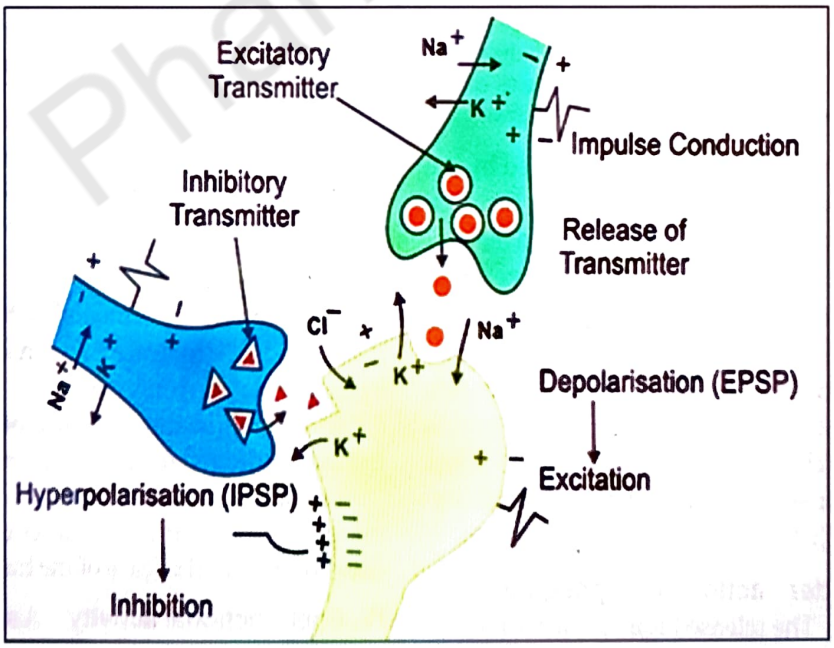
Pharmacology of drug acting on CENTRAL NERVOUS SYSTEM

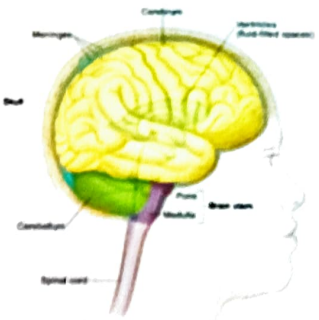
[A] NEURO-HUMORAL TRANSMISSION IN CNS & IMPORTANCE OF VARIOUS NEUROTRANSMITTERS

Points to be covered in this topic

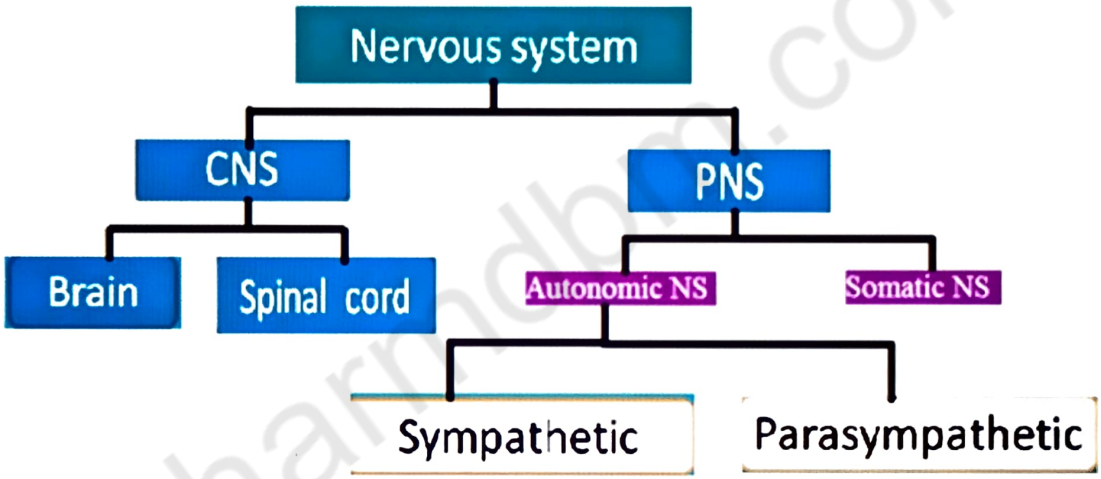
1. Introduction to CNS
2. Neurohumoral transmission in CNS
3. Neurotransmitters of CNS
4. Individual neurotransmitters



❑ INTRODUCTION TO CNS



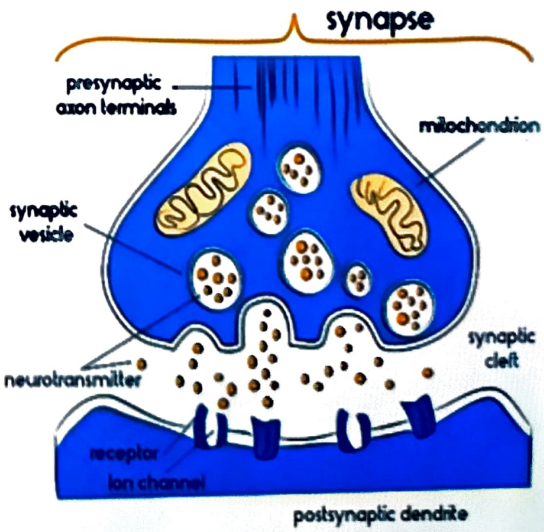
- In the CNS, any **information is carried via synaptic transmission, and neurotransmitters** interact with receptors which are specific recognition sites on adjacent neurons.
- On the other hand, neuromodulators are **released from non-synaptic sites.**
- These neuromodulators are **chemical mediators** [prostaglandins (PGs), some neuropeptides and purines] that can regulate synaptic transmission.
- Neuromediators are agents that **act as second messengers**, mediating intracellular events following postsynaptic activity of a neurotransmitter.



❑ NEUROHUMORAL TRANSMISSION IN CNS

❖ **Four processes occur in relation to nerve transmission within the CNS. These processes are mediated through different transmitters.**

1. Neurotransmission occurs through neurotransmitters, which are **released in to synaptic cleft** to rapidly stimulate or inhibit post-synaptic neurons.



2. Neuro-modulation occurs through neuromodulators, which are released by neurons and by astrocytes and **act either to slow or enhance the pre- or post-synaptic responses.**
3. Neuromediation occurs through neuromediators, which **are second messengers like cAMP, cGMP and IP3.**
4. Neurotropic effects occur through neurotropic factors, which are **secreted by neurons, astrocytes, microglia** and act over a longer time to regulate the growth and morphology of neurons.

❑ NEUROTRANSMITTERS OF CNS

- Neurotransmitters are substances which **neurons use to communicate with one another** and with their target tissues in the process of synaptic transmission (neurotransmission).
- Neurotransmitters are **synthetized in and released from nerve endings** into the synaptic cleft.
- Most neurotransmitters and neuromodulators recognised in CNS **are also present in periphery** either as autacoids or neurotransmitters in ANS.
- The functions of these central neurotransmitters **may vary from their counterparts** present in the periphery.
- **Following are examples of neurotransmitters & neuromodulators:**

S. NO.	TYPES	EXAMPLES
1.	**Major Neurotransmitters**	Acetylcholine, catecholamine (noradrenaline, dopamine & possibly adrenaline), 5-Hydroxytryptamine (5-HT; serotonin), Histamine, Gamma-Aminobutyric Acid (GABA), Glycine, Glutamic acid, Aspartic acid & Opioid peptides.
2.	**Major Neuromodulators**	Prostaglandins (PGs), non-opioid peptides (cholecystokinin, vasoactive peptide, substance P, bradykinin), and Adenosine.
3.	**Major Neuromediators**	Cyclic AMP and Cyclic GMP

❖ Importance of Neurotransmitters

➢ **There are many chemical elements recognised in the CNS; however few elements have condition for accepting them as neurotransmitters. Following are the certain conditions:**

1) Presence of some **specific synthesising, storage & releasing mechanisms** in the presynaptic nerve terminal.
2) Presence of **mechanisms for inactivation of released chemical substance** which comprises of enzymatic metabolism and neuronal reuptake mechanisms.
3) **Recognition of certain receptors**, presynaptic and postsynaptic for the transmitter.
4) Recognition of **certain agonists and antagonists** for these receptor.
5) Explanation of **physiological role for transmitter & their involvement** in etiopathogenesis of a neuropsychiatric disease, if possible.

