the patient. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain

General anesthesia in adults is normally induced with an IV anesthetic like propofol . This often includes coadministration of an IV skeletal muscle relaxant.

**Maintenance of anesthesia**

Maintenance is the period during which the patient is surgically anesthetized. Anesthesia is commonly maintained by the administration of volatile anesthetics, which offer good control over the depth of anesthesia. Opioids such as *fentanyl* are often used for pain relief along with inhalation agents, IV infusions of various drugs may also be used during the maintenance phase.

**Recovery**

Recovery is the time from discontinuation of administration of anesthesia until consciousness and protective physiologic reflexes such as (spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, etc.) are regained depends on how fast the anesthetic drug diffuses from the brain

Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for the return of consciousness. Patients are observed for delayed reactions such as respiratory depression from opioids administered for postoperative pain control.

The depth of anesthesia has traditionally been divided into four sequential stages characterized by increased CNS depression:

- **Stage I—Analgesia**
- **Stage II—Excitement**
- **Stage III—Surgical anesthesia.**

• **Stage IV—Medullary paralysis.**

**Stage I—Analgesia:** Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy. Amnesia and reduced awareness of pain occur as Stage II is approached.

**Stage II—Excitement:**

The patient experiences delirium and possibly combative behavior. There is a rise and irregularity in blood pressure and respiration as well as a risk of laryngospasm. To shorten or eliminate this stage of anesthesia, a rapid acting agent, such as propofol, is given intravenously before inhalation anesthesia is administered.

**Stage III—Surgical anesthesia:**

There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur in this stage. This is the ideal stage of anesthesia for surgery. Continuous careful monitoring is required to prevent undesired progression into Stage IV.

**Stage IV—Medullary paralysis:**

Severe depression of the respiratory and vasomotor centers occur during this stage. Death can rapidly ensue unless measures are taken to maintain circulation and respiration.

**A) Inhalation anesthesia**:

They are administered through respiratory passage. They are used for long term maintenance of anesthesia. They divide into two classes

1. Volatile liquids at room temperature : Hologenated hydrocarbon such as halothan Enflurane and isoflurane and the old non used liquid diethyl ether (it explosive and inflammable) .
2. **Gases at room temperature** : They supplied as tanks ex nitrous oxide (N2O) and cyclopropan

**B) Intravenous anesthesia**:

These are generally employed to induce anesthesia, Provide supplemental anesthesia, Permit anesthesia for short operative procedures eg: ultra short acting barbiturates ; ketamine ; benzodiazepine (diazepam , midozolam); propofol.

## A:Inhalational anesthesia

### MECHANISM OF ACTION

All general anaesthetics depress spontaneous and evoked activity of neurones, especially synaptic transmission in the central nervous system. They cause hyperpolarization of neurones by activating potassium and chloride channels, and this leads to an increase in action potential threshold and decreased firing. - the general anesthetics increase the sensitivity of the γ- aminobutyric acid ($GABA_A$) receptors to the neurotransmitter, GABA. The activity of the inhibitory glycine receptors in the spinal motor neurons is

increased.

**Measure of potency**

The relative potencies of different anesthetics are expressed in terms of their minimum alveolar concentration (MAC), expressed as a percentage of alveolar gas mixture at atmospheric pressure.

The MAC of an anaesthetic is defined as the minimum alveolar concentration that prevents reflex response to a standard noxious stimulus in 50% of the population.

The low the MAC the more potent the drug

**Halothane**

This agent is the prototype to which newer inhalation anesthetics have been compared. Halothane relaxes both skeletal and uterine muscle.

**Pharmacokinetics:**

Halothane is oxidatively metabolized in the body to tissue- toxic hydrocarbons (for example, trifluoroethanol and bromide ion. These substances may be responsible for the toxic reaction that some patients (especially females) develop after halothane anesthesia. This reaction begins as a fever, followed by anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. 50% of affected patients may die of hepatic necrosis. To avoid this condition, halothane anesthesia is not repeated at intervals of less than 2 to 3 weeks. All halogenated inhalation anesthetics have been reported to cause hepatitis, but at a much lower incidence than

with halothane.

**Adverse effects**

halothane has the undesirable property of causing cardiac arrhythmias (sensitize muscle to epinepherine)

**Isoflurane**

It is a very stable molecule that undergoes little metabolism and is **not toxic to the liver or kidney.** Isoflurane (eye-soe-FLUR-ane) does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. It is considered safe in patients with **ischemic heart disease.** It has a pungent odor and stimulates respiratory reflexes (for example, breath-holding, salivation, coughing, and laryngospasm) and is, therefore, **not used for inhalation induction.**

**Sevoflurane**

Sevoflurane [see-voe-FLOOR-ane] has low pungency, low blood solubility enabling **rapid onset without irritating the airway and rapid recovery,** thus making it suitable for inhalation induction in pediatric patients.

**Nitrous oxide**

• Nitrous oxide is frequently employed at concentrations of **30-50** % in combination with oxygen for **analgesia. nitrous oxide at 80 % and 20% oxygen** cannot produce surgical anesthesia alone. Therefore, it is commonly **combined with other, more potent agents to attain pain-free**

**anesthesia.**

Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. This anesthetic does not depress respiration, and it does not produce muscle relaxation

**B) Intravenous anesthetics:**

**Induction** The majority of the Cardiac output (70 %) flows to the brain, liver, and kidney ("vessel-rich organs"). Thus, a high proportion of the initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from the blood into the brain. Once the drug has penetrated the CNS tissue, it exerts its effects.

**Recovery**

Recovery from IV anesthetics is due to **redistribution from sites in the CNS**. The drug starts to diffuse into other tissues with a lesser blood supply. This **initial redistribution** of drug into other tissues leads to the **rapid recovery seen after a single dose** of an induction drug. **Metabolism and plasma clearance** become important only following **infusions and repeat doses of a drug.**

**Adipose tissue** makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply. However, following repeat doses or infusions, **equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery.**

## Propofol

Propofol is an IV sedative/hypnotic used in the induction or maintenance of anesthesia. Propofol is widely used and has replaced thiopental as the **first choice for anesthesia induction and sedation**, because it produces a euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting.

**Onset:** The induction of anesthesia is smooth and occurs **within about 30-40 seconds of administration**

The pharmacokinetics of propofol are **not altered by moderate hepatic or renal failure.**

## Etomidate

Etomidate (ee-TOM-uh-date) is used to induce anesthesia. It is a Hypnotic agent but lacks analgesic activity. Its water solubility is poor, so etomidate is formulated in a propylene glycol solution.

Induction is rapid, and the drug is short acting. *Etomidate* have little to no effect on the heart and circulation. It is usually only used for patients with coronary artery disease or cardiovascular dysfunction such as shock.

## Ketamine

**Ketamine [KET-a-meen]:** a short-acting anesthetic, induces a **dissociated state in** which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative anesthesia provides **sedation, amnesia, and immobility.**

## Mechanism of action :

Ketamine interacts with the N-methyl-D-aspartate receptor. It also stimulates the central sympathetic outflow, which, in turn, causes stimulation of the heart with increased blood pressure and CO.

## Uses:

Kitamine is especially beneficial in patients with either hypovolemic or cardiogenic shock as well as in patients with asthma. On the other hand, kitamine is not used in hypertensive or stroke patients.

## Local anesthetics

Local anesthetics **abolish sensation** and, in higher concentrations, motor activity in a limited area of the body. They are applied or injected to **block nerve conduction** of sensory impulses from the periphery to the CNS.

Local anesthesia is induced when propagation of action potentials is prevented, so that sensation cannot be transmitted from the source of stimulation to the brain.

### Mechanism of action

Local anesthetics work by blocking sodium ion channels to prevent the transient increase in permeability of the nerve membrane to sodium that is required for propagation of action potential to occur.

### Route of administration

Delivery techniques include topical administration, infiltration, ring blocks, peripheral nerve blocks, and neuraxial (spinal, epidural, or caudal) blocks

**The most widely used of the local anesthetic compounds are:**

**Amide:** Bupivacaine- - Lidocaine - prilocaine - Lignicaine

**Ester:** Tetracain - Benzocain- Cocain

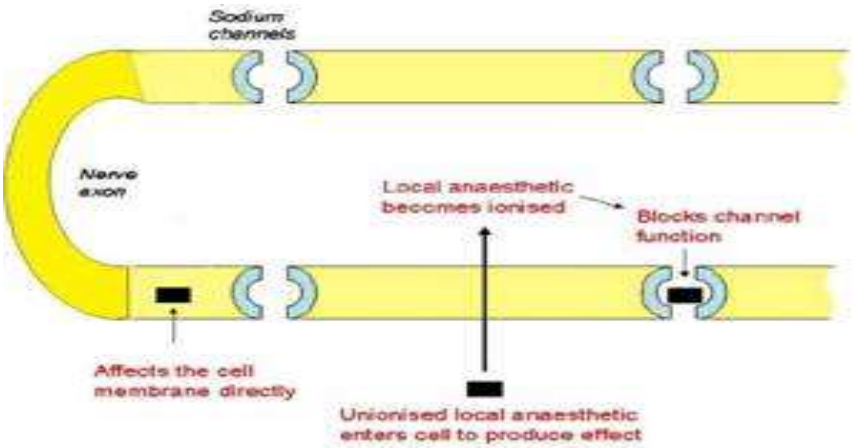
### (Acid-base considerations)

Most local anesthetics are weak bases, Usually prepared as a salt (e.g., with HCl) to increase stability, water solubility. When injected, 5%-40% is converted to the nonionized free base.

$$BH^{+} \longleftrightarrow \mathbf{B} + H^{+}$$

The **uncharged form (B)** is responsible for penetration of epineuronal and neuronal membrane

Once the membrane reach the axoplasm of the neurons the base gain proton and become ionized form **(BH)** this form is responsible for blocking Na channel from the inner side of the neuronal membrane. The equilipruim between ionized and non ionzed form affect the onset of action and of local anethetic




**I.** 25% of Lignocaine is unionized at physiological PH (7.4)

**II.** 15% of bupavacaine is unionized at physiological PH (7.4)

## Lignocaine has a fast onset of action than bupavacaine

Infected tissues is not affected by local anesthetic agent because infected tissues shift the physiological PH into has a acidic PH (local anesthetic become ionized). Infected tissues has a high blood supply which increase removal of drug

# Autacoids

**Autacoid types:**

- **Amines:** Histamine and 5-HT (Serotonin)
- **Eicosanoids (lipid derived autacoides):** Prostaglandins, Leukotrienes and thromboxane
- **Vasoactive peptides:** Kinins, Renin, Angiotensin, Natriuretic peptide, Vasopressin peptide, Substance P
- **Endothelin derived:** Nitric oxide

## HISTAMINIC AGONIST & ANTAGONIST

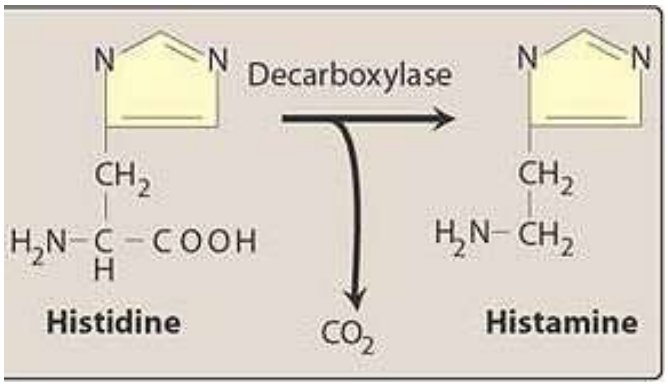
**Place:** Tissues rich in histamine are skin, gastric and intestinal mucosa, lungs, liver, brain, epidermis, gastric mucosa and placenta.

**Synthesis, storage and destruction.**

**Synthesis:** It is synthesized locally from the amino acid histidine by decarboxilation.

**Storage:** It is present mostly within storage granules of mast cells.

**Destruction:** It is degraded rapidly by oxidation and methylation



- **Histamine releasers:**
  1- Alkaloids; Morphine, tubocurarine.
  2- Antibiotics; penicillins, tetracyclines and polymixins.
  3- Basic drugs; amides, amidines, diamidines.
  4- Large molecular weight substances; dextran, PVP, ovalalbumin.
  5- Toxins, venoms, proteolytic enzymes, kinins, substance P.

Four types of histaminergic receptors have now been clearly delineated and cloned.

