بسم الله الرحمن الرحيم

Sedative hypnotics (1)
Benzodiazepines and related drugs

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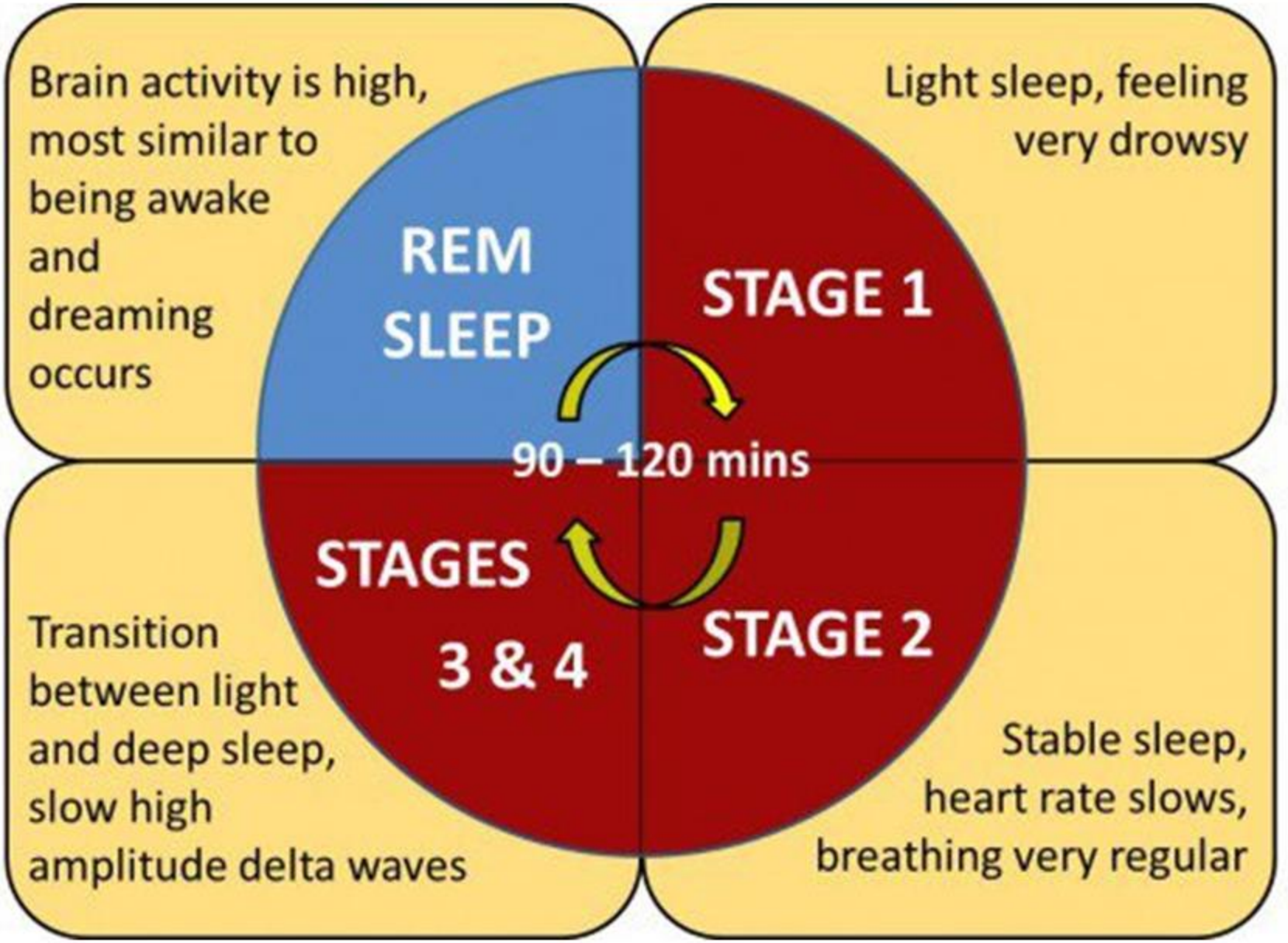
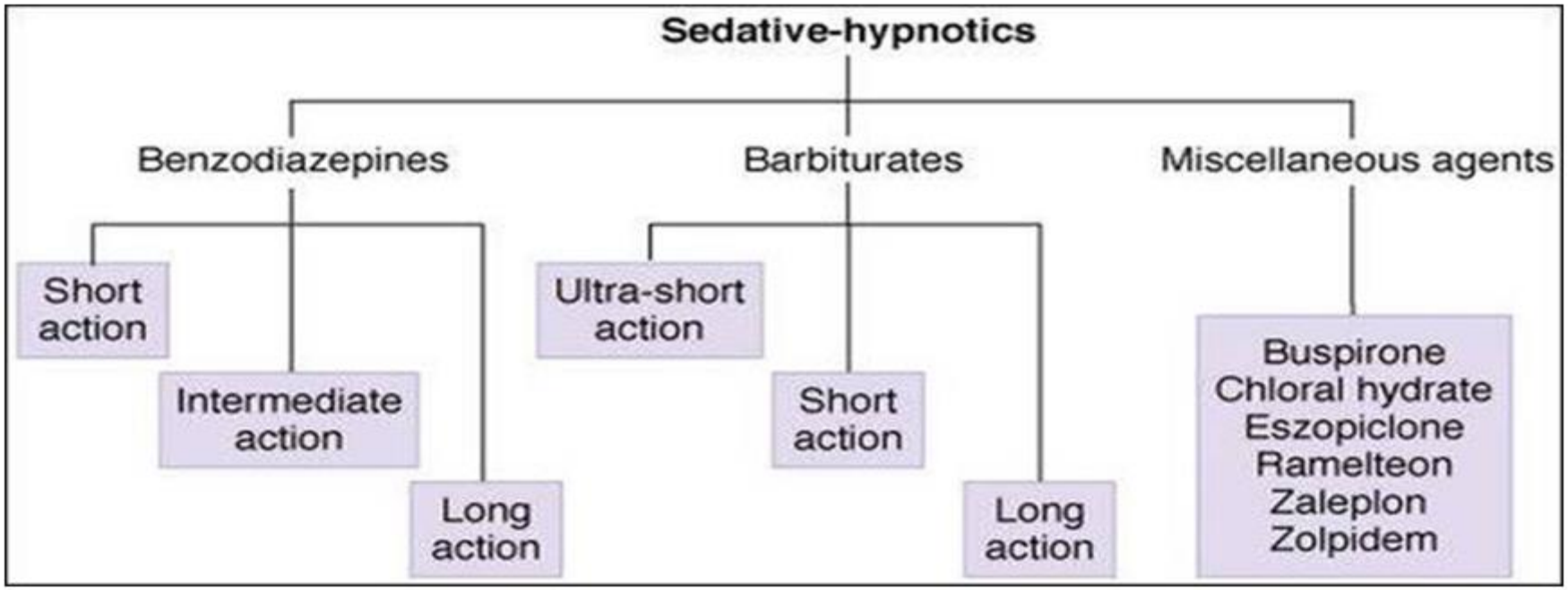
Normal sleep