❑ INDIVIDUAL NEUROTRANSMITTERS

1. INHIBITORY NEUROTRANSMITTER

NEUROTRANSMITTER	COMMENTS
GABA	• GABA plays an important role in anxiety and sedative and hypnotics. **Types: $GABA_A$, $GABA_B$** • These are ionotropic receptors. • They are located post-synaptically • They are directly linked with chloride ion channel opening which causes hyper-polarisation & reduction in membrane excitability.
GLYCINE	• Glycine especially in spinal cord, brainstem and retina. • When glycine receptors are activated, chloride enters the neuron via **ionotropic receptors, causing an inhibitory postsynaptic potential (IPSP).**
DOPAMINE	• Dopamine system plays a central role in several significant medical conditions, including **Parkinson's disease, attention deficit hyperactivity disorder, Tourette syndrome, schizophrenia, bipolar disorder, and addiction.**

2. EXCITATORY NEUROTRANSMITTER

NEUROTRANSMITTER	COMMENTS
GLUTAMATE	• Excitatory neurotransmitter is associated with **stroke, autism, some forms of intellectual disability,** and diseases such as amyotrophic lateral sclerosis, lathyrism, and Alzheimer's disease.
ASPARTATE	• **Aspartate (conjugate of aspartic acid) stimulates NMDA receptor** though not as strongly as amino acid neurotransmitter glutamate does

3. BOTH INHIBITORY NEUROTRANSMITTER & EXCITATORY NEUROTRANSMITTER

NEUROTRANSMITTER	COMMENTS
ACETYLCHOLINE	• Acetylcholine is **parasympathetic neurotransmitter** & functions in both **central nervous system** & **peripheral nervous system.** • In CNS, cholinergic projections from basal forebrain to cerebral cortex & hippocampus support **cognitive functions** of those target areas.
NORADRENALINE	• Norepinephrine widely is classified as a **sympathomimetic receptor** and function on **both CNS and ANS,** • **In ANS:** controls a wide range of involuntary and **unconscious body functions.** • **In CNS:** Activated, exerts effects on large areas of the brain. • The effects are manifested in **alertness, arousal, and readiness for action, role in depression,**

Pharmacology of drug acting on CENTRAL NERVOUS SYSTEM

[C] SEDATIVE, HYPNOTIC & CENTRALLY ACTING MUSCLE RELAXANT

Points to be covered in this topic

1. Introduction to sedative & hypnotic
2. Physiology of sleep
3. Classification of sedative & hypnotic
4. Benzodiazepines (BZDs)
5. Non-benzodiazepine Hypnotics
6. Barbiturates
7. Miscellaneous Drugs
8. Centrally Acting Skeletal Muscle Relaxants (Spasmolytic's)

❑ INTRODUCTION TO SEDATIVE & HYPNOTIC

- **Sedative** is a drug that **produces a calming or quietening effect** and reduces excitement. It may induce drowsiness.
- Sedation indicates **decrease in alertness & decreased responsiveness** to any level of stimulation without inducing sleep.
- **Hypnotic** is a drug that induces sleep resembling natural sleep.
- During hypnosis, a person becomes **passive, highly suggestive and obeys the commands.**
- Hypnosis **resembles natural sleep** but the person can be aroused by strong stimuli like pin prick or the sound of alarm clock.

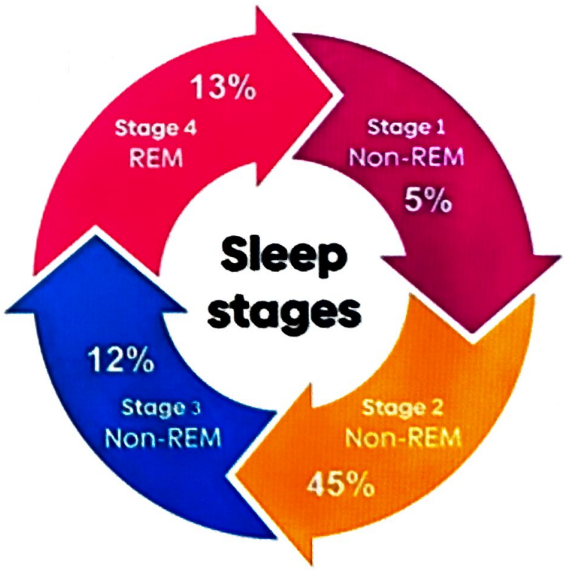
❑ PHYSIOLOGY OF SLEEP

❖ **Sleep can be classified into two types depending on the physiological characteristics:**

1. **REM (rapid eye movement) sleep** is associated with dreaming, enhanced heart rate, breathing and brain activity and relaxation of voluntary muscles; dreams can be recollected; REM sleep makes up 20–25% of total sleep time.
2. **NREM (non-rapid eye movement) sleep**

❖ **Stages or Levels of NREM Sleep**

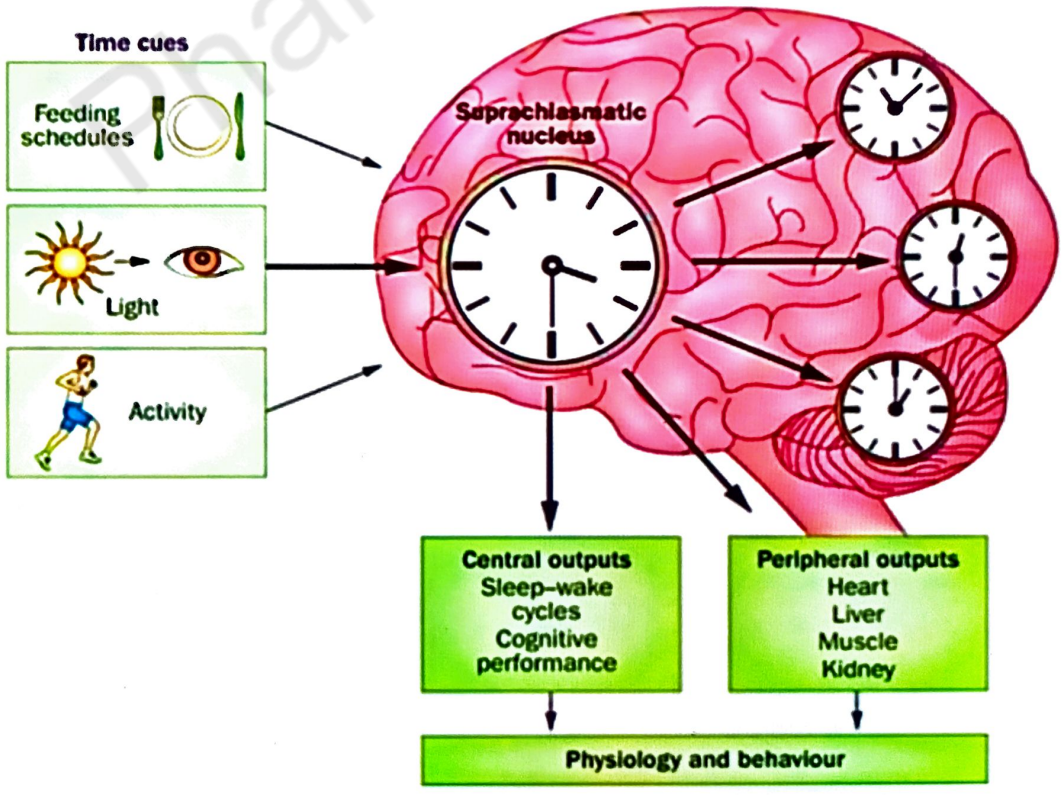
- **Stage 0 :** From lying down to falling asleep.
- **Stage 1 :** Eye movements are less and the body muscles begin to relax — lightest stage of sleep—5 to 10% of total sleep time.



- **Stage 2 :** Eye movements are further reduced but person is still easily arousable — involves 50% of total sleep time.

- **Stage 3 :** Deeper sleep with minimum eye movements and not easily arousable. Stages 3 and 4 together are called delta or slow wave sleep; it is refreshing and a decrease in delta sleep is poor quality sleep.
- **Stage 4 :** It is the deepest level of sleep.
  - ✓ In this stage, the metabolic rate is the lowest and growth hormone secretion is highest.
  - ✓ There are no eye movements and muscles are fully relaxed — if awakened, there is disorientation for 1–2 minutes.
  - ✓ Makes up 20% of total sleep time.

3. **Insomnia** → It is sleeplessness. It is insufficient or poor quality sleep which could lead to undesirable day time consequences. Insomnia may be primary or secondary.
   1. **Primary insomnia** is sleeplessness that is not attributable to medical, psychiatric or environmental causes. This is uncommon.
   2. Insomnia may be **secondary** to a variety of clinical conditions including medical and psychiatric illness, stress, drug induced or simply due to lack of adequate physical activity.