***Histamine receptors:***

- $H_1$: Localised in avascular smooth muscles, bronchial muscles and exocrine glands. Also found in resistance blood vessels of capillaries and venules.
- $H_2$: Localised in gastric parietal cells, cardiac muscle cells and immune cells, as well as in resistance and capacitance vessels.
- $H_3$: Autoregulatory receptors primarily presynaptic (activation causes decrease in transmitter release {transmitters: histamine, acetylcholine, norepinephrine, serotonin)

## PHARMACOLOGICAL ACTIONS OF HISTAMINE.

**Blood vessels:** Histamine causes marked dilatation of smaller blood vessels, including arterioles, capillaries and venules. Dilatation of cranial vessels causes pulsatile headache. Histamine also causes increased capillary permeability due to separation of endothelial cells increase exudation of plasma.

**Heart:** Direct effects of histamine on in situ heart are not prominent.

**Visceral smooth muscle:** Histamine causes bronchoconstriction; patients of asthma are highly sensitive. Smooth muscle contraction is a H1 response.

**Glands:** Histamine causes marked increase in gastric secretion—primarily of acid but also of pepsin. This is a direct action exerted on parietal cells through H2 receptors.

**Sensory nerve endings:** Itching occurs due to capacity of histamine to stimulate nerve endings.

**Autonomic ganglia and adrenal medulla:** These are stimulated and release of Adrinaline occurs, which can cause a secondary rise in BP.

**CNS:** Histamine does not penetrate blood brain barrier—no central effects

## PATHOPHYSIOLOGICAL ROLES

**Gastric secretion:** Histamine has dominant physiological role in mediating secretion of HCl in the stomach through H2 receptors. H2 blockers not only suppress acid secretion induced by histamine but also markedly diminish that in response to ACh and gastrin.

**Allergic phenomena:** Mediation of hypersensitivity reactions.

**As transmitter:** Histamine is believed to be the afferent transmitter which initiates the sensation of itch and pain at sensory nerve endings.

**Inflammation:** Histamine is a mediator of vasodilatation and other changes that occur during inflammation.

**Tissue growth and repair:** Because growing and regenerating tissues contain high concentrations of histamine, it has been suggested to play an essential role in the process of growth and repair.

**Headache:** Histamine has been implicated in certain vascular headaches, but there is no conclusive evidence.

**USES Histamine has no therapeutic use.**

Betahistine: It is an orally active, somewhat H1 selective histamine analogue, which is used to control vertigo in patients of Meniéré's disease: possibly acts by causing vasodilatation in the internal ear. It is contraindicated in asthmatics and ulcer patients.

## ANTIHISTAMINIC DRUGS

***$H_1$-receptor antagonists (anti-histaminics):***

***1. First generation agents:***

***Ethanolamines:*** *Clemastine fumarate, diphenhydramine (dimenhydrinate).*

***Ethylenediamines:*** *Pyrilamine maleate, tripelnnamine citrate.*

***Alkyamines:*** *Chlorpheniramine maleate, brompheniramine maleate.*

***Piperazines:*** *Hydroxyzine HCl, cyclizine HCl, Meclizine HCl.*

***Phenothiazines:*** *Promethazine HCl.*

*The 1st generation antihistaminics are characterized by relatively strong sedating effect (due to more CNS penetration), shorter duration of action ($t_{1/2}$ = 4-12 h). On the other hand the 2nd generation have relatively less sedating effect (less lipid soluble) and longer duration of action ($t_{1/2}$ = 12 – 24 h).*

***2. Second generation agents:***

***Alkyamines:*** *Acrivastine.*

***Piperazines:*** *Cetrizine HCl.*

***Piperidines:*** *Astemizole, Levocabastine HCl, Loratadine, Terfenadine, fenoxyfenadine.*

***3. Third generation agents: desloratadine***

1- H1 antagonist effectively block histamine induced bronchoconstriction, contraction of intestinal and other smooth muscle and triple response—especially wheal, flare and itch.

2. Antiallergic action hypersensitivity (type I reactions) are suppressed. Urticaria, itching and angioedema are well controlled. Anaphylactic fall in BP is only partially prevented.

3. CNS the older antihistamines produce variable degree of CNS depression. This appears to depend on the compound's ability to penetrate the blood-brain barrier and its affinity for the central (compared to peripheral) H1 receptors. **The second generation antihistaminics** are practically nonsedating. Certain H1 antihistamines are effective in preventing motion sickness. It is not clear whether this is due to antagonism of histamine in the brain or reflects antimuscarinic property of these drugs. **Promethazine** also controls vomiting of pregnancy and other causes. Promethazine and few other antihistaminics reduce tremor, rigidity and sialorrhoea of parkinsonism. Some older antihistamines, especially **cyproheptadine,** have appetite stimulating effect. Some H1 antihistamines are also effective antitussives

4. Anticholinergic action many H1 blockers in addition antagonize muscarinic actions of ACh.

**5.** Local anaesthetic: Some drugs like **pheniramine, promethazine, diphenhydramine** have strong while others have weak membrane stabilizing property.

**6. BP** most antihistaminics cause a fall in BP on i.v. injection (direct smooth muscle relaxation or α adrenergic blockade as in **promethazine**). However, this is not evident on oral administration.

**PHARMACOKINETICS** the conventional H1 antihistaminics are well absorbed from oral and parenteral routes, metabolized in the liver and excreted in urine. They are widely distributed in the body and enter brain.

**SIDE EFFECTS AND TOXICITY** Sedation, diminished alertness and concentration, light headedness, motor incoordination, fatigue and tendency to fall asleep are the most common. Dryness of mouth, alteration of bowel movement, urinary hesitancy and blurring of vision can be ascribed to anticholinergic property. Epigastric distress and headache may be felt.

**SECOND GENERATION ANTIHISTAMINICS** the following properties Absence of CNS depressant property. Higher H1 selectivitiy: no anticholinergic side effects. Their principal indications are: (i) Allergic rhinitis and conjunctivitis, hay fever, runny but not blocked nose, and red, watering, itchy eyes. (ii) Urticaria, dermographism, atopic eczema. (iii) Acute allergic reactions to drugs and foods. They have poor antipruritic, antiemetic and antitussive actions. **Fexofenadine** has a free of arrhythmogenic potential, but some cases of ventricular arrhythmiain patients with preexisting long QT interval have been reported. **Fexofenadine** does not cross blood-brain barrier—does not produce sedation or impair psychomotor performance and is free of atropinic side effects. **Loratadine** another long-acting

selective peripheral H1 antagonist which lacks CNS depressant effects and is fast acting. **Desloratadine** It is the major active metabolite of **loratadine** effective at half the dose. **Cetirizine** It is a metabolite of hydroxyzine with marked affinity for peripheral H1 receptors; penetrates brain poorly, but mild sedation and subjective somnolence. **Levocetirizine** It is the active R(–) enantiomer of cetirizine. It is effective at half the dose and appears to produce less sedation and other side effects. **Azelastine** this newer H1 blocker has good topical activity; in addition it inhibits histamine release and inflammatory reaction triggered by LTs. **Mizolastine** this non-sedating antihistaminic is effective in allergic rhinitis and urticaria by single daily dosing despite a t½ of 8–10 hr and no active metabolite.

**USES.**

**Allergic disorders** Antihistaminics do not suppress AG: AB reaction, but block the effects of released histamine—are only palliative.

**Pruritis** many conventional antihistamines have antipruritic action independent of H1antagonism.

**Common cold** antihistaminics do not affect the course of the illness but may afford symptomatic relief by anticholinergic (reduce rhinorrhoea) and sedative actions.

**Motion sickness** Promethazine, diphenhydramine, dimenhydrinate and meclozine have prophylactic value in milder types of motion sickness; should be taken one hour before starting journey. Promethazine can also be used in morning sickness, drug induced and postoperative vomiting, radiation sickness.

**Vertigo** Cinnarizine is the H1 antihistamine having additional anticholinergic, anti-5-HT, sedative and vasodilator properties which has been widely used in vertigo.

**Preanaesthetic medication-** Promethazine has been used for its anticholinergic and sedative properties.

**Cough-** Antihistaminics like chlorpheniramine, diphenhydramine and promethazine are constituents of many popular cough remedies.

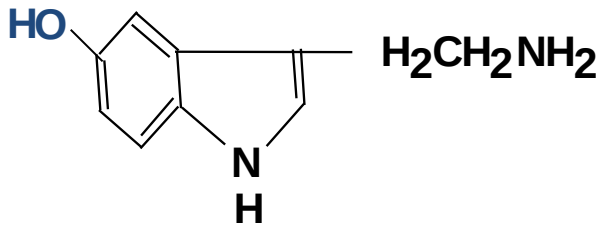
**Parkinsonism**- Promethazine and some others afford mild symptomatic relief in early cases—based on anticholinergic and sedative property.

**As sedative, hypnotic, anxiolytic**- Antihistamines with CNS depressant action have been used as sedative and to induce sleep, especially in children.

H2 antagonist Cimetidine, Ranitidine, famotidine, roxatidine, are primarily used in peptic ulcer, gastroesophageal reflux and other gastric hypersecretory states.

H3 antagonist Though some selective H3 antagonists have been produced, they have not found any clinical utility

**5-HYDROXYTRYPTAMINE: Serotonin SYNTHESIS, STORAGE AND DESTRUCTION**




5-hydroxytryptamine

**SYNTHESIS:** It is synthesized from the amino acid tryptophan by decarboxylase that converts 5-hydroxytryptophan into 5-HT.

**STORAGE:** Most serotonin (> 90%) is stored into enterochromaffin cells of the GI tract.

Blood serotonin is stored in platelets by an active carrier-mediated transport system (similar to nerve endings).

CNS locations: Serotonin is mainly stored in raphe nuclei (brain stem) and is responsible for an array of central effects including mood, sleep, appetite, temperature regulation, pain perception, blood-pressure regulation and vomiting.

**DESTRUCTION:**

Catabolism is achieved by Monoamine oxidase (MAO) to produce 5-hydroxyindoleacetaldehyde.

5-hydroxyindoleacetaldehyde is further oxidized by aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA).

The amount of 5-hydroxyindoleacetic acid (5-HIAA) excreted in urine is a measure of serotonin biosynthesis.

Excessive serotonin synthesis may be helpful as a diagnostic test for certain tumors (e.g. carcinoid)

**RECEPTORS**: Seven families of 5-HT receptors (5-HT1, 5-HT2, 5-HT3, 5-HT4-7) comprising of 14 receptor subtypes have so far been recognized.

5-HT1 Receptors Five subtypes (5-HT1A, B, D, E, F) have been identified.

5-HT2 Receptors There are 3 subtypes of 5-HT2 receptor;

5-HT3 Receptor

5-HT4 receptor has been demonstrated in the mucosa, plexuses and smooth muscle of the gut → probably involved in augmenting intestinal secretion and peristalsis.

## Pharmacology:

### 5-HT involved in everything, but responsible for nothing

1- In the microcirculation 5-HT dilates arterioles and constricts venules: capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

2. Visceral smooth muscles 5-HT is apotent stimulator of g.i.t., both by direct action as well as through enteric plexuses. Peristalsisis increased and diarrhoea can occur (also due to increased secretion). It constricts bronchi, but is less potent than histamine and leukotrienes.

3. Glands 5-HT inhibits gastric secretion (both acid and pepsin), but increases mucus production. It thus has ulcer protective property.

4. Nerve endings and adrenal medulla Afferent nerve endings are activated causing tingling and pricking sensation, as well as pain.

5. Respiration A brief stimulation of respiration and hyperventilation are the usual response, but large doses can cause transient apnoea.

6. Platelets By acting on 5-HT2A receptors 5-HT causes changes in shape of platelets, but is a weak aggregator.

7. CNS Injected i.v., 5-HT does not produce central effects because of poor entry across blood brain barrier.

**ROLES OF SERETONIN**

1. Neurotransmitter 5-HT is a confirmed neurotransmitter in the brain; 5-HT appears to be involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood, appetite, vomiting and pain perception.

2. Precursor of melatonin 5-HT is the precursor of melatonin in pineal gland. It is believed to regulate the biological clock and maintain circadian rhythm.

3. Neuroendocrine function The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

4. Nausea and vomiting Especially that evoked by cytotoxic drugs or radiotherapy is mediated by release of 5-HT and its action on 5-HT3 receptors in the gut.