❑ **Anxiolytic agents** reduce tension, ↓ anxiety and calms the patients with minimum effect on the mental or motor functions.

❑ Some anxiolytics have sedative effects.

➢ **Hypnotics** induce sleep.



Benzodiazepines (BZD)

BZD were previously known as minor tranquilizers

a) Drugs used for anxiety mainly:

Diazepam (has active metabolites)
Clorazepate (has active metabolites)
Chlordiazepoxide (has active metabolites)
Lorazepam (has inactive metabolites)
Oxazepam (has inactive metabolites)

(b) Drugs used for insomnia mainly:

Triazolam (has active metabolites) short acting
Flurazepam (has active metabolites)
Temazepam (has inactive metabolites)
Nitrazepam (has inactive metabolites)

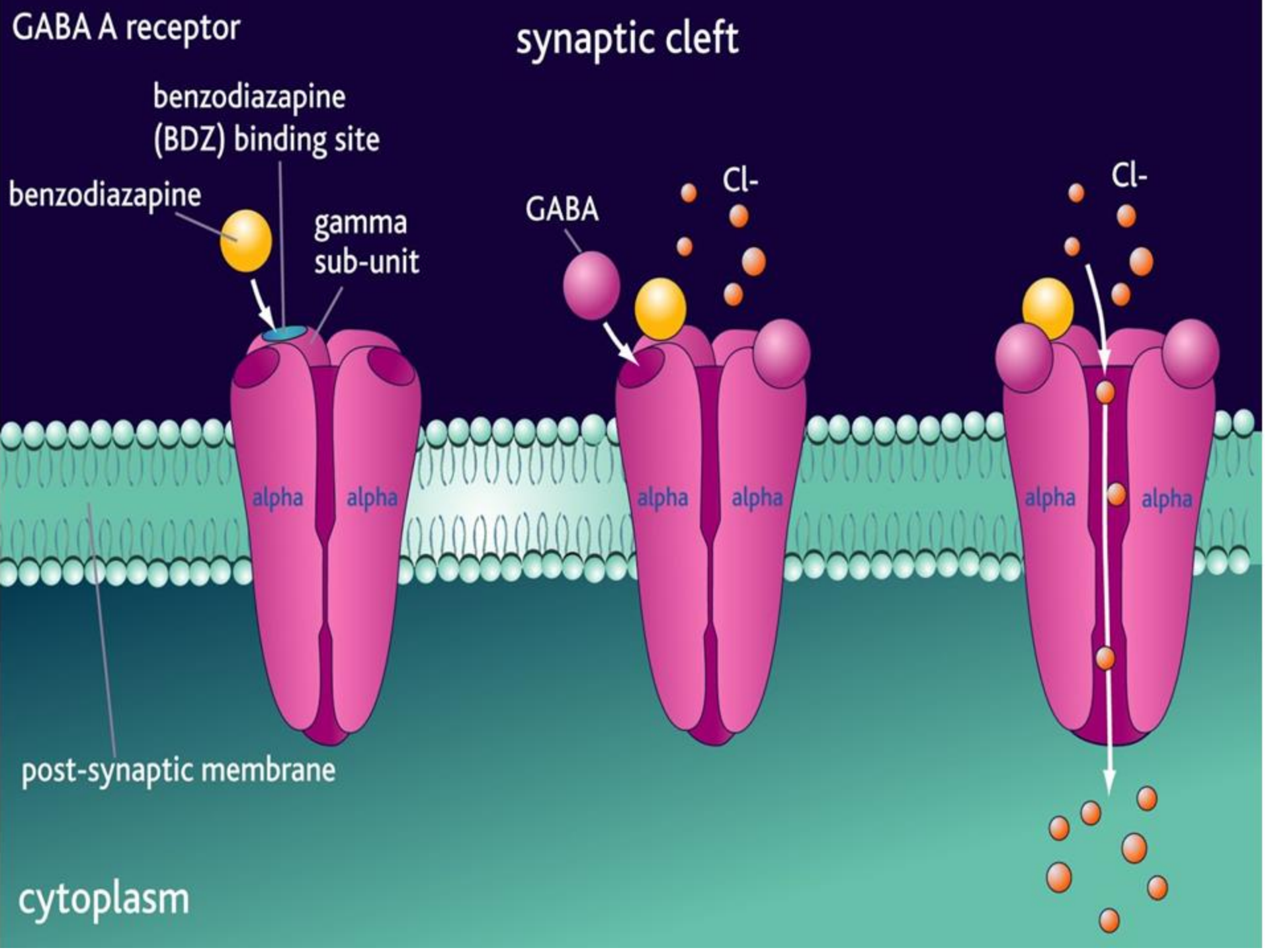
Water soluble (slow onset) **Lipid soluble** (rapid onset)

