بسم الله الرحمن الرحيم

Sedatives & hypnotics (part 1)

Benzodiazepines & related drugs

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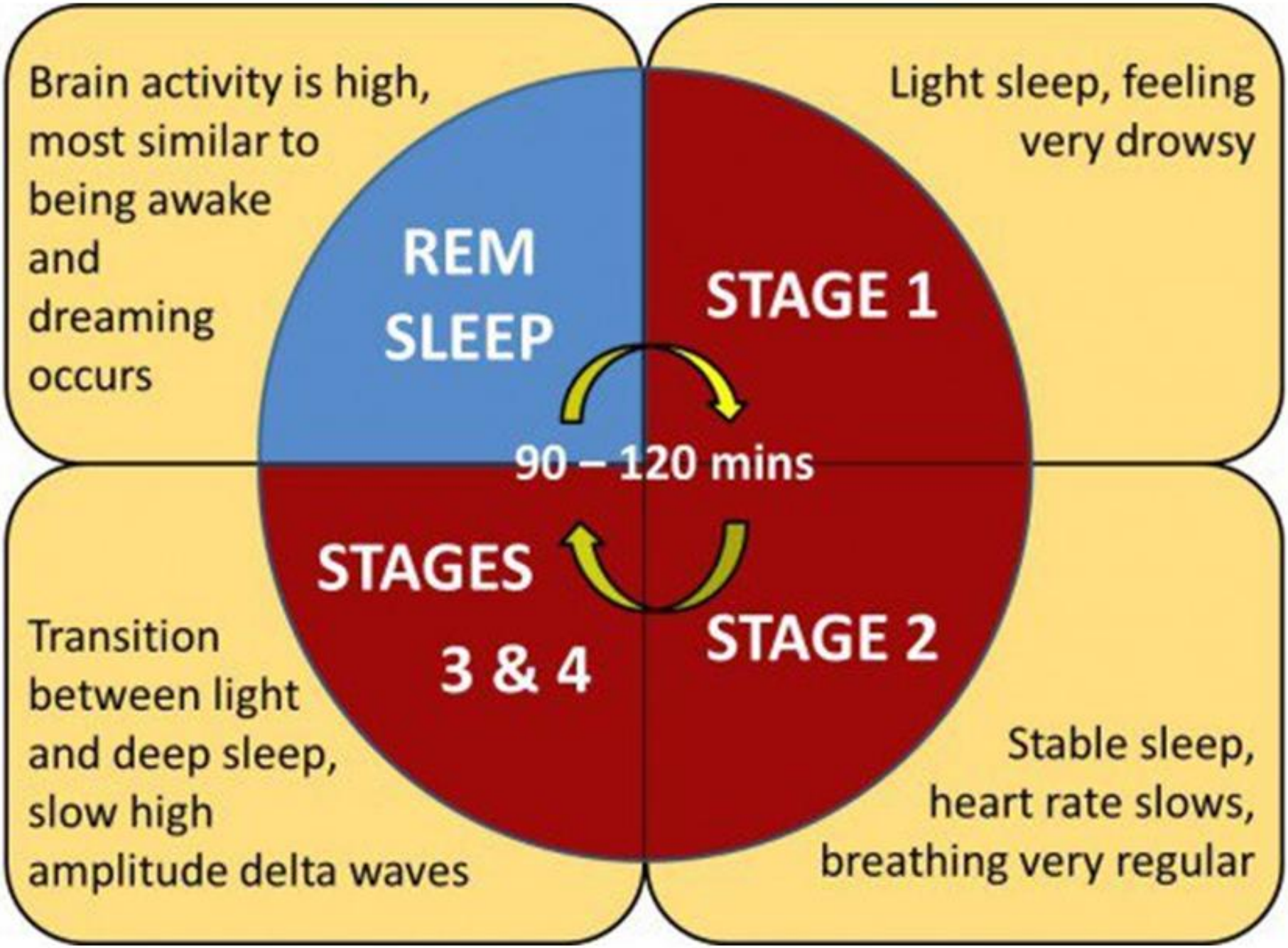
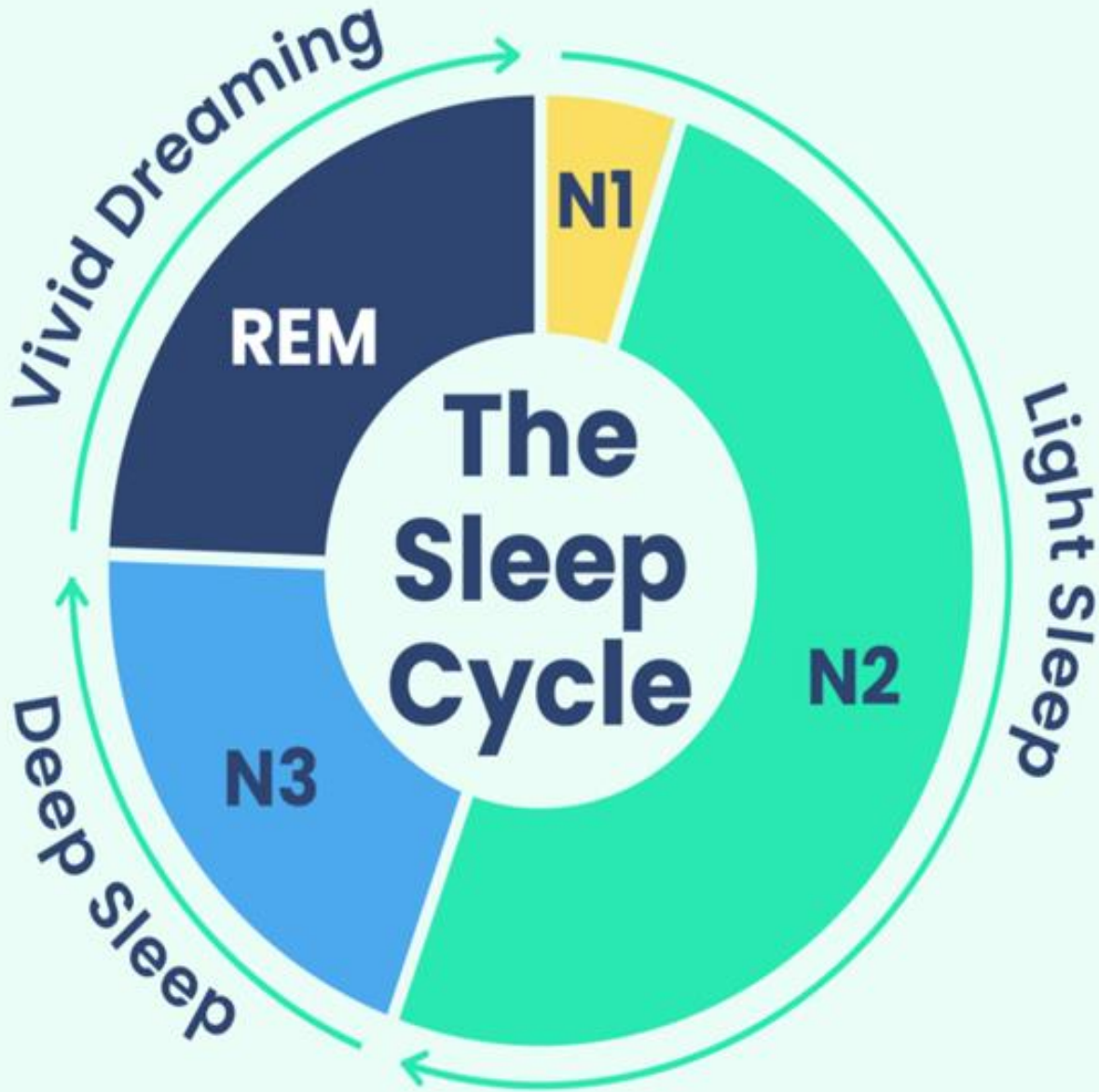
Normal sleep