5. Migraine 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels. Methysergide (5-HT antagonist) is an effective prophylactic and sumatriptan (5-HT1B/1D agonist) can control an attack. 5-HT1D (and 5-HT1B) agonist low or no affinity for other receptor subtypes. The clinical effect of triptans correlates with their affinity for 5-HT1D and 5-HT1B. Causes constriction of intracranial blood vessels. Used to treat acute attacks of migraine but not useful for prophylaxis. Reduces the nausea and vomiting associated with migraine. Note, Sumatriptan is metabolized by MAO-A, so can't be used in patients who are taking MAO inhibitors

Sumatriptan - Imitrex

Naratriptan - Amerge

Rizatriptan - Maxalt

Zolmitriptan - Zomig

6- Haemostasis Platelets release 5-HT during aggregation at the site of injury to blood vessel. 5-HT accelerates platelet aggregation and clot formation.

6. Raynaud's phenomenon Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries involved in Raynaud's phenomena. Ketanserin has prophylactic value.

7. Variant angina Along with thromboxane-A2, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina. However, the inefficacy of anti 5-HT drugs in this condition points to the involvement of other mediators.

8. Hypertension Increased responsiveness to 5-HT as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients. **Ketanserin** has antihypertensive property. 5-HT has been held responsible for pre-eclamptic rise in BP.

9. Intestinal motility Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut. This system appears to be activated by intestinal distension and vagal efferent activity.
Cisapride and renzapride are selective 5-HT4 agonists.

**DRUGS AFFECTING 5-HT SYSTEM.**

1. Uptake inhibitor Tricyclic antidepressants inhibit 5-HT uptake along with that of NA. The selective serotonin reuptake inhibitors (SSRI) like fluoxetine, sertraline, etc. inhibit only 5-HT reuptake and have antidepressant and antianxiety property.
2. Storage inhibitor Reserpine blocks 5-HT and NA uptake into storage vesicles.

Fenfluramine selectively releases 5-HT by promoting its reverse transport at serotonergic nerve endings in the brain.

3. Degradation inhibitor Nonselective MAO inhibitor (tranylcypromine) and selective MAO-A inhibitor (chlorgyline) increase 5-HT content by preventing its degradation.

4. 5-HT receptor agonists A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors. Notable among these are: (i)D-Lysergic acid diethyl amide (LSD) (ii)Azapirones (like buspirone) area novel class of antianxiety drugs which do not produce sedation. They act as partial agonists of 5-HT1A receptors in the brain. (iii) Sumatriptan and other triptans are selective 5-HT1D/1B agonists, constrict cerebral blood vessels and have emerged as the most effective treatment of acute migraine attacks. (iv) Cisapride This prokinetic drug which increases gastrointestinal motility is a selective 5-HT4 agonist. Renzaprideis still more selective for 5-HT4 receptors.

**5-HT receptor antagonists** A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

**5-HT ANTAGONISTS:** Cyproheptadine it primarily blocks 5-HT2A receptors and has additional H1 antihistaminic, anticholinergic and sedative properties.

**Side effects:** Drowsiness, dry mouth, confusion, ataxia, weight gain. **Methysergide** It is chemically related to ergot alkaloids; antagonizes action of 5-HT on smooth muscles including that of blood vessels, without producing other ergot like effects: does not interact with α adrenergic or dopamine receptors. **Methysergide** is a potent 5-HT2A/2C antagonist with some tissue specific agonistic actions as well; but is nonselective—acts on 5-HT1 receptors also. It has been used for migraine prophylaxis. Prolonged use has caused abdominal, pulmonary and endocardial fibrosis. **Ketanserin** It has selective 5-HT2 receptor

blocking property with negligible action on 5-HT1, 5-HT3 and 5-HT4 receptors and no partial agonistic activity. Among 5-HT2 receptors, blockade of 5-HT2A is stronger than 5-HT2C blockade. 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle are antagonized. **Ritanserin** relatively more 5-HT2A selective congener of ketanserin. **Clozapine** atypical antipsychotic is a 5-HT2A/2C blocker. **Clozapine** may also exert inverse agonist activity at cerebral 5-HT2A/2C receptors which may account for its efficacy in resistant cases of schizophrenia. **Ondansetron** It is the prototype of the new class of selective 5-HT3 antagonists that have shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy. **Granisetron and Tropisetron** are the other selective 5-HT3 antagonists. 5-$HT_4$ Agonists and their use in gastrointestinal disorders. 5-HT4 agonists promote GI motility - stimulate coordinated peristaltic activity. Tegaserod–Newer and more specific 5-HT4 agonist. Used to treat irritable bowel syndrome with constipation (abdominal pain, swelling and constipation). Found effective in women only.

**Side effects:** to sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting, but dose related side effects.

***Serotonin Agonists:***

- Buspirone: 5-$HT_{1A}$ agonist: non-benzodiazepine anxiolytic, which can be effective in treatment of smoking addiction.
- Sumatriptan: 5-$HT_{1D}$ agonist: Used in acute migraine and cluster headaches
- Ergotamine is a partial agonist at alpha adrenoceptors and 5-HT receptors. It constricts all peripheral arteries, including those involved in migraine.

***Serotonin Antagonists:***

- *Cyproheptadine:* Blocks serotonergic and histaminergic affects on smooth muscle with no effect on histamine-stimulated gastric secretion. It has significant antimuscarinic and sedative effects. It is mainly used to reduce smooth muscle effects of carcinoid tumor. It also may be given to children to stimulate appetite.
- *Ketanserin:* It blocks 5-$HT_{1c}$ and 5-$HT_2$ receptors (no activity on $H_1$ receptors). It also blocks $a_1$ adrenergic receptors, platelet 5-$HT_2$ receptors (inhibits serotonin-mediated platelet aggregation). It is an effective antihypertensive drug (probably acting through $a_1$ adrenergic receptors).
- *Ritanserin:* It blocks 5-$HT_2$ receptors (no alpha blocking properties) and may alter platelet function.
- *Ondansetron:* It is 5-$HT_3$ receptor blocker with minimal effects on dopamine, histamine, and adrenergic or cholinergic receptors. It has a major role in management of severe nausea and vomiting due to anticancer drugs. It is highly effective in reducing postoperative nausea/vomiting. It has reduced side effects compared to previously used antiemetic drugs such as phenothiazines, antihistamines, butyrophenones.
- *Tropisetron:* It is 5-$HT_3$ receptor blocker, which is effective in managing symptoms induced by carcinoid syndrome and it is effective in preventing chemotherapy/radio therapy-induced emesis, as well as in preventing postoperative nausea/vomiting when administered before general anesthetic induction.
- *Granisetron:* It is a more selective 5-$HT_3$ receptor blocker compared to ondansetron. It has the same clinical use as before. Its relatively longer half-life gives it a slight edge over ondansetron.

- *Dolasetron:* It is a highly potent selective 5-$HT_3$ receptor blocker. Its antiemetic effect is due to long-acting, active metabolite (hydrodolasetron; elimination half-life = approximately 8 hours).

## B- Vasoactive peptides

### 1- Angiotensin:

- Angiotensin I is produced from angiotensinogen by renin, an enzyme released from the juxtaglomerular apparatus of the kidney. An inactive decapeptide, angiotensin I is converted into angiotensin II, an octapeptide, by angiotensin converting enzyme (ACE), also known as peptidyl dipeptidase or kininase. Angiotensin II, the active form of the peptide, is rapidly degraded by peptidase (angiotensinases).

***Actions:***

- Angiotensin II is a potent arteriolar vasoconstrictor and stimulant of aldosterone release. Angiotensin II directly increases peripheral vascular resistance and, through aldosterone, causes renal sodium retention. It also facilitates the release of norepinephrine from adrenergic nerve ending via presynaptic heteroceptor action.
- Its major clinical significance is as a pathologic mediator in some cases of hypertension (high-renin hypertension) and in congestive heart failure. Therefore, angiotensin II antagonists are of considerable.

***Antagonists:***

- Angiotensin II receptor-blockers (e.g., losartan, valsartan) are orally active nonpeptide inhibitors at the angiotensin II $AT_1$ receptor. Saralasin, a peptide partial agonist at this receptor, is not used clinically. Angiotensin converting enzyme inhibitors (e.g., captopril, enalapril) are important agents for the treatment of hypertension and heart failure. Blocking the effects of angiotensin by either of these drug types is often accompanied by a compensatory increase in renin and angiotensin I.

**2- Bradykinin:**

- Bradykinin is one of several vasodilator kinins produced from kininogen by a family of enzymes, the kallikreins. Bradykinin is rapidly degraded by various peptidase, including angiotensin-cnverting enzyme.

***Actions:***

- Bradykinin produces vasodilation in several vascular beds, including the heart, kidney, intestine, skeletal muscle and liver. The peptide is thought to be involved in inflammation and causes edema and pain when released or injected into tissue.
- Bradykinin can be found in saliva and may play a role in stimulating its secretion. Although it has no therapeutic application, bradykinin may play a role in the antihypertensive action of ACEIs. There are no clinically important bradykinin antagonists.

**3- Atrial natriuretic peptide:**

- Atrial natriuretic peptide (ANP) is synthesized and stored in the cardiac atria of mammals. It is released from the atria in response to distention of the chambers.

***Actions:***

- ANP activates guanylyl cyclase in many tissues. It is a vasodilator as well as natriuretic (sodium excretion-enhancing) agent. Its renal action includes increased glomerular filtration, decreased proximal tubular sodium reabsorption, and inhibitory effects on renin secretion. The peptide also inhibits the actions of angiotensin II and aldosterone.

- ANP may play an important compensatory role in congestive heart failure by limiting sodium retention. There are no clinically important products that act as agonists or antagonists at ANP receptors.

**4- Endothelins:**

- Endothelins are peptide vasoconstrictors found in and released by endothelial cells in blood vessels. Three different endothelial peptides (ET1, ET2 and ET3) with minor variations in amino acid sequence have been identified in humans. Two receptors have been identified ($ET_A$ and $ET_B$), both of which are G protein coupled.
- The peptides may be involved in some forms of hypertension and other cardiovascular disorders. Bosentan, endothelin antagonist, has recentaly been discovered and has potential for the treatment of hypertension and vascular disease.

**5- Vasoactive intestinal peptide (VIP):**

- VIP is an exrtremely potent vasodilator but probably is physiologically more important as neurotransmitter. It is found in the central and peripheral nervous systems and in the gastrointestinal tract.

**6- Substance P:**

- Substance P is another neurotransmitter peptide with potent vasodilator action on arterioles. Highest concentrations of substance P are found in those parts of the nervous system that contain neurons subserving pain.

**7- Neuropeptide Y (NPY):**

- NPY is a potent vasoconstrictor that stimulates the heart. It is found in both the CNS and the peripheral nerves.

## C- Cytokines

- Cytokines are peptides produced by immune as well as non-immune cells. They have been shown to regulate immunologic responses, hematopoietic development as well as host responses to infectious agents and inflammatory stimuli. In most instances, cytokines mediate their effects via cell surface receptors in relevant target cells and appear to act in a manner similar to that of hormones.
- Substances considered as cytokines include interleukins 1 to 10, interferons, tumor necrosis factors, platelet-derived growth factor, transforming growth factor, chemokines and colony-stimulating factors.

### *1- Interleukin-1:*

- Interleukin-1 (IL-1) is a cytokine produced in infection and injury, or on antigenic challenge. Its primary source is the activated macrophage, but lymphoid, vascular, epithelial, epidermal tissues and various connective tissue cells can also synthesize it.
- There are two forms of IL-1: IL-1α and IL-1β and an endogenous IL-1-receptor antagonist (IL-1ra). IL-1 is held to be an important mediator in chronic inflammation (e.g., rheumatoid arthritis) and blockade of its receptors offers a therapeutic approach in this condition. IL-1ra binds to the same receptors and plays an antiinflammatory role. The therapeutic effects of glucocorticoids in rheumatoid arthritis may well be due to the fact that it inhibits both IL-1 production and IL-1 activity. Gold compounds also decrease IL-1 production.

### *2- Interferons:*

- Interferons are a group of inducible cytokines synthesized in response to viral and other stimuli. They are so named because they are found to interfer with replication of liver virus in tissue culture.
- There are three classes of interferon (INF), termed IFN-α, INF-β and INF-γ. All interferons have antiviral activity, and all can induce fever and possess antitumor effects in vitro. In addition, INF-γ promotes T cell growth, stimulates proliferation of B cells and activates macrophages. They are used in cancer treatment and to treat virus infections.

