Sedative-Hypnotics

Prepared by
MRIDHULMOHAN
Associate Professor
Dept of pharmacology

Sedative-Hypnotics

- Sedative is a drug that produces a calming or quieting effect and reduces excitement.
- It may induce drowsiness.
- Hypnotics is a drug that induces sleep resembling natural sleep.
- **Sleep**
- Sleep can be classified in to two types depending on the physiological characteristics.
- 1. NREM sleep- Non rapid eye movement
- 2. REM sleep- Rapid eye movement

- **NREM sleep** is divided in to 4 stages(sleep is of 0 to 4 levels of depth)
- 1. Stage 0
- From lying down to falling a sleep
- Constitutes 1-2% of sleep time.
- 2. Stage 1
- Eye movements are less and the body muscles begins to relax.
- 5-10% of total sleep time
- 3. Stage 2
- Eye movements are further reduced, but the person is still easily arousable.
- It involves 50% of total sleep time.
- 4. Stage 3
- Deeper sleep with minimum eye movements and not easily arousable.
- Comprises 5-8% of sleep time

- 5. Stage 4 (cerebral sleep)
- It is the deepest level of sleep
- In this stage, the metabolic rate is lowest and growth hormone secretion is highest.
- There are no eye movements and muscles are fully relaxed.
- **REM sleep(Paradoxical sleep)**
- It is associated with dreaming, enhanced heart rate, breathing and brain activity.
- It makes up 20-25% of total sleep time.
- Stages of NREM sleep alternate with REM sleep through out the night for brief periods.

- **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.
- Primary insomnia is sleeplessness that is not attributable to medical, psychiatric or environmental causes. This is uncommon
- Secondary insomnia- variety of clinical conditions including medical and psychiatric illness, stress, drug induced or simply due to lack of adequate physical activity.

Classification

- **1. Barbiturates**
- A. Long acting- Phenobarbitone
- B. Short acting- Butobarbitone, Pentobarbitone
- C. Ultra-short acting- Thiopentone, Methohexitone
- **2. Benzodiazepines**
- A. Hypnotic- Diazepam, Flurazepam, Nitrazepam, Alprazolam, Temazepam and Triazolam
- B. Anti-anxiety- Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam

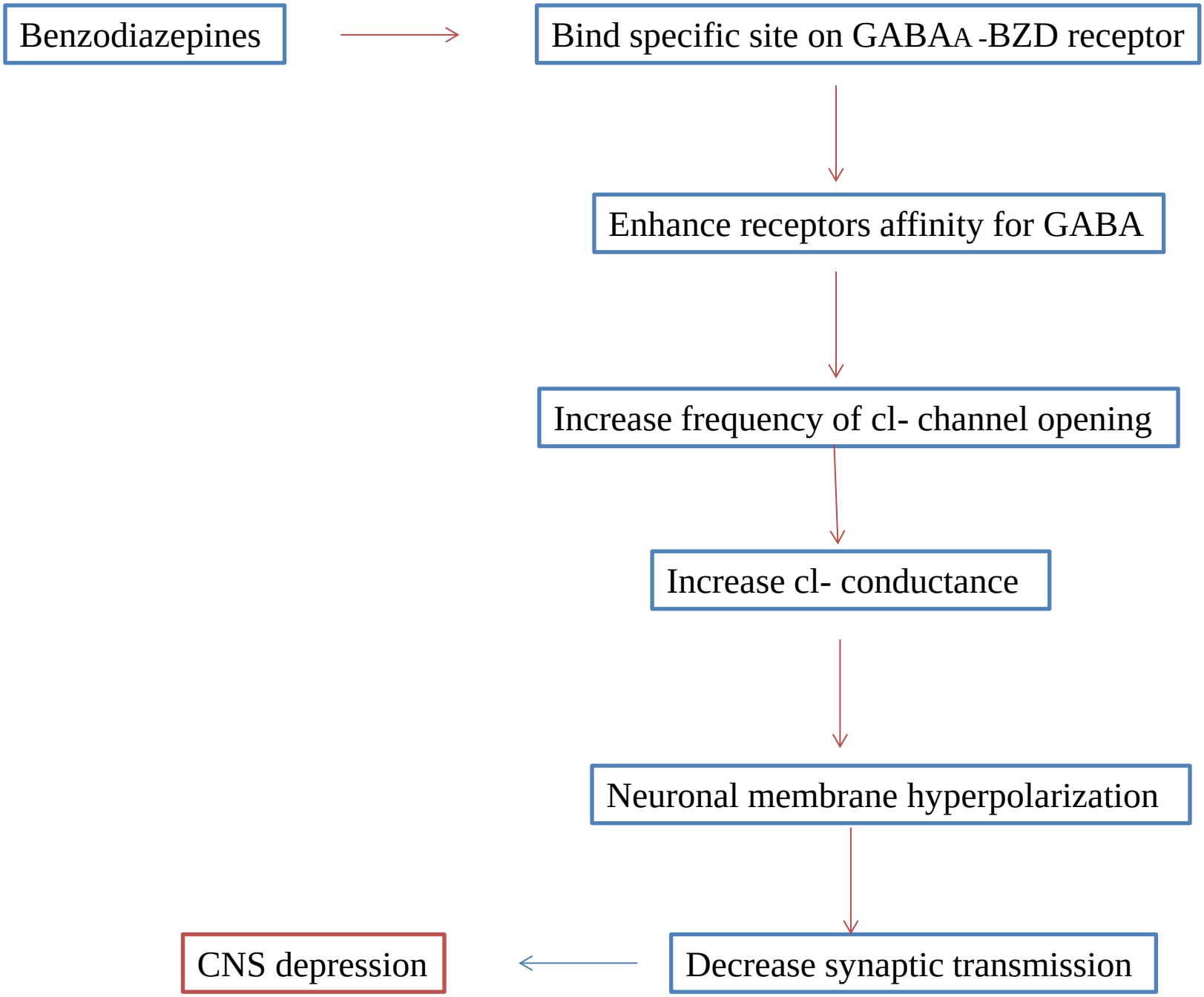
- C. Anti-convulsant- Diazepam, Lorazepam, Clonazepam, Clobazam
- 3. **Newer Non-benzodiazepine hypnotics**
- Zopiclone, Zolpidem, Zaleplon
- 4. **Melatonin receptor agonist**
- Ramelteon, Tasimelteon
- 5. **Miscellaneous**
- Chloral hydrate
- Paraldehyde
- glutethimide