Pharmacodynamics of benzodiazepines

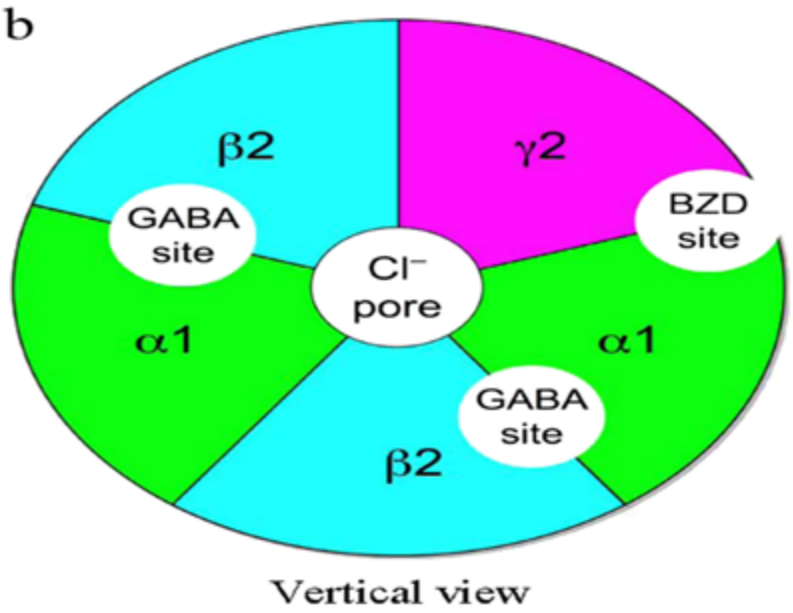
Mechanism of action :

They act by **potentiating the inhibitory effect of GABA** through the following:

1. Benzodiazepines bind to **specific benzodiazepine receptors** (type I and type II) on **GABA A - Chloride channel complex.**
2. This leads to **augmentation** of the binding of GABA to its receptor (GABA-A receptor).
3. Binding of GABA to its specific receptors leads to increase in the frequency of opening of Cl^- channels causing hyperpolarization of the cells of brain and decreasing their excitation.


GABA A receptor
synaptic cleft
benzodiazapine
(BDZ) binding site
benzodiazapine
gamma
sub-unit
GABA
Cl-
Cl-
alpha
alpha
alpha
alpha
alpha
alpha
post-synaptic membrane
cytoplasm

- The **existence of GABA is essential for the action of benzodiazepines**
- The effects of benzodiazepines are prevented by pretreatment with either GABA receptor antagonists (as bicuculline) or a GABA synthesis inhibitor.
- Both benzodiazepines and GABA have <u>independent</u> sites on the same receptor Cl^- channels complex .



Drugs interacting with benzodiazepine receptors

1-Agonists: as benzodiazepines and Z compounds, they potentiate GABA action and used as hypnotics.

2-Inverse agonists: as β-carboline compounds; they act as negative allosteric modulators of GABA-receptor function; they produce effect opposite to BZD (causes anxiety, insomnia and convulsions).

In addition to their direct actions, these molecules can block the effects of benzodiazepines.

3-Antagonists as flumazenil, competitive antagonist to A and B forms, so **prevent the action of both benzodiazepines and B-carboline** and useful in treatment of their toxicities.

Pharmacological actions

A) CNS: BZD produce a dose-dependent **CNS depression**.

Antianxiety effect:

- Benzodiazepines in small dose decrease anxiety, tension and aggression (i.e. calm the patient).

Hypnotic effect:

- Benzodiazepines in enough high doses can induce sleep
- The latency of sleep onset is reduced.
- They increase the total sleeping time by increasing the duration of **stage 2 of NREM sleep**
- They decrease the nightmares and night terrors by decreasing the duration of slow wave sleep (stage 3 and 4 of NREM sleep), but if the reduction is marked can causes day mares.