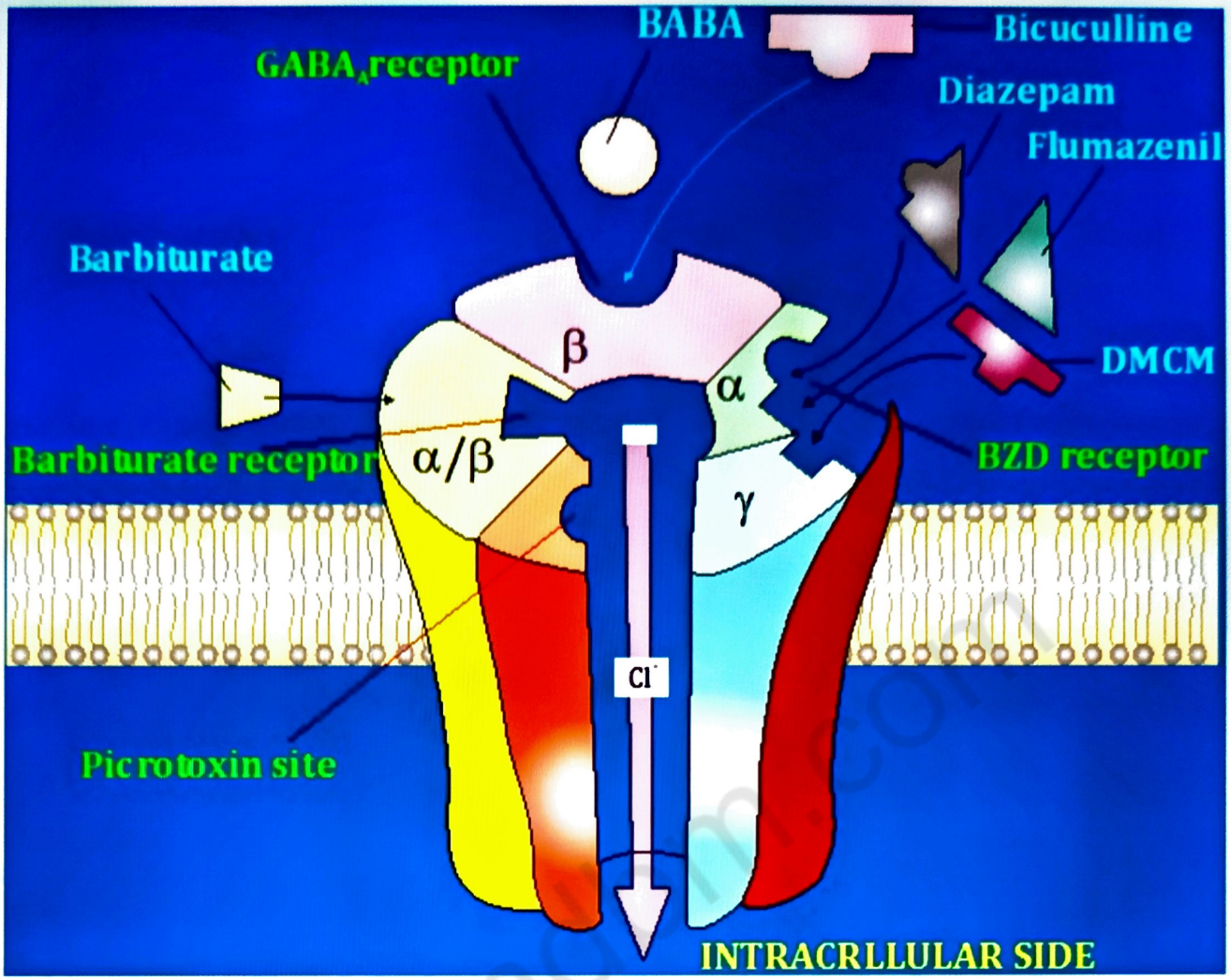


❑ CLASSIFICATION OF SEDATIVE & HYPNOTIC

CLASS	SUBCLASS	DRUGS
Barbiturates	Long acting	Mephobarbitone, Phenobarbitone
	Short acting	Butobarbitone, Secobarbitone, Pentobarbitone
	Ultra-short acting	Hexobarbitone, Methohexitone, Thiopentone
Benzodiazepines	Hypnotics	Diazepam, Flurazepam, Nitrazepam, Alprazolam, Temazepam, Triazolam
	Anti-anxiety	Diazepam, Oxazepam, Lorazepam, Alprazolam, Clonazepam, Chlordiazepoxide
	Anti-convulsant	Diazepam, Clonazepam, Lorazepam, Clobazam,
	Muscle relaxants	Diazepam
Others	Non-Bezodiazepam hypnotics	Zopiclone, Zolpidem, Zaleplon, Eszopiclone, Etizolam
	Other hypnotics	Triclofos, Melatonin, Ramelteon, Suvorexant

❑ BENZODIAZEPINES (BZDs)

- **Chlordiazepoxide**, 1st benzodiazepine was accidentally synthesised in 1961.
- BZD (or the barbiturates) in **lower doses** act as **sedative and antianxiety** drugs; at **higher doses** as → **hypnotics**; at **still higher doses**, → **anaesthesia**; and at **further doses**, → **coma and death**.
- BZDS on the other hand can be **used as an anaesthetic agent**; and in very rare cases, death occurs due to high doses of BZD.
- **Mechanism of Action** → BZDs bind to the **GABA receptor** on the cell membrane, and **facilitate the opening of chloride channel** causing influx of chloride ion.



- Inverse agonist to BZDs is **β-carbolene**.
- Antagonist to BZDs is **flumazenil**. It is clinically useful to treat overdose toxicity of BZDs

- **PHARMACOKINETICS**
  - There are **marked variations** in pharmacokinetics of BZDs.
  - Only Midazolam is given by **IM or IV route**. All other BZDs are given orally.
  - BZDs like diazepam, oxazepam and chlordiazepoxide are **more than 90% bound on proteins.**
  - They have **high volume of distribution**, they cross placental barrier and are to be used cautiously in pregnancy.
  - Many of the **phase I metabolites of BZDs are pharmacologically active**; hence their half-life is extended.

➢ **Active metabolites of parent drugs of BDZ are as follows:**

S. NO.	DRUGS	ACTIVE METABOLITES
1.	**Midazolam**	Hydroxymethyl Midazolam
2.	**Diazepam**	Oxazepam, Nordiazepam (Clorazepate)
3.	**Flurazepam**	Dismethylflurazepam & Hydroxymethyl Flurazepam
4.	**Alprazolam**	α-hydroxyalprazolam
5.	**Chlodiazepoxide**	Dismethyldiazepam &Oxazepam

➢ **PHARMACOLOGICAL ACTIONS**

- The most important actions of BZDs are on the CNS and include:

1. **Sedation and hypnosis** - BZDs hasten the onset of sleep.
2. **Reduction in anxiety** - BZDs reduce anxiety and aggression and produce a calming effect.
3. **Anaesthesia** - BZDs produce CNS depression in dose-dependent manner.
4. **Muscle relaxation** - BZDs reduce muscle tone by a central action.
5. **Anticonvulsant effects** - BZDs increase the seizure threshold and act as anticonvulsants.
6. **Amnesia** - BZDs produce anterograde amnesia, i.e. loss of memory for the events happening after the administration of BZDs.

➢ **ADVERSE EFFECTS**

1. **Hangover** is its main adverse effect. In larger doses of longer acting BZDs, **weakness, blurred vision, and dry mouth** occurs.
2. Discontinuation after prolonged use **produces rebound insomnia** and day time anxiety.
3. **Tolerance and Dependence: Cellular as well as p'kinetic tolerance** develops on repeated use of BZDs.
4. **Paradoxical stimulation, irritability** & **sweating** occur in some patients.

➢ **DRUG INTERACTION** → BZDs show synergism with alcohol and other CNS depressants leading to excessive impairment. Cimetidine and isoniazid delay the metabolism of BZDS.

❑ NON-BENZODIAZEPINE HYPNOTICS

- Two types of BZD receptors have been identified: BZ_1 and BZ_2.
- BZ_1 receptors are found throughout the brain and in large concentrations in the cerebellum.
- They are responsible for antiánxiety, sedative and hypnotic effects.
- Non-benzodiazepines like

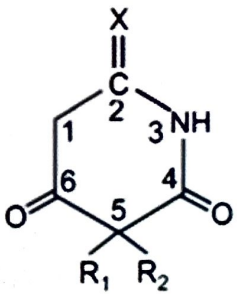
1. Zolpidem
2. Zaleplon
3. Zopiclone
4. Eszopiclone

} **Act on BZ_1 receptors only**

- Benzodiazepines like Clobazam act preferably on BZ2 receptors and exert muscle relaxant anticonvulsant actions.
- As hypnotic, **Zolpidem** (half-life 2-3 hours) and **Zaleplon** (half-life 3-4 hours) have faster onset of action with shorter duration of action.
- Drugs like **Zopiclone** (half-life 6-8 hours) and **Eszopiclone** (half-life 6 hours) are slightly longer acting.
- The problem of rebound insomnia is minimal.
- Their effects can be **blocked by Flumazenil**.
- These drugs have minimal muscle relaxant and anticonvulsant action.
- The risk of tolerance and dependence is less.
- **Dose reduction is needed** in hepatic disease and in elderly patients.
- Adverse reactions → **day time drowsiness** and **nightmares** in high doses.

❑ BARBITURATES

- The general structural formula of barbiturates is shown in Fig.



- **Barbiturates exhibit the following properties:**

1) These are non-selective CNS depressants, **producing sedation and reducing anxiety** which leads to unconsciousness. However, their **overdose is fatal** as they may cause respiratory and cardiovascular failure.

2. They act partly by **enhancing the action of GABA** but are less specific, thus mainly used in anaesthesia, and epilepsy; they are no longer used as sedatives or hypnotics.
3. They are **potent inducers of hepatic drug-metabolising enzymes** (cytochrome P450 system in particular), thus may cause drug interactions.
4. They are also involved in **attacks of acute porphyria** in liable individuals.
5. They may give rise to **tolerance** and **dependence**.

❖ Classification of barbiturates :-

S. NO.	CATEGORY	DRUGS
1.	**Long acting** (8 hrs or more)	Phenobarbitone
2.	**Intermediate acting** (4-8 hrs)	Amylobarbitone, Butobarbital, Pentobarbitone.
3.	**Short acting** (less than 4hrs)	Secobarbital and Hexobarbitone.
4.	**Ultra short acting**	Thiopentone and Methohexitone.

❖ Mechanism of action:

Barbiturates act primarily at the GABA-BZD receptor Cl^- channel complex (different from BZD binding site)

↓

The duration of Cl^- channel kept open is increased

↓

Increase in GABA mediated chloride conductance

↓

Membrane hyperpolarization

↓

CNS depression.

❖ Pharmacological action and therapeutic uses

1. **Sedation and hypnosis** – BZDs now have superseded barbiturates.
2. **Anticonvulsants** - Long-acting barbiturates like Phenobarbital are used.
3. **Antianxiety effect**
4. **General anaesthesia-** (Thiopentone & methohexitone) Ultra-short-acting barbiturates like thiopental are used as i.v. inducing fast anaesthetics.
5. **To treat hyperbilirubinemia:** They ↑ the activity of enzyme ***glucuronyl transferase*** by induction. Hence, bilirubin gets conjugated faster and excreted through bile.