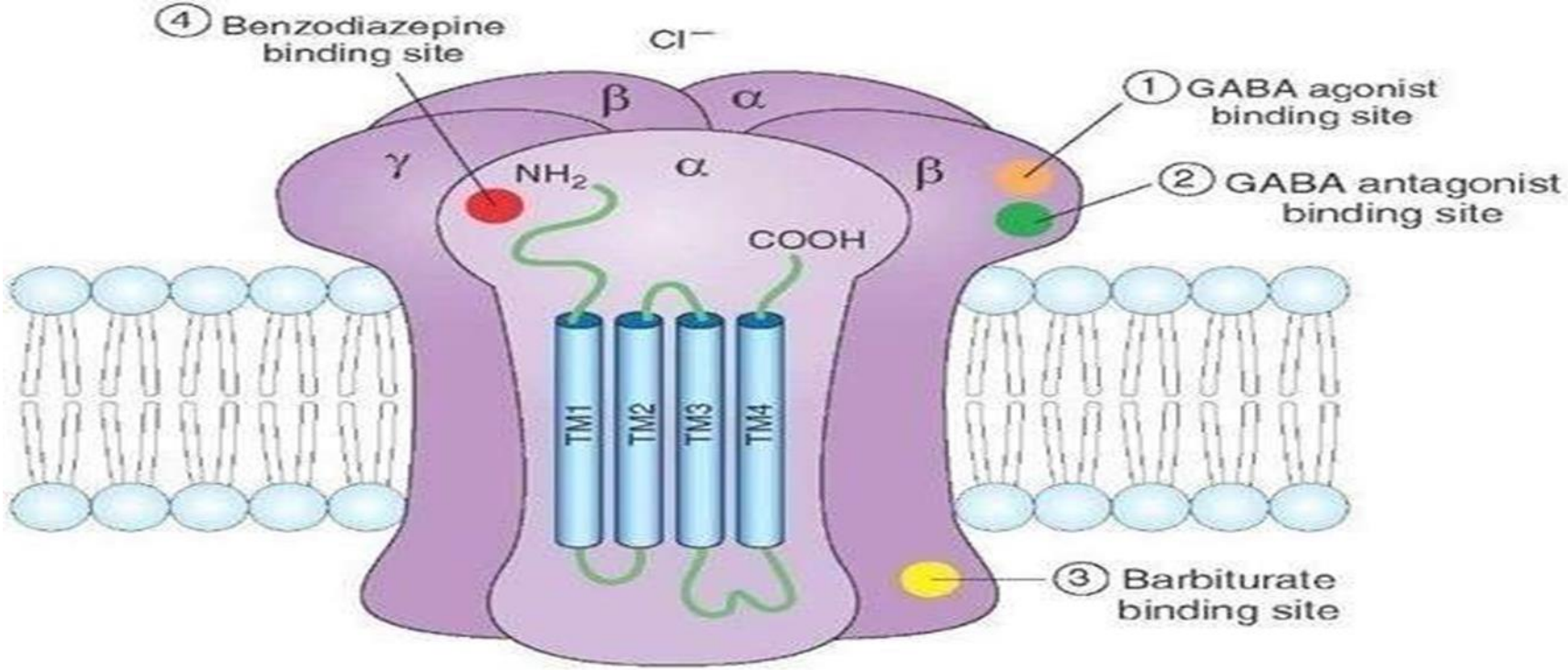
Benzodiazepines(BZDs)

- All benzodiazepines(BZDs) have a benzene ring fused to a seven membered diazepine ring.
- Chlordiazepoxide was the 1st benzodiazepine to be introduced in to clinical medicine in 1961.
- **Site of action**
- Midbrain(Ascending reticular formation)
- Limbic system
- Brain stem

- Benzodiazepines facilitate action of GABA → They potentiate inhibitory effects of GABA
- GABA is the principle inhibitory neurotransmitter of the CNS and it acts through GABA receptors.
- BZDs bring about their effects through GABA, i.e, they modulate the response to GABA by acting on GABA receptors.
- Benzodiazepines bind to the $GABA_A$ receptor present in the neuron of the CNS.

- They bind at a site which is different from the GABA-binding site and enhance the affinity of GABA for the receptor.
- GABA enhances chloride ion conductance through this receptor and this effect is potentiated by BZDs.
- BZDs bind to the receptor and increase the frequency of chloride channel opening in response to GABA.
- This in-turn leads to an increased flow of chloride ions in to the neuron, resulting in hyperpolarization of these neuronal membranes which in turn results in decreased synaptic transmission.


Benzodiazepines
Bind specific site on GABAA -BZD receptor
Enhance receptors affinity for GABA
Increase frequency of cl- channel opening
Increase cl- conductance
Neuronal membrane hyperpolarization
Decrease synaptic transmission
CNS depression



- GABAA receptor is a pentamer made of 5-subunit (2 α, 2 β and 1 ϒ)
- BZDs, GABA, Barbiturates bind to different sites on the $GABA_A$ receptor to facilitate the opening of the cl- channel

Pharmacological actions

- The most important actions of BZDs are on the CNS and includes
- 1. Sedation and hypnosis
- 2. Reduction in anxiety
- 3. Anaesthesia
- 4. Muscle Relaxation
- 5. Anti-convulsant effect
- 6. Amnesia

- **1. Hypnosis**
- BZDs hasten the onset of sleep.
- At slightly higher doses, they induce sleep(hypnosis) and increase the duration of sleep.
- The stage 2 NREM sleep is prolonged while the duration of REM sleep and stage 4 NREM is decreased.
- 2. **Anxiolytic effects**
- BZDs reduce anxiety and aggression and produce a calming effect.
- 3. **Anaesthesia**
- BZDs produce CNS depression in a dose-dependent manner.
- Sedation ,hypnosis, stupor, anaesthesia and coma are the different grades of CNS depression.