- REM sleep duration is reduced causing anxiety, hyper-sexuality, excess eating and reduction in the concentration. However, benzodiazepines are the least hypnotics in reduction of the REM sleep (versus barbiturates).

Anticonvulsant effect:

BZD **can prevent and treat epileptic attacks,** but tolerance limits their chronic use in epilepsy.

Skeletal muscle relaxation:

BZD can decrease muscle tone and decrease muscle rigidity in patients with cerebral palsy and spinal cord lesions. This effect is due to central action and not a direct action on skeletal muscles.

B) CVS:

In **high doses** (used for pre-anesthetic medication), they increase the heart rate and **decrease the blood pressure**.

C) Respiratory system:

In high doses, benzodiazepines cause slight respiratory depression (versus barbiturates), and **acidosis** occurs due to depression of the alveolar ventilation.

This effect is obvious in asthmatics or in patients using morphine or other respiratory depressants like **alcohol**.

D) GIT:

They **improve stress ulcers**, **irritable bowel syndrome** and other anxiety-related GIT diseases.

Pharmacokinetics

Absorption

- Generally; BZD are weak bases that are **completely absorbed** after oral administration from the duodenum.
- Absorption is erratic after I.M. administration for diazepam but the absorption of **IM lorazepam is good**.
- I.V. route achieves rapid effect (suitable in emergencies).

Distribution

- BZD have high lipid solubility, so they cross blood brain barrier easily. This property allows **redistribution** where the effect of single dose of diazepam is terminated quicker due to re-distribution from brain to muscle and fat by blood flow.
- Plasma protein binding (**60-90%**) and they can displace warfarin.
- All the BDZ **cross the placenta** and may depress the CNS of the newborn if given before birth.

Metabolism

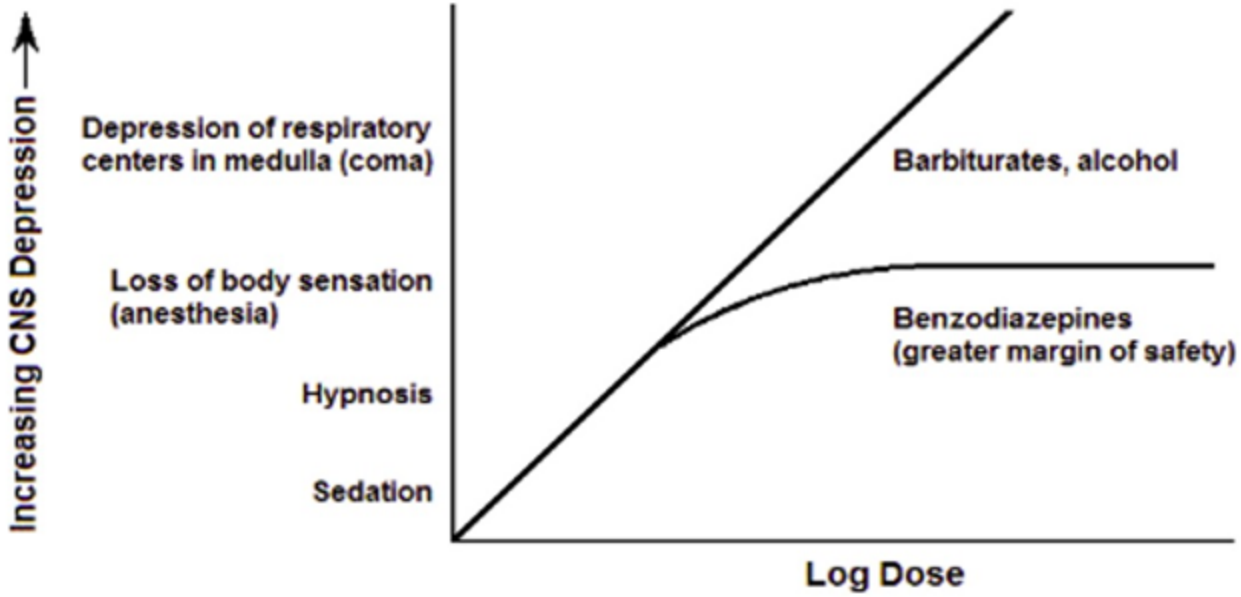
- All BZD are metabolized in the **liver** by oxidation and conjugation.
- Some of BZD give **active metabolites.** For example, diazepam is converted into nordazepam which in turn changes into oxazepam. Both metabolites are active as hypnotic and anxiolytic like diazepam.
- Formation of active metabolites with some BDZ makes no correlation between the **clinical duration of action** and **actual half-life of the parent drug** e.g., **flurazepam** half life is 3 hours, but its active metabolite (n-desalkylflurazepam) has a half life of 50 hours.