❖ Adverse Effects

- Repeated use of barbiturates causes **metabolic tolerance** due to enzyme induction causing accelerated metabolism of several concomitantly drugs.
- They can **cause psychic as well as physical dependence** on withdrawal after prolonged use. Withdrawal symptoms include tremors, insomnia, headache, restlessness and delirium.
- They cause **hangover, impairment of judgement** and drug automatism.
- They cause **respiratory depression, laryngeal edema** and hypersensitivity reactions causing skin rash, swelling of lips and eyelids.

❖ Drug Interactions

- Barbiturates **reduce effectiveness of drugs** like oral contraceptives, anticoagulants, tolbutamide and theophylline due to induction of enzymes.

❖ Contraindications

- **Liver dysfunctions,**
- **kidney disease**
- **severe pulmonary insufficiency.**
- **Porphyria & neurotoxicity** induction of enzyme *ALA-synthetase.*

❖ Acute Barbiturate Toxicity and Treatment

- Barbiturate poisoning is mostly suicidal and rarely accidental.
- Leads to respiratory failure, CVS collapse, coma & renal failure.
- The treatment includes gastric lavage, artificial respiration and forced alkaline dialysis.

❑ MISCELLANEOUS DRUGS

1. MELATONIN

- The hormone **secreted by the pineal gland**, is known to regulate sleep.
- Secreted at night & plays an important role in circadian rhythm (chronobiotic).
- It acts on two types of melatonin receptors — **melatonin 1 (MT_1)** and **melatonin 2 (MT_2)** which are GPCRs.
- MT_1 receptors mediate sleep while MT_2 receptor involved in circadian rhythm.
- Administered orally at bedtime in the dose of 2–10 mg, melatonin is considered a **natural remedy for insomnia** and is free from the disadvantages of BZDs.

❖ Uses

1. **Hypnotic** for short periods and to **help withdraw hypnotics** in elderly dependents.
2. **Jet lag:** Melatonin may be used to **overcome jet lag** and other conditions of disturbed biorhythm.
3. **Ageing:** The secretion of melatonin decreases with age and, therefore, it is supplemented with the hope that it **retards ageing**.

2. RAMELTEON

- It an agonist of melatonin receptors (MT_1 & MT_2), & **novel hypnotic drug.**
- Ramelteon reduces the latency of persistent sleep.
- Advantages are that it does not modify the sleep architecture.
- There is **no rebound insomnia** or other major withdrawal symptoms.
- It is well tolerated and is also useful in chronic insomnia with no known abuse liability.
- **Adverse effects** include **dizziness and fatigue**.
- There could be an **↑ in prolactin levels** and **↓ in testosterone**.

3. Other drug includes –

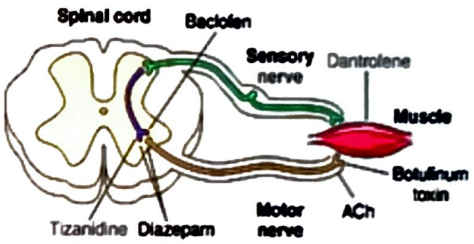
i. **Triclofos** - It is used for short term **management of insomnia in children** for sedation during recurrent colic.

ii. **Hydroxyzine** - It is used for **short term management of anxiety, pre-anaesthetic sedation and pruritus.**

iii. **Promethazine** - It is a sedative antihistamine with antiemetic and anticholinergic properties. It is used for **night time sedation** in a dose of 25 mg at bed time.

❑ CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS (Spasmolytic's)

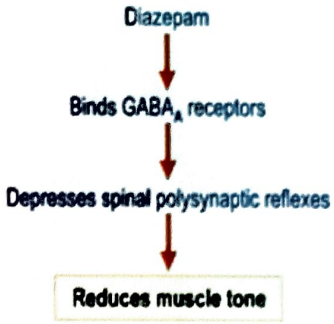
- These drugs **act on higher centres** and cause muscle relaxation without loss of consciousness.
- They also **have sedative properties.**
- **Drugs in this category are:**



S. NO.	CLASS	DRUGS
1.	$GABA_A$ agonists	Benzodiazepines like diazepam
2.	$GABA_B$ agonist	Baclofen
3.	Central α_2 agonist	Tizanidine
4.	Mephenesin & congeners	Carisoprodol, chlorzoxazone, chlormezanone, methocarbamol
5.	Others	Thiocolchicoside, Riluzole, Gabapentin, Progabide.

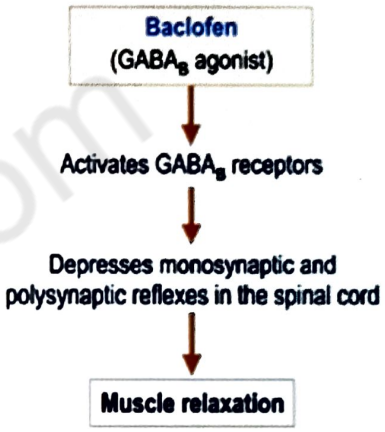
1. Diazepam

- It has useful **antispastic activity**.
- It can be used in relieving muscle spasm of almost any origin including that of local muscle trauma.
- Started with low dose of 4 mg/day, the dose is gradually increased.
- Of the BZDs, diazepam is the most commonly used for this purpose.



2. Baclofen

- It is an **analogue of inhibitory neurotransmitter GABA** & is $GABA_B$ agonist.
- It depresses the monosynaptic and polysynaptic reflexes in the spinal cord.
- Baclofen also inhibits the release of substance P which could contribute to pain relief.
- Baclofen is generally given orally.
- It is rapidly and completely absorbed.



- **Side effects include**
  - ✓ Drowsiness (which is milder than diazepam and tolerance develops),
  - ✓ Weakness, Ataxia
  - ✓ Abrupt withdrawal after prolonged use causes anxiety, palpitations and hallucinations.
- **Other Uses**
  - ✓ Severe low back pain
  - ✓ Reduces craving in chronic alcoholics.
  - ✓ Improve bladder and bowel functions in patients with spinal lesions.
  - ✓ It relieves painful spasms including flexor and extensor spasms.

3. Mephenesin

- It is **not preferred** due to its side effects.
- A number of related drugs like **Carisoprodol, Methocarbamol, Chlormezanone, Chlorzoxazone** are used in acute muscle spasm caused by local trauma. All of them also cause sedation.
- Carisoprodol has **weak analgesic, antipyretic & anticholinergic activity.**

4. **Methocarbamol** can be given orally and parenterally.

   Dose: 500 mg TDS 100 mg/ml IV/IM ROBINAX 500 mg tab, 100 mg/ml inj.

5. **Chlormezanone** also has antianxiety effects.

   Dose: 100–200 mg TDS WINTRAC 100 mg tab.

5. **Chlorzoxazone** is better tolerated and longer acting.

6. **Tizanidine** is a congener of clonidine.

- It is a central α2 agonist like clonidine.
- It ↑ **presynaptic inhibition of motor neurons** & reduces muscle spasms.
- The muscle relaxant effect is seen in lower doses and the CV effects are not significant at such doses.
- **Adverse effects** → drowsiness, weakness, hypotension and dry mouth.
- Tizanidine is used in the treatment of spasticity due to stroke, multiple sclerosis and amyotropic lateral sclerosis.

❑ Uses of Centrally Acting Muscle Relaxants

1. **Musculoskeletal disorders** like muscle strains, sprains, myalgias, cervical root syndromes, herniated disc syndromes, low backache, dislocations, arthritis, fibrositis and bursitis all cause painful muscle spasms. Muscle relaxants are used with analgesics in these conditions.
2. **Spastic neurological disorders** like cerebral palsy, multiple sclerosis, poliomyelitis, hemiplegia and quadriplegia are treated with diazepam or baclofen.
3. **Tetanus:** Diazepam is given IV.
4. **ECT:** Diazepam is given along with peripherally acting SMRs.
5. **Orthopaedic procedures** like fracture reduction may be done after administering diazepam.

UNIT-IV

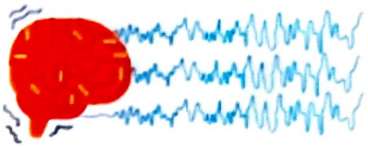
ANTI- EPILEPTIC

Points to be covered in this topic

- ❖ Introduction
- ❖ Classification of Antiepileptic
- ❖ Individual drugs

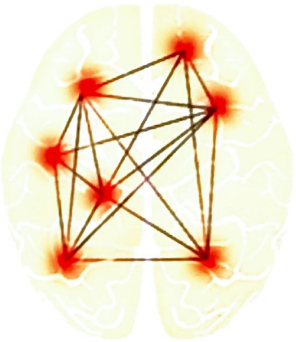
ANTIEPILEPTIC AGENT

❑ Introduction



- **Epilepsies** These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, **manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions)**, sensory or psychiatric phenomena.
- Epilepsy has a **focal origin in the brain**, manifestations depend on the **site of the focus, regions into which the discharges spread** and postictal depression of these regions.
- Recognised from the dawn of history as **'disease of lightening'**. Epilepsies have been classified variously.