## D- Eicosanoids

- The eicosanoids are a family of polyunsaturated fatty acids formed from arachidonic acid. Arachidonic acid is derived mainly from phospholipids of cell membranes, from which it is mobilized by the action of the enzyme phospholipase A2.
- Arachidonic acid is then further metabolized as seen in the schematic diagram below by:
  - Cyclooxygenase to produce the 'classical prostaglandins', thromboxane and prostacyclin, collectively known as the prostanoids.
  - Lipoxygenase to produce the leukotrienes.

### *1. Cyclooxygenase products (prostanoids):*

- The term prostanoid encompasses prostaglandins (PGs), prostacyclins and thromboxanes (TXs).
- Cyclooxygenase enzyme occurs in every cell type bound to the endoplasmic reticulum and it catalyzes the formation of *cyclic endoperoxides*, $PGG_2$ and $PGH_2$ by oxygenation of arachidonate followed by cyclization.

- In platelets, the pathway leads to *thromboxane $A_2$* synthesis, in vascular endothelium it leads to *prostacyclin* synthesis and in macrophages it leads mainly to synthesis of *prostaglandin $E_2$* ($PGE_2$). Mast cells synthesize PGD2.
- The main receptors identified for the natural prostanoids, $PGD_2$, $PGF_{2\alpha}$, $PGI_2$, $TXA_2$ and $PGE_2$- termed DP, FP, IP, TP and EP receptors respectively.

***Actions of prostanoids:***

- The actions of PGD2 on DP receptors result in vasodilatation, inhibition of platelet aggregation, relaxation of gastrointestinal muscles, uterine relaxation, modification of release of hypothalamic/pituitary hormones. It induces bronchospasm via its action on TP receptors.
- $PGF_{2\alpha}$ stimulates FP receptors and causes myometrial contraction and bronchoconstriction. Receptors mediating its effects on the release of gonadotrophins and prolactin are not yet known.
- The action of $PGI_2$ (prostacyclin) on IP receptors causes vasodilatation, inhibition of platelet aggregation and fibrinolysis.
- The action of $TXA_2$ on TP receptors induces vasoconstriction, platelet aggregation and bronchoconstriction.
- $PGE_2$ produces the following effects:
    - On $EP_1$ receptors it causes contractions of gastrointestinal and bronchial muscles.
    - ON $EP_2$ receptors it causes bronchodilatation, vasodilatation, stimulation of intestinal fluid secretion and relaxation of GI smooth muscles.

- ON $EP_3$ receptors it causes contraction of intestinal smooth muscle, inhibition of gastric acid secretion, increased gastric mucus secretion, inhibition of lipolysis and stimulation of pregnant human uterus.

***Role of prostanoids in inflammation:***

- $PGE_2$, $PGI_2$ and $PGD_2$ are powerful vasodilator mediators that are released during inflammatory process.
- They augment the effects of other inflammatory mediators such as histamine and bradykinin resulting in redness and increased blood flow in areas of inflammation.
- They do neither increase capillary permeability nor produce pain *per se*, but they potentiate the actions of histamine and bradykinin.
- PGE series are implicated in the production of fever. Temperature induced by endogenous agents such as IL-1 is suggested to be via increased production of $PGE_2$, and the antipyretic action of NSAIDs is due to inhibition of the synthesis of $PGE_2$ in hypothalamus.

***Clinical uses:***

- $PGF_{2\alpha}$ (dinoprost), $PGE_2$ (dinoprostone) and their analogs; gemeprost and carboprost (15-methyl- $PGF_{2\alpha}$) are effective abortifacients. They are best given intravaginally.
- $PGE_1$ *(alprostodil)* is given by intravenous infusion in the treatment of congenital malformations of the heart of neonates to maintain the patency of the ductus arteriosus prior to surgical correction of the congenital defect.
- *Misoprostol* and enprostil are analogs of $PGE_2$ that act on $EP_3$ receptors to inhibit gastric acid secretion: they have also cytoprotective action, possibly by increasing mucus secretion, thus used in peptic ulcer.

- *Epoprostenol* is a preparation of prostacyclin that inhibits platelet aggregation. *Iloprost* and *cicaprost* are prostacyclin analogs that produce thrombolytic and vasodilator actions. *Butaprost* and *viprostol* are other prostacyclin analogs with bronchodilator and vasodilator effects.

***2. Lipoxygenase pathway products (leukotrienes):***

- 5-lipoxygenase acts on arachidonate to give 5-hydroperoxytetranoic acid, 5-HPETE) which is converted by a dehydrase to leukotriene 4 ($LTA_4$). This can be converted to either $LTB_4$ or to a series of cysteinyl-leukotrienes which have amino acids incorporated in their structure.
- $LTB_4$ is produced mainly by neurophils, and the cysteinyl-leukotrienes mainly by eosinophils, mast cells, basophils and macrophages.

***Actions:***

- $LTB_4$ is a powerful chemotactic agent, when generated by neutrophils during phagocytosis of microorganisms, which could amplify the effect of other chemotaxins such as C5a and PAF in promoting local accumulation of leucocytes.
- Cysteinyl-leukotriens have marked spasmogenic effects on bronchial muscles. $LTE_4$ is less potent than $LTC_4$ and $LTD_4$.
- Given i.v. $LTC_4$ or $LTD_4$ cause a rapid, short-lived fall in blood pressure, and constriction of small coronaries.
- Specific receptors for leukotrienes have been identified and competitive antagonists for these receptors are underway.
- $LTB_4$ is an important mediator in all types of inflammation; the cysteinyl-leukotrienes are thought to be of particular importance in asthma.

***Eicosanoids antagonists:***

1- Corticosteroids inhibit the production of arachidonic acid by phospholipases in the membrane. They also inhibit the synthesis of COX II. These actions are thought to be the major mechanisms of the important anti-inflammatory action of corticosteroids.
2- NSAIDs inhibit cyclooxygenase activity and thus inhibit the synthesis of both thromboxanes and prostaglandins.
3- Leukotriene antagonists (e.g., zileuton, zafirlukast) are approved only for use in asthma.

# Anemia

**Anemia:** the name is derived from Ancient Greek: anaimia, meaning "lack of blood", from - an-, "not" and aimia, "blood".

**Anemia** is the most common blood disorder, affecting about a third of the global population. It is a condition that develops when your blood lacks enough healthy red blood cells (decrease in the total amount of red blood cells (RBCs)) or hemoglobin or a lowered ability of the blood to carry oxygen. Hemoglobin is a main part of red blood cells and binds oxygen. If you have too few or abnormal red blood cells, or your hemoglobin is abnormal or low, the cells in your body will not get enough oxygen. People with chronic diseases are at increased risk of anemia.

**There are many types of anemia**. All are very different in their causes and treatments. There are more than 400 types of anemia, which are divided into three groups:

**Symptoms of anemia may include:**

- Fatigue (because organs aren't getting what they need to function properly). And may feeling tired. And a poor ability to exercise.
- Pale skin
- A fast or irregular heartbeat
- Shortness of breath
- Chest pain
- Dizziness
- Cognitive problems (confusion), loss of consciousness.

- Cold hands and feet
- Headache
- However, some types of anemia may present lifelong health problems.

**What Causes Anemia?**

Anemia can be caused by blood loss, decreased red blood cell production, and increased red blood cell breakdown.

Causes of blood loss include trauma and gastrointestinal bleeding.

Causes of decreased production include iron deficiency, vitamin B12 deficiency, thalassemia, and a number of neoplasms of the bone marrow.

Causes of increased breakdown include genetic conditions such as sickle cell anemia, infections such as malaria, and certain autoimmune diseases.

**Important causes are:**

- Certain forms of anemia are hereditary and infants may be affected from the time of birth.
- Women in the childbearing years are particularly susceptible to iron-deficiency anemia because of the blood loss from menstruation and the increased blood supply demands during pregnancy.
- Older adults also may have a greater risk of developing anemia because of poor diet and other medical conditions.

Macrocytic anemia will be to rule out therapy with drugs that interfere with nucleic acid metabolism, such as hydroxyurea, methotrexate, trimethoprim, zidovudine or

5-fluorouracil, as well as habitual intake of alcohol. Many therapeutic agents can induce this change in hemoglobin as an unwanted side effect.

**Classification:**

Anemia can also be classified based on the size of the red blood cells and amount of hemoglobin in each cell.

If the cells are small, it is called microcytic anemia;

If they are large, it is called macrocytic anemia; and

If they are normal sized, it is called normocytic anemia.

Anemia can also be classified based on the severity:

The anemia is also classified by severity into mild (110 g/L to normal), moderate (80 g/L to 110 g/L), and severe anemia (less than 80 g/L) in adult males and adult non pregnant females. Different values are used in pregnancy and children.

There are three major methods for classifying anemia. These are:

1. Classification of anemia based on mean cell (corpuscular) volume (MCV) and red cell distribution width (RDW)
2. Morphologic classification
3. Pathophysiologic classification

**Anemia Caused by Blood Loss**

Red blood cells can be lost through bleeding, which often can occur slowly over a long period of time, and can go undetected. This kind of chronic bleeding commonly results from the following:

- Gastrointestinal conditions such as ulcers, hemorrhoids, gastritis (inflammation of the stomach), trauma and cancer.
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen, which can cause ulcers and gastritis.
- Menstruation, especially if menstrual bleeding is excessive.

**Anemia Caused by Decreased or Faulty Red Blood Cell Production**

With this type of anemia, the body may produce too few blood cells or the blood cells may not function correctly. In either case, anemia can result. Red blood cells may be faulty or decreased due to abnormal red blood cells or a lack of minerals and vitamins needed for red blood cells to work properly. Conditions associated with these causes of anemia include the following:

- Sickle cell anemia
- Iron-deficiency anemia
- Vitamin deficiency
- Bone marrow (neoplasm) and stem cell problems
- Other health conditions

**Sickle cell anemia** is an inherited disorder. Red blood cells become crescent-shaped because of a genetic defect. They break down rapidly, so oxygen does not get to the body's organs, causing anemia. The crescent-shaped red blood cells can also get stuck in tiny blood vessels, causing pain.

**Iron-deficiency anemia** the most common type, is very treatable with diet changes and iron supplements. Iron-deficiency anemia affects nearly 1 billion people. In

2013, anemia due to iron deficiency resulted in about 183,000 deaths – down from 213,000 deaths in 1990. It is more common in women than men, during pregnancy, and in children and the elderly. Anemia lowers a person's productivity through a decreased ability to work. RBCs often appear hypochromic (paler than usual) and microcytic (smaller than usual) when viewed with a microscope. In the United States, 12% of all women of childbearing age have iron deficiency, compared with only 2% of adult men. The incidence is as high as 20% among African American and Mexican American women. Studies have shown iron deficiency without anemia causes poor school performance and lower IQ in teenage girls, although this may be due to socioeconomic factors. Worldwide, the most common cause of iron deficiency anemia is parasitic infestation (hookworms, amebiasis, schistosomiasis and whipworms).

Oral administration of ferrous salts (generic ferrous sulphate, ferrous fumarate, or ferrous gluconate) is preferred, but parenteral iron (iron dextran*)* can be given if oral therapy fails. Toxic reactions occur more frequently after parenteral iron administration. Gastrointestinal disturbances are common following oral dosages. Antacids may decrease the gastrointestinal absorption of iron. Iron may chelate or decrease the gastrointestinal absorption of drugs like levodopa and tetracycline. The stomach upset can be alleviated by taking the iron with food; however, this decreases the amount of iron absorbed. Vitamin C aids in the body's ability to absorb iron, so taking oral iron supplements with orange juice is of benefit. In the anemia of chronic kidney disease, recombinant erythropoietin or epoetin alfa is recommended to stimulate RBC production. In cases where oral iron has either proven ineffective, or where absorption is impeded (for example in cases of

inflammation), parenteral iron can be used concurrently with erythropoietin to ensure sufficient iron for increased rates of erythropoiesis.

Iron deficiency anaemia occurs because of a lack of the mineral iron in the body. Bone marrow in the centre of the bone needs iron to make hemoglobin, the part of the red blood cell that transports oxygen to the body's organs. Without adequate iron, the body cannot produce enough hemoglobin for red blood cells. The result is iron-deficiency anemia. This type of anemia can be caused by:

- An iron-poor diet, especially in infants, children, teens, vegans, and vegetarians
- The metabolic demands of pregnancy and breastfeeding that deplete a woman's iron stores
- Menstruation
- Frequent blood donation
- Endurance training
- Digestive conditions such as Crohn's disease or surgical removal of part of the stomach or small intestine
- Certain drugs, foods, and caffeinated drinks

**Megaloblastic Anemia,** It is characterized by the appearance of large cells in the bone marrow and blood due to defective maturation of hematopoietic cells. Folic acid or vitamin B12 deficiency will result in this type of anemia. Malabsorption, impaired use, chronic infections, and drugs can lead to folic acid or vitamin B12 deficiency. Folic acid or folate salts are administered to correct folate-deficient megaloblastic anemia. Vitamin B12–deficient patients receive cyanocobalamin supplements.