Excretion

- BZD and their metabolites are exerted in urine.
- Nursing infants may also become exposed to these drugs in **breast milk**.

BDZ are widely used anxiolytic hypnotics (more than barbiturates) as they have the following pharmacological advantages **over barbiturates:**

1. Less depressant effect on respiration.
2. Less tendency for abuse & dependence
3. Less tendency for interaction with other drugs (less induction effect on liver microsomal enzyme)
4. Little disturbance of rapid eye movement stage of sleep
5. Have wider therapeutic index



Therapeutic uses of Benzodiazepines

1-Anxiety disorders:

- The longer acting drugs like **diazepam & lorazepam** are often preferred.
- The antianxiety effects of BDZ are less subject to tolerance than the anticonvulsant and hypnotic effects.
- Alprazolam is also effective in **panic disorder.**
- Alprazolam is used with other medications for management of **chemotherapy related vomiting.**

2- Sleep disorders:

- Triazolam (short acting useful in initial insomnia i.e., difficult to enter sleep).
- Temazepam (intermediate acting) and flurazepam (long acting) which both are suitable in latent insomnia (early awakening) or intermittent sleep.

3- Seizures:

- BZD which have can rapid entry into the brain (**diazepam** and **lorazepam)** are used in status epilepticus.
- **Clonazepam** is used in absence seizures (petit mal).

4-Preanesthetic medication: BZD induce sedation & anterograde amnesia to facilitates and helps smooth anesthesia.

- **Diazepam, midazolam & lorazepam** are common agents used for this purpose and for endoscopy without using inhalational anesthetics.

5-Skeletal muscle relaxants: BZD may alleviate muscle spasticity in cerebral palsy and spinal cord lesions.

6-To control withdrawal symptoms in alcoholics (anxiety and insomnia).

Adverse effects

1- At the time of peak concentration in plasma, hypnotic doses of BZD may cause drowsiness, increased reaction time, motor incoordination, impairment of mental & motor functions and anterograde amnesia.

All these residual effects can impair driving & other psychomotor skills.

When BZD are given at night time, these residual effects may persist at the morning (waking hours).

2- Dis-inhibition (paradoxical) reaction: Sometimes, BZD may produce bizarre behavior like nightmares, anxiety, irritability, restlessness & excitement.

Such paradoxical reactions are **dose related** and may lead to criminal behaviors.

3- Chronic use of BZD carries the risk of dependence and abuse (but less than barbiturates).

4- Over-dosage may cause cardiovascular or respiratory depression.

5- If given with ethanol (alcohol), CNS depression is increased (pharmacodynamic interaction, additive effect) and death could occur due to respiratory arrest.

6- They may induce or aggravate hepatic encephalopathy in patients with chronic liver disease.

7- Tolerance for the anticonvulsant and hypnotic effects.