❖ Classification of Epilepsy

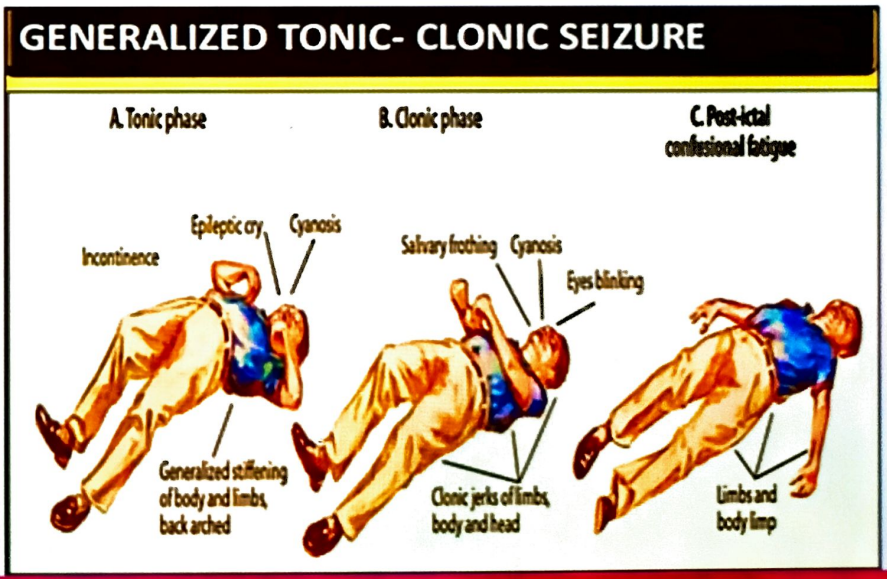


❑ Generalised seizures

They have a diffuse origin **involving both hemispheres of the brain**; manifestations and EEG abnormalities are bilateral.

1. Generalised tonic-clonic seizures (major epilepsy, grand mal):

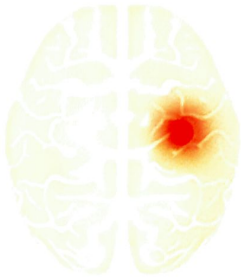
lasts 1–2 min. The usual sequence is **aura—cry—unconsciousness** and **patient falls—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep** and depression of all CNS functions.



2. **Absence seizures (minor epilepsy, petit mal):** prevalent in children, lasts about 1/2 min. **No or only momentary loss of consciousness, no fall, patient apparently freezes and stares in one direction,** no muscular component or minimal bilateral jerking or blinking of eyes, EEG shows characteristic 3 cycles per second spike and wave pattern.

3. **Atonic seizures (Akinetic epilepsy):** Brief **loss of consciousness with relaxation of all muscles** due to excessive inhibitory discharges. Patient may fall.
4. **Myoclonic seizures Shock-like momentary contraction of muscles of a limb or the whole body**. Myoclonic jerking may accompany any type of generalised or partial seizures.
5. **Infantile spasms (Hypsarrhythmia) Seen in infants**. Probably not a form of epilepsy. **Intermittent muscle spasm and progressive mental deterioration**. Diffuse changes in the interseizure EEG are noted.

❑ Partial seizures



They have a **unilateral localized origin in the brain,** but may spread to small or large area, or to the whole brain.

1. **Simple partial seizures (SPS):**

   There is sudden onset unilateral **clonic jerking of a group of muscles or a limb lasting 30–90 sec**, or localized sensory disturbances such as **pin pricks, visual/auditory hallucinations**, etc. The patient remains conscious and aware of the attack.

2. **Complex partial seizures (temporal lobe epilepsy, psychomotor):** attacks of bizarre and confused behaviour, **dream-like state and purposeless movements, or even walking unaware, emotional changes** lasting 1–2 min along with impairment of consciousness. The **seizure focus is located in the temporal lobe.**

3. **Simple partial or complex partial seizures** secondarily generalized
The **partial seizure occurs first** and **evolves into generalized tonic-clonic seizures with loss of consciousness.**

❑ Classification of Antiepileptic

Barbiturate - Phenobarbitone
Deoxybarbiturate - Primidone
Hydantoin - Phenytoin ,Fosphenytoin
Iminostilbene – Carbamazepine, Oxcarbazepine , Eslicarbazepine
Succinimide -Ethosuximide
Aliphatic carboxylic acid – Valproate sod. (valproic acid), Divalproex
Benzodiazepines – Clonazepam,Diazepam,Lorazepam,Clobazam
Phenyltriazine - Lamotrigine
Cyclic GABA analogues – Gabapentin , Pregabalin
Newer drugs – Topiramate , Levetiracetam , Zonisamide , Vigabatrin , Tiagabine , Lacosamide

❖ Mechanism of Action of Anti-Epileptic Drugs

Anticonvulsant drugs act by different mechanisms to suppress repetitive firing action potentials by an epileptic focus in the brain. The mechanisms are classified in two types:

(i) Mechanisms in Grand mal and Partial Seizures:

They are further sub-classified into following sub-types:

- **Inhibition of Use-Dependent Sodium Ion Channels.** Drugs like **Phenytoin, Carbamazepine, Valproate, Lacosamide and Lamotrigine** block voltage-gated sodium channels.
- **Enhancement of GABAergic action.** Drugs like **Phenobarbital and Benzodiazepines** activate $GABA_A$ receptors to facilitate opening of chloride channels.

- **Blockade of NMDA or AMPA receptors.** Drugs like **Felbamate** block NMDA receptors. Drugs like **Phenobarbital, Topiramate and Lamotrigine** block AMPA receptors.
- **Blockade of voltage-gated N type calcium channels.** Drugs like **Lamotrigine and GABApentin** decrease synaptic release of glutamate.
- **Selective blocking of synaptic vascular protein.** Drug like **Levetiracetam** decrease synaptic release of glutamate and increase release of GABA.
- **By blocking effects of neurotropic factors,** drug like **Lacosamide** inhibit specific proteins involved in genesis of epilepsy.

(ii) Mechanisms in Petit mal (Absence Seizures):

It involves inhibition of **T-type calcium channels.** Drug like **Ethosuximide** inhibit calcium channels. Valproic acid also shows this kind of action.

❑ Individual drugs

➢ Phenytoin

- It is an oldest **non-sedative antiepileptic drug**. Chemically, it is **diphenylhydantoin.** It provides a good example of application of pharmacokinetics for successful prescribing.

❑ Mechanism of action

- In therapeutic plasma levels of 10-20 µg/ml, it **blocks use-dependent sodium channels** and thus inhibits generation of repetitive action potentials.
- At higher doses it also **reduces influx of calcium** and suppresses repetitive firing of neurons. **Both these actions decrease glutamate release.**

❑ Therapeutic uses and plasma levels

- **Antiepileptic use** It is the drug of choice for **psychomotor seizures.** As a second choice, it is used to **treat generalised tonic-clonic and status epilepticus.** Fosphenytoin is its pro-drug. **Phenytoin is contraindicated in Petit mal (absence) and myoclonic seizures.**

- **Non-antiepileptic use** It is used to treat **trigeminal neuralgia, ventricular arrhythmia** and also for wound healing.

❑ Pharmacokinetics

- Its oral absorbtion is slow but complete (80-90%).
- Phenytoin is **not given by IM or IV route.**
- IM phenytoin precipitates in **muscle and causes intense pain.** IV phenytoin causes **thrombophlebitis and hypotension.**
- It is **90-92% protein bound.**
- It is a potent enzyme inducer both for CYP3A4 and glucuronyl transferase. Metabolites are eliminated through urine.

❑ Adverse reactions

Following adverse effects are observed with chronic toxicity:

- Gingival hyperplagia and coarsening of facial features.
- Megaloblastic anaemia
- Vitamin K deficiency and Vitamin D deficiency
- Hirsutism (in females) and acne
- Hyperglycemia, decrease of ADH release
- Congenital malformation like cleft lip, cleft palate and heart disease
- Hypersensitivity reactions like skin rashes, fever, hepatitis, vertigo, nausea, tremors
- Withdrawal seizures, if discontinued abruptly.

❑ Drug interactions

- It **increases metabolism** of Corticosteroids, Oral contraceptives, Doxycycline, Rifampicin, Theophylline, Levodopa, Vit. K and Vit. D due to enzyme-induction.
- **Enzyme-inhibitors like Disulfiram, Cimetidine, Isoniazid and Chloramphenicol decrease metabolism of Phenytoin** leading to increase in plasma concentration.
- Carbamazepine and Phenytoin or Phenobarbital and Phenytoin increase each other's metabolism.
- Sodium valproate displaces protein bound Phenytoin and inhibits its metabolism. Hence, plasma level of phenytoin increases.

➤ Phenobarbital and Primidone

- Barbiturates having an aromatic ring at **position-5 exhibit anticonvulsant** action. Primidone is a deoxyphenobarbital.

❑ Mechanism of action

- Phenobarbital **binds to GABA receptor and enhances GABA-mediated inhibitory effect** by increasing the duration of chloride channel opening.
- It also **inhibits glutamate mediated excitatory effects by blocking AMPA receptor.** Both the increase in GABA mediated inhibition and decrease in glutamate mediated excitation are observed with Phenobarbital and primidone.
- At higher doses they **block calcium and sodium channels.**

❑ Therapeutic uses

- Both are effective against **partial seizures and generalised tonic-clonic seizures** but are less effective than Phenytoin and Carbamazepine.
- These drugs are contraindicated in Petit mal (absence) seizures and in porphyria.