Dosage is very important, since patients with severe megaloblastic anemia may develop hypokalemia and die suddenly if treated intensively with vitamin B12. Vitamin B12 deficiency due to a lack of gastric intrinsic factor results in pernicious anemia. This type of megaloblastic anemia causes neurological damage if it is not treated. Treatment of Vitamin B12–deficient megaloblastic anemia with folic acid may improve the symptoms; however, neurological damage may still occur if vitamin B12 intake is not supplemented. Parenteral injections of vitamin B12 must be given.

**Sideroblastic Anemia,** It is characterized by excessive iron in the cells that cannot be incorporated into porphyrin to form heme. Although it is rare, the most common cause of sideroblastic anemia is alcoholism and pyridoxine deficiency. Pyridoxine is required for the formation of pyridoxal phosphate, a coenzyme in porphyrin synthesis.

**Diagnosis**

The blood test we use in our office is called “zinc protoporphyrin” or ZPP. A ZPP higher than 70 micromoles per mole usually indicates iron deficiency; less than 70 indicates normal iron stores. Other tests for iron deficiency include serum iron, per cent transferrin saturation, and serum ferritin. Just measuring hemoglobin or hematocrit is not an adequate test for iron deficiency. The diagnosis of anemia in men is based on a hemoglobin of less than 130 to 140 g/L (13 to 14 g/dL); in women, it is less than 120 to 130 g/L (12 to 13 g/dL). When the cause is not obvious, clinicians use other tests, such as: ESR, ferritin, serum iron, transferrin, RBC folate level, serum vitamin B12, hemoglobin electrophoresis, renal function tests (e.g. serum creatinine). When the diagnosis remains difficult, a bone marrow examination allows direct examination of the precursors to red cells, although is rarely used as is painful, invasive and is hence reserved for cases where severe

pathology needs to be determined or excluded. A decrease in hemoglobin stimulates erythropoiesis through an increase in circulating erythropoietin. The simple analysis of different parameters provided by the hematological analyzer gives a diagnosis of microcytic anemia. RDW helps to distinguish thalassemia from IDA. RDW is normal in thalassemia; on the contrary, microcytic anemia with RDW > 15 is probably IDA.

**Drug interactions:**

You can give the iron directly in the mouth or mix the iron medicine with a juice containing Vitamin C (orange juice, for example). This will improve iron absorption and prevent staining of the teeth. **Do not give iron with milk or formula because they reduce absorption.** Try to avoid giving the iron with food, as this also reduces absorption.

**Iron-Rich Diet**

The following foods contain iron:

- Meats, fish, and poultry have iron that is more easily absorbed than iron from plant sources.
- Raisins, dried fruits, sweet potatoes, lima beans, kidney beans, chilli beans, pinto beans, green peas, peanut butter, enriched cereals, and breads are other iron-rich foods. Spinach and egg yolks also contain iron, but it is in a form that is not readily available to the body to absorb.

**Vitamin-deficiency anemia** may occur when vitamin B12 and folate are deficient. These two vitamins are needed to make red blood cells. Conditions leading to anemia caused by vitamin deficiency include:

- Megaloblastic anemia: Vitamin B12 or folate or both are deficient
- Pernicious anemia: Poor vitamin B12 absorption
- Dietary deficiency: Eating little or no meat may cause a lack of vitamin B12, while overcooking or eating too few vegetables may cause a folate deficiency.
- Other causes of vitamin deficiency: pregnancy, certain medications, alcohol abuse, intestinal diseases such as tropical sprue and celiac disease

During early pregnancy, sufficient folic acid can help prevent the fetus from developing neural tube defects such as spina bifida.

**Bone marrow and stem cell problems**. Anemia resulting from bone marrow or stem cell problems include:

- Aplastic anemia occurs when there's a marked reduction in the number of stem cells or absence of these cells. Aplastic anemia can be inherited, can occur without apparent cause, or can occur when the bone marrow is injured by medication, radiation, chemo-therapy, or infection.
- Thalassemia occurs when the red cells can't mature and grow properly. Thalassemia is an inherited condition that typically affects people of Mediterranean, African, Middle Eastern, and Southeast Asian descent. This condition can range in severity from mild to life-threatening.
- Lead exposure is toxic to the bone marrow, leading to fewer red blood cells. Lead poisoning occurs in adults from work-related exposure and in children who eat paint chips, for example. Improperly glazed pottery can also taint food and liquids with lead.

## Anemia Caused by Destruction of Red Blood Cells

When red blood cells are fragile and cannot withstand the routine stress of the circulatory system, they may rupture prematurely, causing hemolytic anemia. Hemolytic anemia can be present at birth or develop later. Sometimes there is no known cause. Known causes of hemolytic anemia may include:

- Inherited conditions, such as sickle cell anemia and thalassemia
- Stressors such as infections, drugs, snake or spider venom, or certain foods
- Toxins from advanced liver or kidney disease
- Inappropriate attack by the immune system (called hemolytic disease of the newborn when it occurs in the fetus of a pregnant woman)
- Vascular grafts, prosthetic heart valves, tumors, severe burns, exposure to certain chemicals, severe hypertension, and clotting disorders
- In rare cases, an enlarged spleen can trap red blood cells and destroy them before their circulating time is up.

## Red blood cell size

The size is reflected in the mean corpuscular volume (MCV). If the cells are smaller than normal, the anemia is said to be microcytic; if they are normal size, normocytic; and if they are larger than normal, the anemia is classified as macrocytic.

### *Microcytic*

Microcytic anemia

Microcytic anemia is primarily a result of hemoglobin synthesis failure/insufficiency, which could be caused by several etiologies:

- Heme synthesis defect
    - Iron deficiency anemia (microcytosis is not always present)
    - Anemia of chronic disease (more commonly presenting as normocytic anemia)
- Globin synthesis defect
    - Alpha-, and beta-thalassemia
    - HbE syndrome
    - HbC syndrome
    - Various other unstable hemoglobin diseases
- Sideroblastic defect
    - Hereditary sideroblastic anemia
    - Acquired sideroblastic anemia, including lead toxicity[43]
    - Reversible sideroblastic anemia

***Macrocytic***

Macrocytic anemia

- Megaloblastic anemia, the most common cause of macrocytic anemia, is due to a deficiency of either vitamin $B_{12}$, folic acid, or both. Deficiency in folate or vitamin $B_{12}$ can be due either to inadequate intake or insufficient absorption. Folate deficiency normally does not produce neurological symptoms, while $B_{12}$ deficiency does.
    - Pernicious anemia is caused by a lack of intrinsic factor, which is required to absorb vitamin $B_{12}$ from food. A lack of intrinsic factor may arise from an autoimmune condition targeting the parietal cells

(atrophic gastritis) that produce intrinsic factor or against intrinsic factor itself. These lead to poor absorption of vitamin $B_{12}$.

- Macrocytic anemia can also be caused by removal of the functional portion of the stomach, such as during gastric bypass surgery, leading to reduced vitamin $B_{12}$/folate absorption. Therefore, one must always be aware of anemia following this procedure.

- Hypothyroidism
- Alcoholism commonly causes a macrocytosis, although not specifically anemia. Other types of liver disease can also cause macrocytosis.
- Drugs such as methotrexate, zidovudine, and other substances may inhibit DNA replication such as heavy metals

***Normocytic***

Normocytic anemia

Normocytic anemia occurs when the overall hemoglobin levels are decreased, but the red blood cell size (mean corpuscular volume) remains normal. Causes include:

- Acute blood loss
- Anemia of chronic disease
- Aplastic anemia (bone marrow failure)
- Hemolytic anemia

**Hyperanemia**

Hyperanemia is a severe form of anemia, in which the hematocrit is below 10%.

**Refractory anemia**

Refractory anemia, an anemia which does not respond to treatment, is often seen secondary to myelodysplastic syndromes. Iron deficiency anemia may also be refractory as a manifestation of gastrointestinal problems which disrupt iron absorption or cause occult bleeding.

**Blood transfusions**

Blood transfusions in those without symptoms is not recommended until the hemoglobin is below 60 to 80 g/L (6 to 8 g/dL). In those with coronary artery disease who are not actively bleeding transfusions are only recommended when the hemoglobin is below 70 to 80g/L (7 to 8 g/dL).

**Erythropoiesis-stimulating agents**

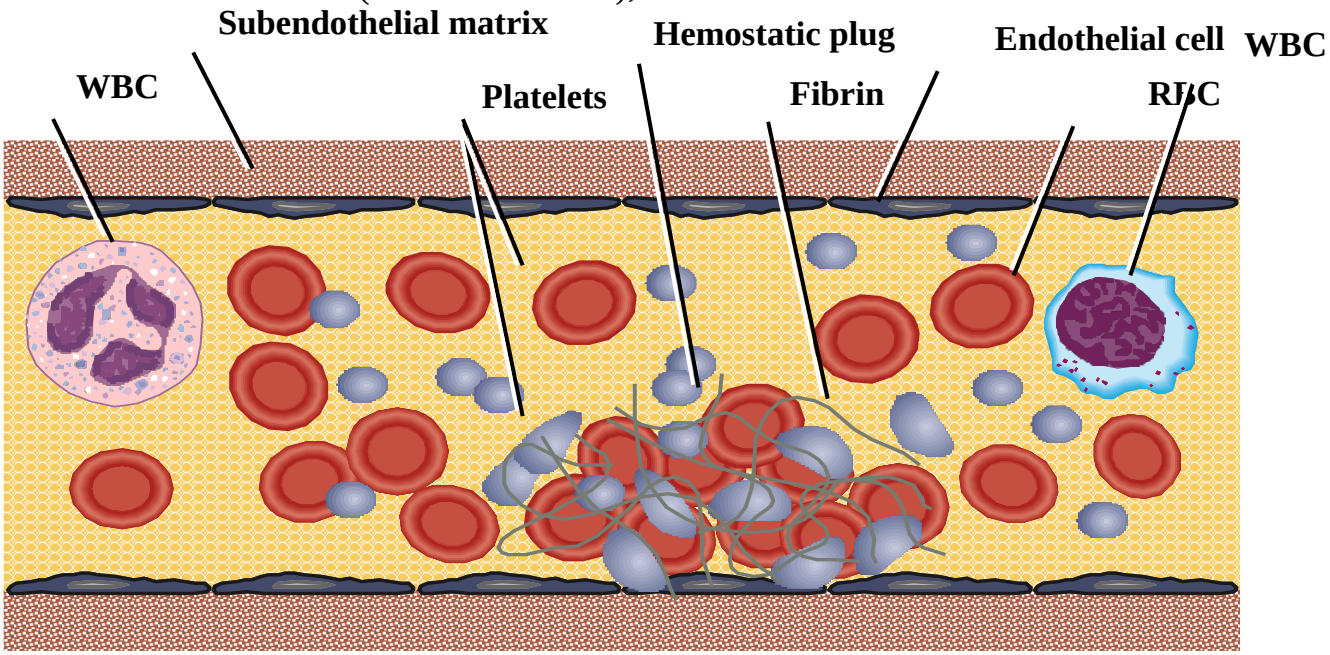
The objective for the administration of an erythropoiesis-stimulating agent (ESA) is to maintain hemoglobin at the lowest level that both minimizes transfusions and meets the individual person's needs. They should not be used for mild or moderate anemia. They are not recommended in people with chronic kidney disease unless hemoglobin levels are less than 10 g/dL or they have symptoms of anemia. Their use should be along with parenteral iron.

# Antithrombotic drugs

## Anticoagulant, Antiplatelet, Fibrinolytic (Thrombolytic) Drugs

Little intravascular coagulation of blood occurs in normal physiological conditions. Hemostasis involves the interplay of three procoagulant phases (*vascular*, *platelet*, and *coagulation*) that promote blood clotting to prevent blood loss.