8- Abrupt withdrawal may cause rebound insomnia

BZD Dependence

- BZD abuse and dependence is common in **elderly**. It is one of the commonest prescribed drugs addiction.
- Chronic abusers can have some impairment of cognition.
- Stopping BDZs suddenly in addict leads to withdrawal symptoms that include **rebound** anxiety , insomnia, hallucinations , and rarely convulsions. Flulike symptoms develops also.
- To prevent BDZ dependence : avoid prescribing longer than 3 weeks and avoid use in past or present addicts.
- **Gradual withdrawal of BZD is recommended if used for more than 3-4 weeks.**

Acute BDZ toxicity

Manifestations

1. Coma
2. Respiratory depression
3. Hypotension.

Treatment

A specific pharmacological antagonist at BDZ receptors is Flumazenil; it is short-acting . When given IV ; it reverses the respiratory depression and coma.

Mechanical ventilation may be needed.

Contraindications of benzodiazepines

1- In severe asthma, bronchitis, and COPD (BZD may cause hypoxia through minimal respiratory depression).

2-Patients with **myasthenia gravis, sleep apnea syndrome** (Because of their muscle relaxant action).

3- In **personality disorders**; BZD had more **paradoxical reactions** .

4- In patients suffering from **major depression**, BZD may precipitate suicidal tendencies and are sometimes used for suicide.

5- Individuals with a history of **excessive alcohol** use or non-medical use of **opioids** or **barbiturates** should avoid benzodiazepines, as there is a risk of **life-threatening CNS depression** with these drugs.

6- Pregnancy: BZD are FDA category (D or X) meaning potential for harm in the unborn has been demonstrated.

7- **Elderly** where the risks of BZD and abuse potential are greatest.

8- Hepatic disease (may precipitate hepatic coma).

Novel BZD receptor agonists (Z compounds)
Zolpidem, Eszopiclone and zaleplon

- They are chemically unrelated to BZD.
- They have only **hypnotic action**.
- They bind selectively to **omega-1 part of the BZD receptor**.
- No **anxiolytic**, **muscle relaxant** or **anticonvulsant actions**.
- They are used only as hypnotics.
- They have **sustained hypnotic efficacy**
- Less rebound insomnia on abrupt discontinuation.
- Less **tolerance** (versus BZD).
- They have shorter half-life than BZD.
- Z compounds are FDA **category C** for use during pregnancy.

Zaleplon has a shorter half-life (1 hour), so it is effective in reducing sleep latency and treat initial insomnia.

Zolpidem

- Oral, Sublingual and oral spray formulations.
- **Extended-release formulation** to ↑duration of action.
- Zolpidem is rapidly inactivated by hepatic CYP3A4.
- The half-life of the drug is greater in women and is increased significantly in the **elderly**.
- It should not be used for more than 6 weeks to avoid dependence.
- It may increase risk of depression and sleep-walking.
- Common adverse effects; drowsiness, sleepiness, eye pain, headache and diarrhea.

Eszopiclone

- t½ is longer, about 6 h , and gives better sleep time (7-8 h) .
- It can be used for 6-12 months with little risk of tolerance or dependence.
- Eszopiclone is metabolized by hepatic CYP3A4.
- The elimination half-life of Eszopiclone is prolonged in elderly and in the presence of inhibitors of CYP3A4 (e.g., ketoconazole).

The side effects of eszopiclone can include:

1. unpleasant taste in your mouth (bitter)and dry mouth
2. Drowsiness, dizziness, and headache.
3. Rash and other allergic reactions (angioedema).
4. common cold like (sneezing , fever and chills).
5. Hallucinations and suicidal ideas (rare).
6. Urination problems.
7. Sleepiness in high doses.

Flumazenil

- It is a competitive antagonist to BZD receptors.
- It has extensive first pass metabolism, so it is given i.v. and it has a short duration of action (30-60 minutes).
- It is used primarily to treat overdose of BZD or to reverse their sedative effect when given in diagnostic procedures (e.g. endoscopy).
- Its half-life is shorter than most of BZD, so, repeated i.v doses (series of small injections than single bolus injection) are preferred.
- It is used effectively in treating hepatic encephalopathy especially following exposure to BZD.
- Administration of flumazenil may precipitate agitation, confusion or withdrawal symptoms in BZD dependent patients.


THANK
YOU