❑ Pharmacokinetics

- **Plasma half-life of Phenobarbital is around 100 hours**; hence after steady state, **there is less fluctuation in plasma for 24 hours**.
- Therapeutic levels for Phenobarbital range from **10-40 µg/ml**. In febrile seizures, **levels below 15 µg/ml are ineffective**.
- **Usual doses for Phenobarbital are 60-180 mg daily orally at night.** For Primidone initially, **125 mg daily at night can be slowly increased to 250 mg twice a day.**

❑ Adverse effects

- Adverse **effects due to enzyme induction** are same as that of phenytoin.
- Phenobarbital does not cause **gingival hyperplasia, coarsening of facial features and hirsutism.**
- It can cause **irritability and hyper-excitability** in children.
- The chances of dependence are less.
- It is **less teratogenic**; but when given with phenytoin, teratogenecity increases.

➢ Carbamazepine and Oxcarbazepine

- Carbamazepine is structurally related to **tricyclic antidepressants** and Oxcarbazepine is a derivative of Carbamazepine.

❑ Mechanism of action

- **Carbamazepine blocks sodium channels** and **Carbamazepine blocks sodium channels and** inhibits high frequency repetitive firing.

❑ Therapeutic uses

- **Antiepileptic use** It is a drug of choice for **partial and generalised tonic-clonic seizures**. It is contraindicated in absence seizures.
- **Non-antiepileptic use** It is a drug of choice **for trigeminal neuralgia** and in other neuropathic pain. It is not an analgesic. It is also effective in treating manic depressive psychosis.

❑ Adverse effects

- Dose-dependent adverse effects start with **drowsiness** followed by **dizziness, headache, slurred speech, vertigo, ataxia and diplopia.**
- Allergic reactions like **rashes and fever** are observed. Other **idiosyncratic reactions are blood dyscrasias, aplastic anaemia, leukopenia, hepatitis and systemic lupus erythematosis.**
- It stimulates ADH secretion and can **cause water retention and hyponatremia.**
- **Risk of teratogenecity is low**, but can induce finger nail hypoplasia and delayed development of foetus.
- Oxcarbazepine shows lesser hypersensitive reactions and has milder side effects.

❑ Drug interactions

- Erythromycin, Fluoxetine and Isoniazid **inhibit metabolism of Carbamazepine and precipitate toxicity.**
- Carbamazepine and Phenytoin **increase each other's metabolism.**
- It is an **enzyme inducer and reduces plasma concentration of Haloperidol and Oral contraceptives.**

➢ Ethosuximide

- It belongs to succinimide group of anticonvulsants. **It is a drug of choice for Petit mal (absence) seizures.**
- It inhibits the low **threshold T-type calcium channels**. The therapeutic plasma levels are 60-100 μg/ml.
- It causes **GIT distress, headache, dizziness, hiccups, lethargy and euphoria. Idiosyncratic** adverse effects include **skin rashes, fever, eosinophilia and bone marrow depression.**
- It is lesser teratogenic and can be given during pregnancy.
- Valproic acid inhibits Ethosuximide metabolism and clearance and increases its plasma levels.

➢ Valproic acid (sodium valproate)

❑ Mechanism of action

- It is known to **block sodium channels**, increase GABA activity by **activating the enzyme glutamic acid decarboxylase** (GAD) and **by inhibiting the enzyme GABA transaminase**. It decreases release of glutamate and **blocks T-type calcium channels.**

❑ Therapeutic uses

- Antiepileptic use It is effective against absence seizures. It is preferred if the patient has concomitant **generalised tonic-clonic attacks and myoclonic seizures.** It is used in combination with clonazepam to **treat cortical myoclonus**.
- Non-antiepileptic use Enteric coated tablet of Semi-sodium valproate is used to treat **manic depressive bipolar disorder**. It is also used for **prophylaxis of migraine** and tension type cluster headache.

❑ Adverse effects

- Adverse effects include **weight gain, increase in appetite, GIT distress, tremors and reversible alopecia.**
- Idiosyncratic toxicity is limited to **fatal hepatotoxicity**. The risk is greater in children below 3 years and those taking a combination of Valproate with Phenobarbital.

❑ **Drug interactions**

- It is not a CNS depressant, but it **potentiates depressant actions of Phenobarbital and BZDs.**
- o It increases plasma concentration of Phenobarbital.
- It decreases metabolism as well as displaces Phenytoin resulting in toxicity of phenytoin.

➢ Benzodiazepines (BZDs)

- Although BZDs have anticonvulsant action, it has two limitations: **pronounced sedative effects and development of tolerance** to anticonvulsant action.
- They **enhance the frequency of GABA-mediated chloride channel opening.** At higher doses they **block sodium channels** which have an advantage in **controlling generalised status epilepticus.**
- Diazepam as a slow IV injection in a dose of 20-30 mg is used to treat seizures. It is also useful for controlling local anaesthetic induced seizures.

➢ Vigabatrin

- It is an **irreversible inhibitor of GABA transaminase** and thus elevates GABA levels in brain.
- It is useful in the **treatment of simple and complex partial seizures** as well as generalised seizures.
- It is also useful in treating **drug-refractory epilepsy and infantile spasm.** It should not be used in cases of absence epilepsy or myoclonic seizures.
- **Adverse effects** include **behavioural changes, sedation, amnesia and weight gain.**
- Rarely, it may cause **irreversible visual field defects** due to peripheral retinal atrophy. It **should be used with caution in patients with visual field defects** and in children suffering from infantile spasm, in whom visual field monitoring is difficult.

➢ Tiagabine

- It **inhibits GABA uptake by neurons** and increases its content in brain. It is used for treatment of partial complex seizures.

➢ Gabapentin and Pregabalin

- Both are **GABA analogs** and can cross BBB and increase GABA concentration in brain.
- They **inhibit calcium channels** and decrease synaptic release of glutamate. They also function as **$GABA_B$ receptor agonist.**
- It is useful in treating **drug resistant partial seizures and generalised tonic-clonic seizures.**
- It is useful in treating **diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia and pain** associated with multiple sclerosis in doses of 1800 mg/day in divided doses.
- **Adverse reactions** include **drowsiness, fatigue, dizziness, weight gain and ataxia.**

➢ Topiramate

- It is a broad spectrum anticonvulsant drug acting by multiple mechanisms like **blockade of sodium channels**, activation of **$GABA_A$ receptor** and **inhibition of AMPA receptors for glutamate**.
- It is most useful for generalised tonic-clonic, partial and absence seizures.
- Usual adult oral dose is 300-600 mg/day in divided doses.
- **Adverse reactions** include sedation, somnolence, amnesia, urolithiasis and teratogenic risk.

➢ Zonisamide

- It is a broad spectrum anticonvulsant drug with multiple actions including **blockade of sodium channels and inhibition of calcium channels.**
- It is effective against partial, generalised tonic-clonic and myoclonic seizures. It is also useful against infantile spasm.
- Adverse reactions include **drowsiness, amnesia, skin rash and kidney stones.**

➢ Lamotrigine

- It **blocks voltage-gated sodium channels as well as calcium channels** and inhibits release of glutamate.
- It is effective in treating **partial, generalised tonic-clonic, secondary generalised, absence and atonic seizures.** It is effective in myoclonic

seizures in children.

- It is effective in treating **bipolar disorder** as a additional drug.
- Adverse reactions include **dizziness, ataxia, diplopia and skin rash**, especially in children.

❑ Levetiracetam

- It is used specifically for **treating partial seizures.**
- Adverse reactions include **somnolence, asthenia and dizziness**.

➢ Lacosamide

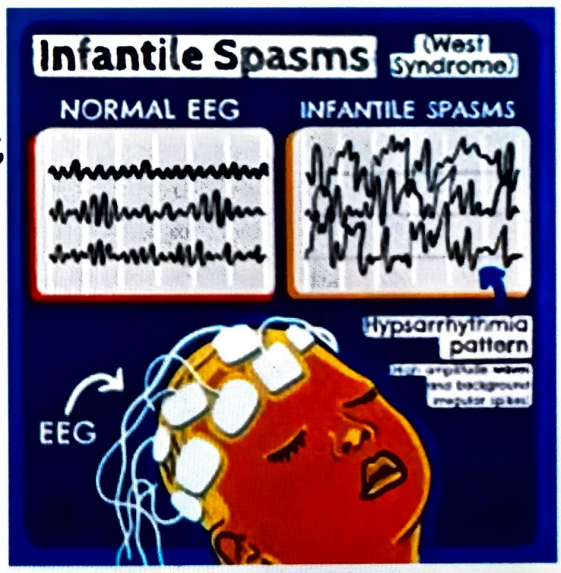
- It is useful for treatment of **partial seizures.**
- Usual oral dose is **50 mg twice daily and can be increased by 100** mg every week till 300 mg.
- Adverse reactions include headache, nausea and dizziness. Oral bioavailability is 100%.