- **4. Muscle relaxant action**
- BZDs reduce muscle tone by a central action.
- They depress the spinal poly synaptic reflexes which maintain the muscle tone.
- High doses also depress transmission at the NMJ.
- **5. Anticonvulsant effect**
- BZDs increases the seizure threshold and acts as anticonvulsants.
- They suppress the development and spread of seizures.
- **6. Amnesia**
- BZDs produce anterograde amnesia, i.e, loss of memory for the events happening after the administration of BZDs.

- 7. Other actions
- **CVS**
- In higher doses, BZDs decreases BP, increase heart rate and also depress respiration.
- In patient with impaired cardiac function, regular therapeutic doses of BZDs can cause significant CVS depression especially on parentral administration.
- Toxic doses result in depressed myocardial contractility and vascular tone leading to cardiovascular collapse.
- Respiration
- BZDs in higher doses can cause respiratory depression.

Pharmacokinetics

- Benzodiazepines are usually given orally or intravenously.
- All BZDs are completely absorbed on oral administration.
- Intramuscular absorption is slow- hence oral route is preferred.
- Most BZDs are extensively bound to plasma proteins.
- BZDs are widely distributed in the tissues.
- They cross the placental barrier.
- Metabolized in liver(oxidation and hydroxylation)
- The metabolites are excreted in urine.

ADR

- Drowsiness
- Confusion
- Dizziness
- Amnesia
- Lethargy
- Weakness
- Headache
- Blurred vision
- Ataxia
- Disorientation
- Day-time sedation

- Withdrawal after chronic use causes symptoms like tremor, insomnia, restlessness, nervousness and loss of appetite.
- Use of BZDs during labour may cause respiratory depression and hypotonia in the newborn(Floppy baby syndrome).
- **Drug interactions**
- 1. Microsomal enzyme inhibitors like ketoconazole, omeprazole, erythromycin prolong t1/2 of BZDs.
- 2. BZDs are extensively bound to plasma proteins, displacement interactions are not clinically significant.

Uses of BZDs

- Insomnia
- In anxiety states
- As anti-convulsants- IV diazepam-5-10mg
- Diagnostic and minor operative procedures like endoscopies, fracture reduction and cardiac catheterization.
- Useful in spinal injuries, tetanus, cerebral palsy
- Reduce spasm due to joint injury or spasm
- In psychiatry- for the initial control of mania
- General anaesthesia- IV midazolam or diazepam is used.

Benzodiazepine antagonist

- **Flumazanil**
- It is a competitive antagonist at the BZDs receptors
- It competes for the same binding sites as BZDs on the GABA receptors and blocks the effects of BZDs.
- It is given IV as to overcome the effects of BZDs.
- It is not used orally because of it’s high first pass metabolism.
- **ADR**- confusion, dizziness, nausea
- **Uses**-
- To reverse BZDs sedation/ Anaesthesia
- In BZDs overdosage.

Barbiturates

- All barbiturates are derivatives of barbituric acid.
- They are Non-selective CNS depressants and act at many sites, Ascending reticular activating system.
- **Pharmacological actions**
- 1. **CNS**
- Barbiturates causes depression of all excitable tissues, of which CNS is the most sensitive.