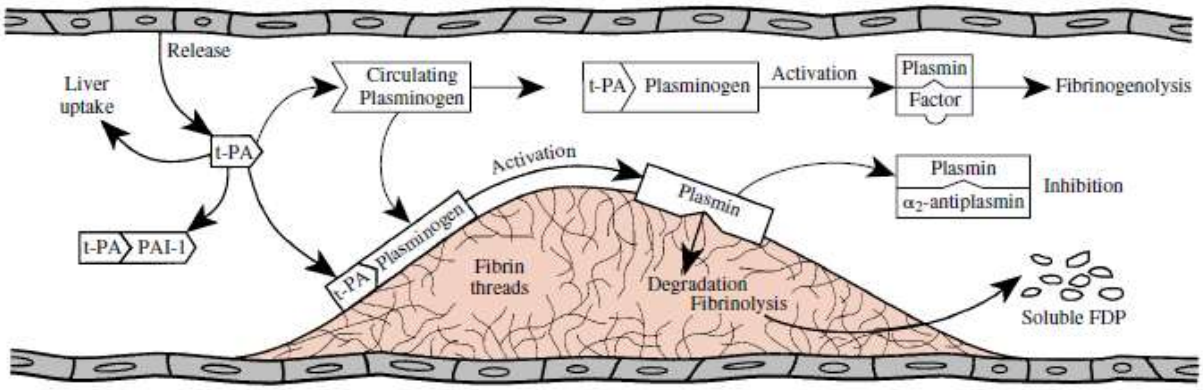
**During vascular phase:** The blood is maintained in a liquefied form during flow in healthy endothelial cells, when injury occurs and blood is exposed to subendothelial wall matrix, the blood vessels constrict to retared blood loss and stimulate tissue factors (Extrinsic factors), and ADP.




**During platelet phase:** After influence of ADP, the circulating platelets start to change its shape, increase in adhesion properties, IIb/IIIa receptor upregulated, increase in coagulation factor finally platelet aggregation; following platelet aggregation further increase in ADP, endoperoxides and thromboxane A2 (TxA2) occurs, which reversibly enhance further platelet aggregation.

**During coagulation phase:** as a result of expossure of blood to subendothelial wall matrix activate of the intrinsic factors, and tissue factors occure which that activate the extrinsic factors which finally convert prothrombin to thrombin that convert fibrinogen into fibrin monomer which attach together to make polymers.

The fibrinolytic system prevents propagation of clotting beyond the site of vascular injury and it is involved in clot dissolution, or lysis.




The fibrinolytic system in blood vessels showing the physiological mechanisms of activation of plasminogen on fibrin to cause fibrinolysis and the pathophysiological mechanism in the blood to cause fibrinogenolysis.

The release of t-PA from vascular endothelium and the inhibitory effect of α2-antiplasmin on plasmin activity.

## HEMOSTATIC MECHANISMS

Endothelial cells maintain a nonthrombogenic lining in blood vessels. This results from several phenomena, including

(1) the maintenance of a transmural negative electrical charge, which is important in preventing adhesion of circulating platelets;

(2) the release of plasminogen activators, which activate the fibrinolytic pathway;

(3) the activation of protein C, which degrades coagulation factors, a process involving thrombin and its endothelial cofactor (thrombomodulin);
(4) the production of heparinlike proteoglycans, which inhibit coagulation; and
(5) the release of prostacyclin (PGI2), a potent inhibitor of platelet aggregation.
Ordinarily, unstimulated platelets do not adhere to the endothelial cell surface.

## COAGULATION SYSTEMS

Two interrelated processes, the *intrinsic* and *extrinsic* coagulation systems, converge on a common pathway that leads to the activation of factor X, the formation of thrombin (factor IIa), and the conversion of the soluble plasma protein fibrinogen into insoluble fibrin by thrombin. The extrinsic pathway appears to be important for initiating fibrin formation, while the intrinsic pathway is involved in fibrin growth and maintenance; both systems constitute the coagulation cascade.

Exposure of blood to tissue factors activates the extrinsic system, beginning with the proteolytic conversion of factor VII into factor VIIa. Degradation of factors V and VIII:C by protein C at locations distant from the site of vascular injury aids in the localization of clot formation.

## ANTICOAGULANT DRUGS

Anticoagulant drugs inhibit the development and enlargement of clots by acting in the coagulation phase. They do not lyse clots or affect the fibrinolytic pathways.

### *Heparin*

Two types of heparin are used clinically. The standard (unfractionated) heparin, is an animal extract. The second and newer type, called low-molecular-weight heparin (LMWH), is derived from unfractionated heparin. The two classes are similar but not identical in their actions and pharmacokinetic characteristics.

## Standard (Unfractionated) Heparin

**Heparin (*heparin sodium*)** is a highly electronegative acidic mucopoly-saccharides. It is produced and released from mast cells and is abundant in liver, lungs and intestines.

## Mechanism of Action

The anticoagulant action of heparin depends on the presence of thrombin, antithrombin III, in normal blood. Heparin binds to antithrombin III and induces a conformational change that accelerates the interaction of antithrombin III with the coagulation factors. Heparin also catalyzes the inhibition of thrombin by heparin cofactor II, a circulating inhibitor.

## Absorption, Metabolism, and Excretion

Heparin is not absorbed after oral administration and therefore must be given parenterally. Intravenous administration results in an almost immediate anticoagulant effect.There is an approximate 2-hour delay in onset of drug action after subcutaneous administration. Intramuscular injection of heparin is to be avoided because of unpredictable absorption rates, local bleeding, and irritation. Heparin is not bound to plasma proteins or secreted into breast milk, and it does not cross the placenta. Heparin is terminated by metabolism in the liver and by renal excretion of the unchanged drug. Renal insufficiency reduces the rate of heparin clearance from the blood. Heparin inhibits both in vitro and in vivo clotting of blood. Whole blood clotting time and activated partial thromboplastin time (aPTT) are prolonged in proportion to blood heparin concentrations.

## Adverse Effects

The major adverse reaction is hemorrhage. Bleeding can occur in the urinary or gastrointestinal tract and in the adrenal gland. The incidence of life-threatening hemorrhage is low but variable. Heparin-induced thrombocytopenia of immediate

and delayed onset may occur in 3 to 30% of patients. Heparin-associated thrombocytopenia may also be associated with irreversible aggregation of platelets (white clot syndrome). Hypersensitivity reactions (e.g., rash, urticaria, pruritus), fever, alopecia, hypoaldosteronism, osteoporosis, and osteoalgia may also occure.

**Contraindications, Cautions, and Drug Interactions**

Absolute contraindications include serious or active bleeding; intracranial bleeding; recent brain, spinal cord, or eye surgery; severe liver or kidney disease; dissecting aortic aneurysm; and malignant hypertension. Drugs that inhibit platelet function (e.g., aspirin) or produce thrombocytopenia increase the risk of bleeding when concurrently administered with heparin.

**Oral anticoagulants and heparin produce synergistic effects.**

Many basic drugs precipitate in the presence of the highly acidic heparin (e.g., antihistamines, quinidine, quinine, phenothiazines, tetracycline, gentamicin, neomycin).

**Heparin Antagonist**

The specific heparin antagonist protamine can be employed to neutralize heparin in case of serious hemorrhage. Protamines are basic low-molecular-weight, positively charged proteins that have a high affinity for the negatively charged heparin molecules.

**Low-Molecular-Weight Heparin**

Low-molecular-weight fragments produced by chemical depolymerization and extraction of standard heparin consist of heterogeneous polysaccharide chains of molecular weight 2,000 to 9,000. The LMWH molecules contain the penta-saccharide sequence necessary for binding to antithrombin III. Compared to standard heparin, LMWH has a 2- to 4-fold antifactor Xa activity greater than antithrombin activity. LMWH has greater bioavailability than standard heparin, a

longer-lasting effect, and dose-independent clearance pharmacokinetics. The predictable relationship between anticoagulant response and dose allows anticoagulant control without laboratory tests. LMWH is more effective than standard heparin in preventing and treating venous thromboembolism. The incidence of thrombocytopenia after administration of LMWH is lower than with standard heparin. Adverse drug reactions like those caused by standard heparin have been seen during therapy with LMWH, and overdose is treated with protamine. LMWH is available for subcutaneous administration as enoxaparin (*Lovenox*), dalteparin (*Fragmin*), ardeparin (*Normiflo*), and tinzaparin (*Innohep*). Danaparoid (*Orgaran*), a heparinoid composed of heparin sulfate, dermatan sulfate, and chondroitin sulfate, has greater factor Xa specificity than LMWH. Bleeding due to danaparoid is not reversed by protamine.

**Orally Effective Anticoagulants**

The orally effective anticoagulant drugs are fat-soluble derivatives of 4-hydroxycoumarin or indan-1,3-dione, and they resemble vitamin K. *Warfarin is the oral anticoagulant of choice.* The indandione anticoagulants have greater toxicity than the coumarin drugs.

**Mechanism of Action**

Unlike heparin, *the oral anticoagulants induce hypocoagulability only in vivo.* They are vitamin K antagonists. Vitamin K is required to catalyze the conversion of the precursors of vitamin K–dependent clotting factors II, VII, IX, and X. This involves the posttranslational γ-carboxylation of glutamic acid residues at the *N*-terminal end of the proteins. The γ-carboxylation step is linked to a cycle of enzyme reactions involving the active hydroquinone form of vitamin K (K1H2). The regeneration of K1H1 by an epoxide reductase is blocked by the oral

anticoagulants. Commercial warfarin is a racemic mixture of S- and R-enantiomers; S-warfarin is more potent than R-warfarin.

**Absorption, Metabolism, and Excretion**

Warfarin is rapidly and almost completely absorbed after oral administration and is bound extensively (more than 95%) to plasma proteins. Since it is the unbound drug that produces the anticoagulant effect, displacement of albumin-bound warfarin by other agents may result in bleeding. Although these drugs do not cross the blood-brain barrier, they can cross the placenta and may cause teratogenicity and hemorrhage in the fetus.

Warfarin is inactivated by hepatic P450 isozymes; hydroxylated metabolites are excreted into the bile and then into the intestine. Hepatic disease may potentiate the anticoagulant response.

**Pharmacological Actions**

The onset of anticoagulation is delayed, the latency being determined in part by the time required for absorption and in part by the half-lives of the vitamin K–dependent hemostatic proteins. Warfarin is administered in conventional doses or minidoses to reduce bleeding.

**Adverse Effects**

The principal adverse reaction to warfarin is hemorrhage. Bleeding may be observable (e.g., skin, mucous membranes) or occult (e.g., gastrointestinal, renal, cerebral, hepatic, uterine, or pulmonary). Rarer effects include diarrhea, small intestine necrosis, urticaria, alopecia, skin necrosis, purple toes, and dermatitis.

**Contraindications, Cautions, and Drug Interactions**

Oral anticoagulants are ordinarily contraindicated in the presence of active or past gastrointestinal ulceration; thrombocytopenia; hepatic or renal disease; malignant hypertension; recent brain, eye, or spinal cord surgery; bacterial endocarditis;

chronic alcoholism; and pregnancy. Minor hemorrhage caused by oral anticoagulant overdosage can be treated by discontinuing drug administration.

Oral or parenteral vitamin K1 (phytonadione) administration will return prothrombin time to normal by 24 hours. This period is required for de novo synthesis of biologically active coagulation factors.

*Serious hemorrhage may be stopped by administration of fresh frozen plasma or plasma concentrates containing vitamin K–dependent factors.*

Dietary intake of vitamin K and prior or concomitant therapy with a large number of pharmacologically unrelated drugs can potentiate or inhibit the actions of oral anticoagulants. Laxatives and mineral oil may reduce the absorption of warfarin. The patient's prothrombin time and international normalized ratio (INR) should be monitored when a drug is added or removed from therapy.

**Direct Thrombin Inhibitor Anticoagulants**

Two drugs that are direct inhibitors of thrombin but that do not involve antithrombin III or vitamin K in their mechanism of action have been approved to provide intravenous anticoagulation in patients with heparin-induced thrombocytopenia.

Lepirudin (*Refludan*) and bivalirudin (*Angiomax*), which are analogues of the leech peptide anticoagulant hirudin, bind in a 1:1 complex with thrombin to inhibit its protease activity.

**Argatroban (*Acova, Novastan*),** a synthetic analogue of arginine, interacts reversibly with and inhibits thrombin's catalytic site. Both drugs have a short half-life.

**Lipuridin** is cleared following metabolism and urinary excretion of changed and unchanged drug; hepatic metabolism of argatroban is a therapeutic advantage in patients with renal insufficiency. No antagonists for these drugs are available.

**CLINICAL INDICATIONS FOR ANTICOAGULANT THERAPY**

Anticoagulant therapy provides prophylactic treatment of venous and arterial thromboembolic disorders.