Febrile convulsions

- Some children, **especially under 5 years age, develop convulsions during fever.**
- Seizures may **recur every time with fever** and few may become chronic epileptics.
- Every attempt should be made to see that they do not develop fever, but when they do, **temperature should not be allowed to rise by using paracetamol and external cooling.**
- The best treatment of febrile convulsions is **rectal diazepam 0.5 mg/kg given at the onset of convulsions.**

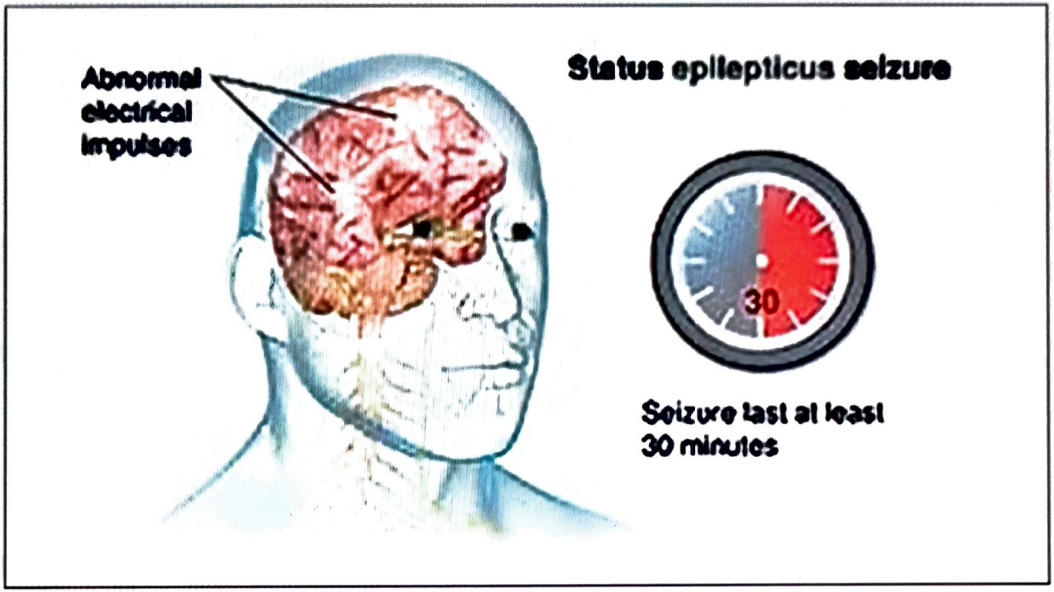
Infantile spasms (hypsarrhythmia)

- Therapy of this condition is unsatisfactory, **antiepileptic drugs are generally useless.**
- **Corticosteroids afford symptomatic relief** but cannot be used for long-term due to adverse effects.
- Clonazepam, valproate and vigabatrin may afford some relief.



Status epilepticus

- When seizure activity **occurs for >30 min, or two or more seizures occur without recovery of consciousness**, the condition is called status epilepticus.
- **Recurrent tonic-clonic convulsions without recovery of consciousness** in between is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.



UNIT-IV

ALCOHOL AND DISULFIRAM

Points to be covered in this topic

- ❖ Introduction
- ❖ Pharmacological actions
- ❖ Pharmacokinetic
- ❖ Contraindications
- ❖ Toxicity
- ❖ Aldehyde dehydrogenase inhibitor

Alcohol and Disulfiram

❑ Introduction

Ethyl alcohol (Ethanol)

- Alcohols are **hydroxy derivatives of aliphatic hydrocarbons**. When unqualified, 'alcohol' refers to ethyl alcohol or ethanol.
- Pharmacology of alcohol is important for its presence in beverages, **alcoholism and for alcohol intoxication**, rather than as a medicinal substance.
- Alcohol is manufactured by **fermentation of sugars:**

$$\underset{\text{Glucose}}{C_6H_{12}O_6} \xrightarrow[\text{(in yeast)}]{\text{Zymase}} 2CO_2 + \underset{\text{Ethanol}}{2C_2H_5OH}$$

- Fermentation proceeds till **alcohol content reaches ~ 15%.** Then the reaction is **inhibited by alcohol itself**. Starchy cereals, e.g. barley, when soaked produce malt:

$$\text{Starch} \xrightarrow{\text{Convertase}} \text{Maltose}$$

- Which can then be **fermented by yeast to produce alcohol**. The major source of commercial alcohol is mollases, the leftover byproduct of sugar industry.

❖ Alcoholic beverages

A. **Malted liquors** Obtained by **fermentation of germinating cereals;** these are **undistilled—alcohol content is low (3–6%)** e.g. Beers, Stout. Now strong beers (upto 10%) are also available.

B. **Wines** Produced by **fermentation of natural sugars** as present in grapes and other fruits. These are also **undistilled.**

✓ **Light wines Claret, Cider; alcohol content 9–12%,** can not exceed 15%.

✓ **Fortified wines Port, Sherry (alcohol 16–22%).**

✓ **Effervescent wines Champagne (12–16% alcohol):** these are bottled before fermentation is complete; the CO_2 **produced after botteling remains dissolved under pressure**. Wines are called 'dry' when all sugar present has been fermented and 'sweet' when some is left.

C. **Spirits** These are produced by **distillation of the fermented broth; e.g. Rum, Gin, Whiskey, Brandy, Vodka, etc.** Though the alcohol content of these beverages can vary from **40–55%**, in India (and almost internationally) for all licenced brands it is standardized to **42.8% v/v or 37% w/w.**

Other forms of alcohol

1. **Absolute alcohol 99% w/w ethanol (dehydrated alcohol).**
2. **Rectified spirit 90% w/w** ethyl alcohol produced from fermented mollases, by distillation.
3. **Proof spirit** It is an old term. If whiskey is poured on gun powder and ignited and it explodes, then it was labelled to be of 'proof strength'. If water is mixed to it, the gun powder will not ignite. **100% proof spirit is 49.29% w/w or 57.1% v/v alcohol.**
4. **Methylated spirit (industrial)** Also called **'denatured spirit'** is produced by adding 5 parts of wood naphtha (methyl alcohol) to 95 parts of rectified spirit so as to render it unfit for drinking. It is tinted blue by methylene blue dye for distinction. It **can be applied on the skin for antiseptic, cleaning and astringent purposes.**

❑ Pharmacological actions

❑ Local actions

- Ethanol is a **mild rubefacient and counterirritant** when rubbed on the skin. By evaporation it **produces cooling**. Applied to delicate skin (scrotum) or mucous membranes **it produces irritation and burning sensation.**
- **Concentrated alcohol** (spirit) should not be applied in the mouth, nose, etc. Injected s.c. it causes **intense pain, inflammation and necrosis** followed by fibrosis.

- Injected around a nerve it produces permanent nerve damage. Applied to the surface, **alcohol is an astringent—precipitates surface proteins and hardens the skin.** By precipitating bacterial proteins it acts as an antiseptic.

❑ CNS

- Alcohol is a **neuronal depressant.**
- Since the highest areas are most easily deranged and these are **primarily inhibitory—apparent excitation and euphoria are produced at lower plasma concentrations** (30–60 mg/dl). Hesitation, caution, self-criticism and restraint are lost first.
- Mood and feelings are altered; anxiety may be allayed. **At 50–100 mg/dl** some individuals may experience what is labelled as **'high'.**
- With increasing concentration (100–150 mg/dl) **mental clouding, disorganization of thought, impairment of attention, memory and other faculties, alteration of gait and perception, and drowsiness supervene.**
- At 150–200 mg/dl the **person is sloppy, ataxic and drunk, 'black-outs'** occur;
- 200–300 mg/dl result in **stupor and above this unconsciousness prevails, medullary centres are paralysed and death** may occur.

➢ Mechanism of action

- **Alcohol act by specific effect on multiple receptor operated and voltage gated ion channels** as well as other critical proteins has been demonstrated at concentrations attained during moderate drinking.
- Other depressants like barbiturates and benzodiazepines, **which predominantly facilitate $GABA_A$ receptor mediated Cl^- channel opening.** Alcohol has been shown to **enhance GABA release at $GABA_A$ sites in the brain.**
- It also **inhibits NMDA type of excitatory amino acid receptors** (operating through cation channels) which has been implicated in memory impairment caused by alcohol.

- **Action of 5-HT on 5-HT_3 inhibitory autoreceptor** (having an intrinsic ion channel) is augmented.
- Some studies suggest that cerebral **nicotinic cholinergic receptor** (operating through Na+ channel) may also be one of the targets of alcohol action.
- Ethanol can indirectly reduce neurotransmitter release by **inhibiting voltage sensitive neuronal Ca^{2+} channels.**
- It also **activates specific type of K^+ channels** in certain brain areas.
- Release and turnover of **DA in brain is enhanced through β endorphin release** in nucleus accumbens and an opioid receptor dependent mechanism.
- Activity of membrane bound enzymes **like Na^+ K^+ ATPase and adenylyl cyclase is also altered.**

❑ CVS

The effects of alcohol are dependent on the dose.

- **Small doses:** produce only **cutaneous(especially on the face) and gastric vasodilatation**. Skin is warm and flushed and there may be conjunctival injection; BP is not affected.
- **Moderate doses:** cause **tachycardia and a mild rise in BP** due to increased muscular activity and sympathetic stimulation.
- **Large doses:** cause **direct myocardial as well as vasomotor centre depression and there is fall in BP.** Epidemiological studies have confirmed that **chronic alcoholism contributes to hypertension and can lead to cardiomyopathy**. Atrial fibrillation and other cardiac arrhythmias may occur due to conduction defects and Q-T prolongation.

❑ Blood

- Regular intake of **small to moderate amounts of alcohol (1–2 drinks) has been found to raise HDL-cholesterol levels** and decrease LDL oxidation.
- This may be responsible for the **15–35% lower incidence of coronary artery disease in such individuals.**
- **Mild anaemia** is common in **chronic alcoholics. Megaloblastic anaemia occurring in chronic alcoholism.**

❑ Body temperature

- Alcohol is reputed to **combat cold.** It does produce a sense of warmth due to **cutaneous and gastric vasodilatation**, but heat loss is actually increased in cold surroundings.