- A. Sedation and hypnosis
- In hypnotic dose, barbiturates induce sleep and prolong the duration of sleep.
- The REM-NREM sleep cycle is altered with decreased duration of REM and prolonged NREM sleep.
- On waking up, there is some hangover with headache and residual sedation.
- Barbiturates reduce anxiety, impair short term memory and judgement.

- They can produce euphoria and are drugs of addiction while some people may experience dysphoria.
- Barbiturates produce hyperalgesia (increased sensitivity to pain).
- Sedative dose given at day time can produce drowsiness, reduction in anxiety and excitability.
- B. Anaesthesia
- In higher doses, barbiturates produce general anaesthesia.
- C. Anticonvulsant effects
- All barbiturates have anti-convulsant effect.
- Phenobarbitone and mephobarbitone have specific anti-convulsant activity.

- 2. Respiratory system
- Barbiturates cause significant depression of respiration.
- High doses cause pro found respiratory depression and also bring about a direct paralysis of the medullary respiratory centre.
- 3. CVS
- Hypnotic doses of barbiturates produce a slight reduction in blood pressure and heart rate.
- Toxic doses of barbiturates produce a significant fall in BP due to direct decrease in myocardial contractility and vasomotor centre depression.

- 4. **Skeletal muscles**
- Higher doses of barbiturates depress the excitability of the neuromuscular junction.
- 5. Smooth muscles
- Tone and motility of bowel is decreased slightly by hypnotic doses.
- 6. Kidney
- Barbiturates reduce urine flow by decreasing BP and increasing ADH release

MOA

Barbiturates

↓

Bind to specific site on $GABA_A$ receptors

↓

Prolong duration of cl- channel opening

↓

Cl- conductance

↓

Neuronal membrane hyperpolarization

↓

CNS depression(GABA mimetic effect)

Pharmacokinetics

- Barbiturates are well absorbed and widely distributed in the body.
- The highly lipid-soluble barbiturates, like thiopentone, have a fast onset of action, while duration of action is short due to redistribution in to adipose tissues.
- It is metabolized in the liver
- They are hepatic microsomal enzyme inducers.
- The metabolites are excreted in the urine.

ADR

- Drowsiness
- Confusion
- Headache
- Ataxia
- Hypotension
- Respiratory depression
- Hypersensitivity reactions like skin rashes, itching, swelling of face
- Excitement

- Irritability
- Vertigo
- Vomiting
- Diarrhoea
- Nausea
- Tolearance, Dependence
- **Contraindication**
- Porphyria

Uses

- 1. Anaesthesia- Thiopentone sodium is used IV for the induction of general anaesthesia.
- 2. Neonatal jaundice
- Phenobarbitone is a microsomal enzyme inducer because of which it enhances the production of glucuronyl transferase- the enzyme required for metabolism and excretion of bilirubin. It, therefore, helps in the clearance of jaundice in the neonates.
- 3. Antiepileptic- Phenobarbitone is used

Acute barbiturate poisoning

- The fatal dose of phenobarbitone is 6-10g.
- **Symptoms**
- Respiratory depression
- Hypotension
- Drowsiness
- Restlessness
- Hallucination
- Convulsion
- Cardiovascular collapse
- Renal failure
- Coma
- Death

Treatment

- There is no specific anti-dote
- The measures include-
- Maintain airway, breathing and circulation
- Maintain electrolyte balance
- Gastric lavage- after stomach wash, administer activated charcoal to prevent further absorption of barbiturates.
- Artificial ventilation and oxygen administration.

- Forced alkaline diuresis- IV sodium bicarbonate
- Alkalinizes urine, barbiturates are weakly acidic drug. In alkaline urine, barbiturates exist in ionized form. So they are not reabsorbed while passing through renal tubules and are rapidly excreted in urine.
- Haemodialysis should be done, especially if there is renal failure.

Non-benzodiazepine hypnotics

- **MOA**

Zolpidem, Zopiclone, Zaleplon → Binds selectively to BZD binding site on $GABA_A$ receptor

↓

Facilitate GABA-mediated neuronal inhibition

↓

CNS depression