*Anticoagulant drugs are ineffective against already formed thrombi,* although they may prevent their further propagation. Generally accepted major indications for anticoagulant therapy with heparin and warfarin include the following:

***Deep Vein Thrombosis***

***Arterial Embolism***

***Atrial Fibrillation***

***Unstable Angina and Myocardial Infarction***

*Thrombolytic drugs are more effective than anticoagulants in treating coronary thromboembolism and in establishing reperfusion of occluded arteries after an infarction.*

***Disseminated Intravascular Coagulation***

**ANTIPLATELET DRUGS**

The antiplatelet drugs are administered as adjuncts to thrombolytic therapy, along with heparin, to maintain perfusion and to limit the size of the myocardial infarction. Recently, antiplatelet drugs have found new importance in preventing thrombosis in percutaneous coronary intervention procedures (angioplasty and stent). Administration of an antiplatelet drug increases the risk of bleeding.

Aspirin inhibits platelet aggregation and prolongs bleeding time. It is useful for preventing coronary thrombosis in patients with unstable angina, as an adjunct to thrombolytic therapy, and in reducing recurrence of thrombotic stroke. It acetylates and irreversibly inhibits cyclooxygenase (primarily cyclooxygenase-1) both in platelets, preventing the formation of TxA2, and in endothelial cells, inhibiting the synthesis of PGI2. *The goal of therapy with aspirin is to selectively inhibit the synthesis of platelet TxA2 and thereby inhibit platelet aggregation.*

This is accomplished with a low dose of aspirin (160 to 325 mg per day), which spares the endothelial synthesis of PGI2.

**Dipyridamole** (*Persantine*), a coronary vasodilator, is a phosphodiesterase inhibitor that increases platelet cyclic adenosine monophosphate (cAMP) concentrations. It also may potentiate the effect of PGI2, which stimulates platelet adenylate cyclase. However, dipyridamole itself has little effect on platelets in vivo. Dipyridamole in combination with warfarin is beneficial in patients with artificial heart valves; it is also useful in combination with aspirin (*Aggrenox*) for the secondary prevention of stroke.

**Ticlopidine** (*Ticlid*) and **clopidogrel** (*Plavix*) are structurally related drugs that irreversibly inhibit platelet activation by blocking specific purinergic receptors for ADP on the platelet membrane. This action inhibits ADP-induced expression of platelet membrane GPIIb/IIIa and fibrinogen binding to activated platelets.

Ticlopidine and clopidogrel are useful antithrombotic drugs. Oral ticlopidine is indicated for prevention of thrombotic stroke in patients who cannot tolerate aspirin and for patients who have had thrombotic stroke.

Inhibition of ADP-induced platelet aggregation occurs within 4 days, and the full effect requires approximately 10 days.Ticlopidine is taken with food, is well absorbed, binds extensively to plasma proteins, and is metabolized by the liver.

**Side effects:**

Gastrointestinal disturbances, neutropenia, and agranulocytosis have been observed. Clopidogrel produces fewer side effects than ticlopidine.

Pharmacological agents, such as **abciximab** (*ReoPro*), **eptifibatide** (*Integrillin*), and **tirofiban** (*Aggrastat*), that interrupt the interaction of fibrinogen and Von Willebrand's factor with the platelet GPIIb/IIIa complex are capable of inhibiting aggregation of platelets activated by a wide variety of stimuli.These drugs are

given intravenously. The chimeric monoclonal antibody abciximab binds to the GPIIb/IIIa complex, preventing interactions of fibrinogen and Von Willebrand's factor with the integrin receptor. Abciximab is used in conjunction with angioplasty and stent procedures and is an adjunct to fibrinolytic therapy. Eptifibatide, a cyclic peptide, and tirofiban, a small nonpeptide molecule, both bind reversibly to the GPIIb/IIIa complex and competitively prevent the interaction of the clotting factors with this receptor.

**FIBRINOLYTIC SYSTEM**

The fibrinolytic system is involved in restricting clot propagation in the blood and in the removal of fibrin as wounds heal. *The purpose of thrombolytic therapy is rapid lysis of already formed clots.*

Fibrinolysis is initiated by the activation of the proenzyme *plasminogen* (present in clots and in plasma) into plasmin, a protease enzyme not normally present in blood. Plasmin catalyzes the degradation of fibrin. The conversion of plasminogen to plasmin is initiated normally by the plasminogen activators, tissue-type plasminogen activator (t-PA) and single-chain urokinasetype plasminogen activator (scu-PA). t-PA and scu-PA are serine protease enzymes synthesized by the endothelium and released into the circulation. The endothelium also releases plasminogen activator inhibitor-1 (PAI-1), which complexes with and inactivates t-PA in the plasma. t-PA and scu-PA bind with high affinity to fibrin on the clot surface. Circulating plasmin is rapidly neutralized by α2-antiplasmin, a physiological serine protease inhibitor that forms an inert complex with plasmin.

***Thrombolytic (Fibrinolytic) Drugs***

Thrombolytic drugs cause lysis of formed clots in both arteries and veins and reestablish tissue perfusion.

**Mechanism of Action**

*Thrombolytic drugs are plasminogen activators.* The ideal thrombolytic agent is one that can be administered intravenously to produce clot-selective fibrinolysis without activating plasminogen to plasmin in plasma.

**Pharmacological Actions and Clinical Uses**

Thrombolytic drugs are indicated for the management of severe pulmonary embolism, deep vein thrombosis, and arterial thromboembolism and are especially important therapy after myocardial infarction and acute ischemic stroke. Thrombolysis must be accomplished quickly after myocardial or cerebral infarction, since clots become more difficult to lyse as they age. Recanalization after approximately 6 hours provides diminishing benefit to the infarcted area. The incidence of rethrombosis and reinfarction is greater when thrombolytic drugs with shorter plasma half-lives are used. Concurrent administration with heparin followed by warfarin, as well as antiplatelet drugs, is advocated to reduce reocclusion. Adjunctive anticoagulant and antiplatelet drugs may contribute to bleeding during thrombolytic therapy.

**Adverse Effects**

Bleeding, hypofibrinogenemia may occur and should be monitored with laboratory tests. At effective thrombolytic doses, the second- and third-generation agents cause less extensive fibrinogenolysis, but bleeding occurs with a similar incidence for all agents. Life-threatening intracranial bleeding may necessitate stoppage of therapy, administration of whole blood, platelets or fresh frozen plasma, protamine (if heparin is present), and an antifibrinolytic drug.

**Contraindications**

The contraindications to the use of thrombolytic drugs are similar to those for the anticoagulant drugs.

**First-Generation Thrombolytic Drugs Streptokinase** (*Streptase, Kabikinase*), a nonenzymatic protein from Lancefield group C β-hemolytic streptococci, is an *indirectly acting* activator of plasminogen into plasmin.

**Complications** associated with the administration of streptokinase include hemorrhage, pyrexia, and allergic or anaphylactic reactions.

**Urokinase** (*Abbokinase*) is directly activates both circulating and fibrin-bound plasminogen. Urokinase is derived from human cells and thus is not antigenic.

Second- and Third-generation Thrombolytic Drugs The principal physiological activator of plasminogen in the blood, tissue-type plasminogen activator (t-PA, **alteplase)** (*Activase*), has a high binding affinity for fibrin and produces, after IV administration, a fibrin-selective activation of plasminogen. Alteplase causes less fibrinogenolysis than streptokinase, but bleeding occurs with a similar incidence. Alteplase is a product of recombinant DNA technology and consists predominantly of the single-chain form (recombinant human tissue-type plasminogen activator, rt-PA).

**Reteplase** (*Retavase*) contains only the peptide domains required for fibrin binding and protease activity. These changes increase potency and speed the onset of action. Reteplase may penetrate further into the fibrin clot than alteplase. The half-life of the drug remains short, however.

**Tenecteplase** (TNK-tPA) (*TNKase*) has a longer half-life than alteplase, binds more avidly to fibrin, and in contrast to many other thrombolytic agents, may be administered as an IV bolus.

***Antifibrinolytic Drugs***

Hyperplasminemia resulting from thrombolytic therapy exposes fibrinogen and other coagulation factors, plasminogen, and α2-antiplasmin to nonspecific proteolysis by plasmin, a process normally regulated by α2-antiplasmin.

These interactions are blocked by antifibrinolytic drugs such as aminocaproic acid (*Amicar*) and tranexamic acid (*Cyklokapron*); plasminogen activation primarily and plasmin proteolytic activity are inhibited.

In addition to being an *antidote to fibrinogenolysis* during thrombolytic therapy, antifibrinolytic drugs are used orally and intravenously to control bleeding following surgery. Antifibrinolytic drugs are contraindicated if intravascular coagulation is present.

# Hyperlipidemia and Antihyperlipidemic Drugs

**Hyperlipidemia:** Hyperlipidemia means there is too much cholesterol in the blood. Cholesterol is a waxy fat molecule that the liver produces. It is essential for healthy cell membranes; brain functioning, hormone production and vitamin storage. Atherosclerosis is the primary cause of coronary heart disease. Markedly lowering blood cholesterol can halt and even reverse to some extent the progression of atherosclerosis. Although hypercholesterolemias are linked to specific genetic mutations, most have a multifactorial basis that can respond to lifestyle changes.

**Symptoms:** Usually, people with hyperlipidemia do not experience any symptoms. However, those with familial, or inherited hyperlipidemia, may develop yellow, fatty growths around the eyes or joints. A doctor usually detects hyperlipidemia during a routine blood test or following a cardiovascular event, such as a heart attack or stroke. An excessive buildup of fat over time can cause atherosclerosis. This is when plaques develop on the walls of the arteries and blood vessels and narrow the openings. This can lead to unstable blood flow through the vessels and can greatly increase the risk of heart disease and stroke.

**Risk factors:**

The causes of hyperlipidemia include:

- Genetic factors: as primary hyperlipidemia.
- Poor diet and other factors.
- Excessive alcohol consumption.
- Obesity.

- Taking medications, such as hormones or steroids.
- Diabetes.
- Metabolic syndrome
- Long term kidney disease
- Premature menopause
- An underactive thyroid gland, or hypothyroidism
- Pregnancy
- Sedentary lifestyle

Familial hyperlipidemia stems from a genetic disorder.

A parent passes down a mutated gene that leads to a missing or malfunctioning LDL receptor. This means that the body cannot clear LDL from the bloodstream, which can result in dangerous levels of LDL in the blood.

The principal risk factors for heart disease are elevated levels of:

- LDL cholesterol,
- Family history of heart disease,
- Hypertension.
- Other risks include being male,
- Smoking,
- Low levels of high density lipoprotein (HDL) cholesterol,
- Diabetes mellitus,
- Hyperhomocystinemia,
- High levels of lipoprotein a (Lpa),
- High blood levels of C-reactive protein. It is a marker for cellular inflammation.

Homocysteine blood levels (>15 µmol/L) promote atherosclerosis, perhaps by stimulating proliferation of arterial wall smooth muscle cells. Supplementing the diet with folic acid can reduce high levels. Lpa is a modified LDL particle that is both atherogenic and prothrombic.

**Types:**

There are several types of hyperlipidemia that have different effects on the body. **Type I:** Type I, or hyperlipidemia familial lipoprotein lipase deficiency, typically occurs in childhood and is severe. It is an inherited condition that disrupts the normal breakdown of fats and can lead to abdominal pain, repeated infections of the pancreas, and enlargement of the liver and spleen.

**Type II (a and b):** Type IIa, or familial hypercholesterolemia, and type IIb, or familial combined hyperlipidemia, both results in high levels of LDL. They can lead to deposits of fat in the skin and around the eyes and can also increase the risk of heart problems.

**Type III:** Type III, or familial dysbetalipoproteinemia, affects lipoproteins. It occurs when levels of LDL in the blood are too low, but HDL levels remain normal. A typical feature of type III is the occurrence of xanthomas, or flat, yellow-gray plaques on the eyelids and around the eyes. Type III increases the risk of early onset cardiovascular and peripheral artery disease.

**Type IV:** Type IV, or hypertriglyceridemia, increases levels of triglycerides in the blood rather than cholesterol. This type may also lead to obesity, high blood glucose, and high insulin levels.

## MANAGEMENT OF HYPERLIPIDEMIAS WITH DRUGS

### Non-Pharmacological

Strong advice should also be given on the need and benefits of adding life style changes. These changes include:

- Reduction of body weight,
- Decreased dietary total fat,
- Decreased cholesterol intake,
- Decreased saturated fatty acids, and trans fatty acids intake,
- Increased exercise and stress management.