❑ Respiration

- Brandy or whiskey are reputed as **respiratory stimulants in collapse.** They **irritate buccal and pharyngeal mucosa which may transiently stimulate respiration reflexly.**

❑ GIT

- Alcoholic beverages have **variable effect on gastric secretion depending on the beverage itself.**
- However, dilute alcohol (optimum 10%) put in the stomach by Ryle's tube is a strong stimulant of gastric secretion.
- Higher concentrations (above 20%) **inhibit gastric secretion, cause vomiting, mucosal congestion and gastritis.** Alcoholism is an important cause of chronic gastritis.

❑ Liver

- Neither brief alcohol intoxication nor chronic intake of small-to-moderate amounts cause significant liver damage, **provided adequate nutrition is maintained.**
- However, it **does mobilize peripheral fat and increases fat synthesis in liver in a dose-dependent manner producing 'fatty liver'.** This is reversible, but may progress to **cirrhosis** if prolonged or excessive.

❑ Skeletal muscle

- Alcohol produces little direct effect. **Fatigue is allayed by small doses,** but muscle work is increased or decreased depending on the predominating central effect. **Weakness and myopathy occurs in chronic alcoholism.**

❑ Kidney

- **Diuresis is often noticed after alcohol intake.** This is due to water ingested along with drinks as well as alcohol **induced inhibition of ADH secretion.** Alcohol does not impair renal function.

❑ Sex

- Alcohol is reputed as an **aphrodisiac**. Though, **loss of restraint and inhibition may provoke sexual behaviour** in some individuals or on some occasions, there is no uniform effect of alcohol on sexual desire.
- Chronic alcoholism can produce **impotence, testicular atrophy, gynaecomastia and infertility** in both men and women.

❑ Endocrine effects

- Moderate amounts of alcohol **increase Adr release** which can cause **hyperglycaemia** and other sympathetic effects.
- However, acute intoxication is often associated with **hypoglycaemia and depletion of hepatic glycogen, because gluconeogenesis is inhibited**. Glucagon, therefore fails to reverse alcohol induced hypoglycaemia, and glucose must be given to counteract it.

❑ Uterine

contractions are suppressed at moderate blood levels.

❑ Pharmacokinetics

- Rate of alcohol absorption from the stomach generally **quite slow.** Absorption from intestines is very fast.
- **Limited first pass metabolism occurs in stomach and liver**. Absorption of alcohol from skin of adults is minimal but may be significant in infants given alcohol sponges.
- Alcohol gets **distributed widely in the body** (vol of distribution 0.7 L/kg, i.e. equal to volume of total body water),
- **Crosses blood-brain barrier efficiently**: concentration in the brain is very near blood concentration. It also **crosses placenta freely.**
- Alcohol is **oxidized in liver to the extent of 98%.** The primary pathway sequentially utilizes **alcohol dehydrogenase and aldehyde dehydrogenase.**

❑ Contraindications

1. Patients with **peptic ulcer, hyperacidity and gastroesophageal reflux disease** (alcohol increases gastric secretion and relaxes LES).
2. **Epileptics:** seizures may be precipitated.
3. Severe **liver disease** patients.
4. **Unstable personalities:** they are likely to abuse it and become excessive drinkers.
5. **Pregnant women:** Even moderate drinking during pregnancy can produce **foetal alcohol syndrome** resulting in intrauterine and postnatal growth retardation, low IQ offspring, microcephaly, cranio-facial (flat face) and other abnormalities, and immunological impairment causing increased susceptibility to infections. **Heavy drinking during pregnancy, in addition, increases the incidence of miscarriage, stillbirths and low birth-weight babies**

❑ Toxicity

A. Side effects of **moderate drinking** **Nausea, vomiting, flushing, hangover, traffic accidents.**

B. **Acute alcoholic intoxication** Unawareness, unresponsiveness, stupor, hypotension, gastritis, hypoglycaemia, respiratory depression, collapse, coma and death.

Treatment: **Gastric lavage is helpful only when the patient is brought soon after ingesting alcohol**, which is rare.

- **First priority is to maintain patent airway** and prevent aspiration of vomitus.
- **Tracheal intubation and positive pressure** respiration may be needed.
- **Analeptics** should not be given. They may precipitate convulsions. Most patients will recover with supportive treatment, **maintenance of fluid and electrolyte balance and correction of hypoglycaemia by glucose infusion** till alcohol is metabolized.
- **Thiamine (100 mg in 500 ml glucose solution infused i.v.) should be added.**

C. Chronic alcoholism On chronic intake, **tolerance develops to subjective and behavioural effects of alcohol, but is generally of a low degree.**

❖ Withdrawal syndrome

- When an alcohol dependent subject stops drinking, withdrawal syndrome appears within a day. Its severity depends on the duration and quantity of alcohol consumed by the subject.
- It consists of **anxiety, sweating, tachycardia, tremor, impairment of sleep, confusion, hallucinations, delirium tremens, convulsions and collapse.**

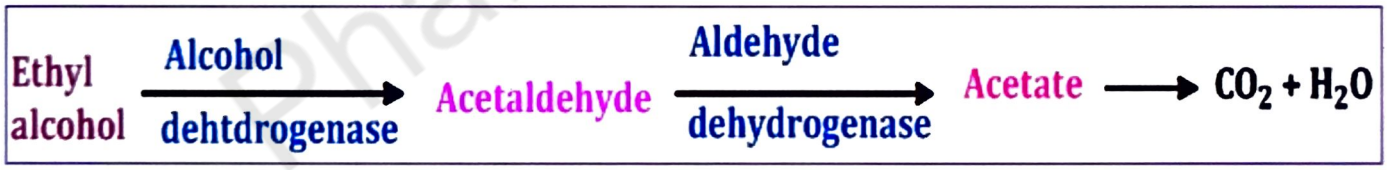
❖ Clinical Uses of Ethanol

It is used for following purposes:

- As a skin antiseptic (76% v/v), alcohol is most effective.
- It has astringent action and hardens the skin to prevent the bed sores.
- It is used to treat methanol poisoning.

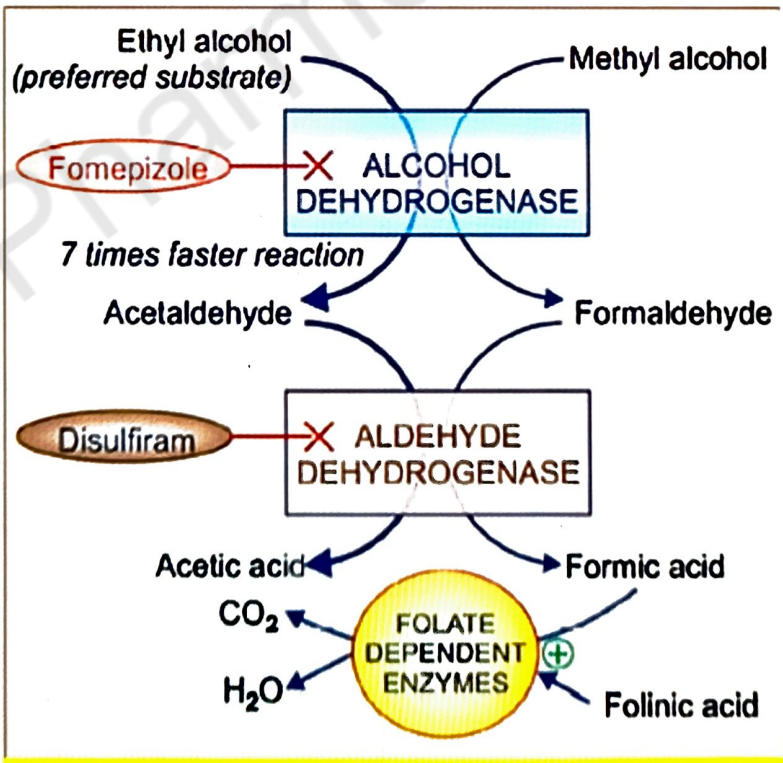
❑ Aldehyde dehydrogenase inhibitor

- Disulfiram It inhibits the **enzyme aldehyde dehydrogenase** probably after conversion into active metabolites.



- When alcohol is ingested after taking disulfiram, the concentration of acetaldehyde in tissues and blood rises and a number of highly distressing symptoms (aldehyde syndrome) are produced promptly.
- These are **flushing, burning sensation, throbbing headache, perspiration, uneasiness, tightness in chest, dizziness, vomiting, visual disturbances, mental confusion, postural fainting and circulatory collapse.**
- Duration of the syndrome (1–4 hours) depends on the amount of alcohol consumed. Because of risk of severe reaction, disulfiram is to be used with great caution, only in well motivated subjects.

- Disulfiram aversion therapy is indicated in abstinent subjects who **sincerely desire to leave the habit.**
- After making sure that the **subject has not taken alcohol in the past 12 hours, disufiram is given at a dose of 500 mg/day for one week followed by 250 mg daily.**
- Sensitization to alcohol develops after 2–3 hours of first dose, reaches its peak at **~12 hours** and **lasts for 7–14** days after stopping it, because **inhibition of aldehyde dehydrogenase with disulfiram is irreversible**: synthesis of fresh enzyme is required for return of activity.
- The subject's resolve not to drink is reinforced by the distressing symptoms that appear if he drinks a little bit. **The subject should be cautioned to avoid alcohol altogether.** Disulfiram should not be given to patients who are physically dependent on alcohol.
- **Side effects of disulfiram** (as such) are infrequent, include **rashes, metallic taste, nervousness, malaise and abdominal upset.** It inhibits a number of other enzymes as well **including alcohol dehydrogenase, dopamine β hydroxylase.**



metabolic pathway of ethyl and methyl alcohols