Lifestyle and dietary options are an important way to prevent and treat hyperlipidemia. Options include eating a "heart-healthy" diet, taking regular exercise, not smoking, and maintaining a healthy body weight.

**Diet:** Eating a diet that contains plenty of healthful fats can help prevent hyperlipidemia. A heart healthy diet includes minimizing the intake of saturated fat, trans fats, and dietary cholesterol, and consuming a variety of whole fruits and vegetables, plenty of fibre, lots of water, and whole grain foods.

**Weight:** People who are overweight or have obesity are also at greater risk of developing hyperlipidemia and heart disease. Losing weight can help a person reduce LDL, total cholesterol, and triglyceride levels. It can also boost HDL, which helps to remove the LDL from the blood.

**Physical activity:** A lack of physical activity is another risk factor for heart disease. Regular exercise and activity help a person reduce LDL, raise HDL, and encourage weight loss. The American Heart Association recommend people do 150 minutes of moderately intense physical activity every week.

**Not smoking:** smoking triggers many problems that contribute to heart disease. It promotes atherosclerosis, increases LDL levels, and encourages inflammation and the formation of blood clots. Quitting smoking will result in higher HDL levels. This may be one reason why the risk of cardiovascular disease (CVD) decreases after a person stops smoking. A person with hyperlipidemia can reduce the risk of cardiovascular problems later in life by strictly following the diet and treatment plan recommended by their doctors.

**Drug Treatment of Hypercholesterolemia**

**1- Statins: Mechanism of Action, t**he statin family of six closely related hypocholesterolemic drugs are all potent competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis. The liver is their target organ, and decreased hepatic cholesterol synthesis ultimately leads to increased removal of LDL particles from the circulation. As a consequence, all other hypocholesterolemic drugs have been relegated to secondary status.

Clinical trials with lovastatin, simvastatin (*Zocor*) and pravastatin provided much of the evidence supporting the observation that lowering of blood cholesterol lowers the risk of CHD. Drug-induced inhibition of hepatic cholesterol synthesis leads to lowering of liver cholesterol concentrations and feedback up-regulation at the gene level of both HMG CoA reductase and the LDL receptor.

However, the increased hepatic LDL receptor protein results in increased rates of removal of LDL particles from the circulation by the liver, lowering of blood LDL-cholesterol levels, slowing of atherosclerosis, and decreased risk of heart attack.

**Clinical Uses:**

The statins are used to lower LDL cholesterol in familial or polygenic (multifactorial) hypercholesterolemia (type IIa) and in combination with

triglyceride-lowering drugs to treat combined hyperlipidemia (type IIb) when both LDL and VLDL (very low density lipoproteins) are elevated. However, the statins probably should not be given with the fibrates (triglyceride lowering drugs), since this combination may greatly increase statin toxicity. Atorvastatin, the most potent of the available statins, has also been shown to lower blood triglycerides significantly. This effect may be due to decreasing hepatic cholesterol and cholesterol ester levels to such an extent that hepatic formation of VLDL is impaired. The statins also have been claimed to reduce blood cholesterol levels modestly in some patients with homozygous familial hypercholesterolemia, a condition often fatal in childhood or in early adulthood. The statins may lower the risk of CHD by decreasing inflammation, an important component of atherogenesis.

Lovastatin decreased elevated plasma levels of C reactive protein, a marker for cellular inflammation, and acute coronary events in patients with relatively low plasma cholesterol levels. Recent studies also suggest that use of statins may decrease the risk of stroke, dementia, and Alzheimer's disease and may improve bone density in postmenopausal women. These broad actions may be related to the hypocholesterolemic, antiproliferative, antiinflammatory, or antioxidant properties of the statins or some combination of these properties.

**Adverse Effects:**

The statins generally appear to be well tolerated, with muscle pain and liver dysfunction. Myositis, that is, inflammation of skeletal muscle accompanied by pain, Weakness, High levels of serum creatine kinase. Rhabdomyolysis, i.e., disintegration of muscle with urinary excretion of myoglobin and kidney damage, was considered to be a rare and extreme toxic outcome. The risk of muscle damage is said to increase with simultaneous use of the triglyceride-lowering fibrates.

Pravastatin may be less toxic than other statins because it does not readily penetrate extrahepatic cells and may be more confined to the liver after oral dosage.

**Drug Interactions:**

Most of the statins (lovastatin, simvastatin, atorvastatin, and cerivastatin) are metabolized by the cytochromal P450 3A4 system of intestines and liver to more water soluble metabolites that are excreted in both the bile and urine. Drugs that inhibit P450 3A4, such as itraconazole, cyclosporine, and erythromycin, can vastly (10-fold) increase plasma statin levels and thus increase the risk of toxicity. Unexpectedly, grapefruit juice can inhibit intestinal metabolism of the statins and can result in an 8- to 10-fold increase in simvastatin serum levels. Since fluvastatin is metabolized by cytochrome P450 2C9, which is also responsible for metabolism of warfarin, warfarin toxicity may be increased if these drugs are simultaneously given. Grapefruit juice should obviously not be consumed within several hours of statin administration. Drugs that induce the P450 3A4 system, such as barbiturates, can accelerate statin metabolism and suppress statin blood levels.

**2- Resins**

**Mechanism of Action:** These drugs are basically anion exchange resins that remain in the gut, bind intestinal bile acids, and greatly increase their fecal excretion. Alone, the resins can achieve 20 to 25% reductions in LDL cholesterol, but when used with a statin, such as lovastatin, reductions of 50% and more can be seen. Prior to the introduction of the statins in the mid to late 1980s, the bile acid–sequestering drugs cholestyramine (*Questran*) and colestipol (*Colestid*) were primary drugs for lowering plasma cholesterol. Today they are second-line drugs that can safely be given with a statin to enhance cholesterol lowering or as an

alternative for patients intolerant to a statin or concerned with statin's potential for toxicity. The lowered concentration of bile acids returning to the liver by the enterohepatic circulation results in derepression of 7-α-hydroxylase, the rate-limiting enzyme for conversion of cholesterol to bile acids. This results in increased use of cholesterol to replace the excreted bile acids and lowering of hepatic cholesterol. Thus, similar to the statins, the ultimate actions of the bile acid–sequestering resins are upregulation of transcription of the LDL receptor gene, increased hepatic receptor activity, and lowering of plasma LDL cholesterol.

**Clinical Uses:**

The bile acid sequestering resins lower elevated LDL cholesterol and therefore are useful in the treatment of type IIa hyperlipoproteinemia. However, because the resins can raise plasma VLDL in some patients, they are not recommended for treatment of combined hyperlipidemias (type IIb) when both LDL cholesterol and VLDL triglycerides are high or in other conditions of elevated triglycerides.

**Adverse Effects:** The resins are relatively safe, with constipation being the chief complaint. It is given as the chloride salt and the chloride is exchanged for the negatively charged bile salt, bile acid resins can lead to hyperchloremic acidosis in vulnerable patients (children and patients with kidney failure).

**Drug Interactions:** The principal precaution with use of the bile acid resins is the possibility of impaired absorption of other drugs given orally at the same time. Cholestyramine and colestipol can bind many other drugs, such as digitoxin, phenobarbital, chlorothiazide, and warfarin, and delay or prevent their absorption. For this reason, other drugs should always be taken at least 1 hour before or 4 to 6 hours after the resin. The resins can also decrease absorption of fat-soluble vitamins.

**3- Nicotinic Acid (Niacin):**

Nicotinic acid has three special features as a hypolipidemic drug: it has multiple beneficial effects on serum lipoproteins, it is the least expensive, and it is the least well tolerated.

**Mechanism of Action:** Nicotinic acid decreases formation and secretion of VLDL by the liver. This action appears secondary to its ability to inhibit fatty acid mobilization from adipose tissue. Circulating free fatty acids provide the main source of fatty acids for hepatic triglyceride synthesis, and lowering triglyceride synthesis lowers VLDL formation and secretion by the liver. Since plasma VLDL is the source of LDL, lowering VLDL can ultimately lower LDL. In addition, nicotinic acid shifts LDL particles to larger (more buoyant) sizes. The larger LDL particles are thought to be less atherogenic. Nicotinic acid can also significantly increase plasma HDL levels; the mechanism is unknown.

**Clinical Uses:** Used alone, nicotinic acid can decrease plasma LDL cholesterol levels. It can also be used in combination therapy with the statins or the bile acid–sequestering resins to augment reduction of very high LDL levels. Because nicotinic acid can lower plasma triglycerides by 40% or more, it is useful in treating familial hypertriglyceridemia type IV, and in combination with the statins it is useful in treating combined hyperlipidemia type IIb. As described later with the fibrates, patients with high plasma triglycerides plus low HDL are at increased risk for CHD. Nicotinic acid is useful for treating these patients, since it can both lower triglycerides and raise HDL.

**Adverse Effects:** Compliance with nicotinic acid therapy can be poor because the drug can produce an intense cutaneous flush. This can be reduced by beginning the drug in stepped doses of 250 mg twice daily and increasing the dose monthly by 500 to 1000 mg per day to a maximum of 3000 mg per day. Taking nicotinic acid

on a full stomach (end of meal) and taking aspirin before dosage can reduce the severity of flushing. Time-release forms of nicotinic acid may also decrease cutaneous flushing. Nicotinic acid can cause gastrointestinal (GI) distress, Liver dysfunction (especially at high doses), Decreased glucose tolerance, Hyperglycemia, Hyperuricemia. Thus, it is contraindicated in patients with hepatic dysfunction, peptic ulcer, hyperuricemia, or diabetes mellitus.

**4- Fibrates:**

**Mechanism of Action:** The three structurally related fibrates are gemfibrozil (*Lopid*), fenofibrate (*Tricor*) and clofibrate (*Atromid-S*). They share common uses and toxicities. The fibrates typically lower VLDL triglyceride by 40% or more and elevate plasma HDL cholesterol by 10 to 15%. The reduction of plasma triglycerides in humans appears due to increased lipoprotein lipase (LPL) activity. The fibrates activate a nuclear receptor (transcription factor) termed peroxisomal proliferation activated receptor (PPAR) that is a member of the steroid hormone receptor superfamily. PPAR increases transcription of the LPL gene and decreases transcription of the apolipoprotein CIII gene (apo CIII). Since LPL is responsible for catabolism of VLDL triglyceride and apo CIII is an inhibitor of LPL activity, the combined consequences of these changes are increased LPL activity and enhanced removal of triglyceride from the circulation. The elevation of HDL levels by fibrates may be due to two drug actions: induced synthesis of apo-A1, the principal apoprotein of HDL, and increased assembly of new HDL particles in the circulation. Surface components of VLDL contribute to formation of HDL, as the VLDL particles are reduced in size through the action of LPL.The increased rate of catabolism of VLDL caused by the fibrates would provide more components for assembly of HDL particles.

**Clinical Uses:**

The fibrates are mainly used to treat

- Hyperlipidemias,
- Familial hypertriglyceridemia (type IV) and
- Dysbetalipoproteinemia (type III).
- They are also useful in the treatment of hypertriglyceridemia associated with type II diabetes (secondary hyperlipidemia).
- The fibrates are the drugs of choice in treating hypertriglyceridemias, particularly those associated with low levels of HDL cholesterol.
- The fibrates additionally appear to shift LDL particles to larger, hence less atherogenic, species.

**Adverse Effects:**

The fibrates are generally well tolerated, with GI distress being the most likely complaint. Other adverse effects include myositis and erectile dysfunction, particularly with clofibrate. There is ongoing concern about the fibrates increasing the risk of gallstones. Because clofibrate was associated with increased mortality in early clinical trials, it should be considered as a second-line drug.

**Drug Interactions:**

The fibrates potentiate the actions of the coumarin anticoagulants, such as warfarin, so care should be taken to reduce the dose of simultaneously administered anticoagulants, and plasma prothrombin should be frequently measured until the level stabilizes. As mentioned earlier, great care should be given to combining a statin with a fibrate, since this combination may increase the risk of myositis and perhaps rhabdomyolysis.

## Other Approaches to Prevention of Coronary Heart Disease with Drugs:

### 5- Probucol

Probucol (*Lorelco*) is a hypocholesterolemic drug with few side effects that modestly (15–30%) decreases elevated plasma LDL cholesterol levels. The marginal LDL-lowering action plus reports that it can lower HDL cholesterol resulted in its discontinuation as a hypocholesterolemic drug. However, it still may reduce the risk of CHD because it is a powerful antioxidant.