Vivid Dreaming
REM
N1
Light Sleep
The Sleep Cycle
N2
N3
Deep Sleep

Sedatives & hypnotics

❑ **Sedative** (anxiolytic) drugs ↓**anxiety** & produce **calming** effect.

❑ The degree of CNS depression caused by a sedative should be the minimum consistent with therapeutic efficacy.

➢ A **hypnotic** drug produce **drowsiness** and **encourage sleep**.

➢ **Hypnotics** produce more CNS depression than sedatives.

○ Graded dose-dependent CNS depression is characteristic for most sedative-hypnotics.

○ However, individual drugs differ in the relationship between the **dose** and **the degree of CNS depression**.

Benzodiazepines (BZD)

BZD were previously known as minor tranquilizers

1- Drugs used for anxiety mainly: for hypnosis

1. Diazepam (has active metabolites)
2. Clorazepate (has active metabolites)
3. Chlordiazepoxide (has active metabolites)

lipid Soluble. rapid onset

4. Lorazepam (has inactive metabolites)
5. Oxazepam (has inactive metabolites)

water Soluble.

2- Drugs used for insomnia mainly:

Triazolam (has active metabolites) **short acting**

lipid Soluble. rapid onset

Flurazepam (has active metabolites)

Temazepam (has inactive metabolites)

Nitrazepam (has inactive metabolites)

water Soluble.

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

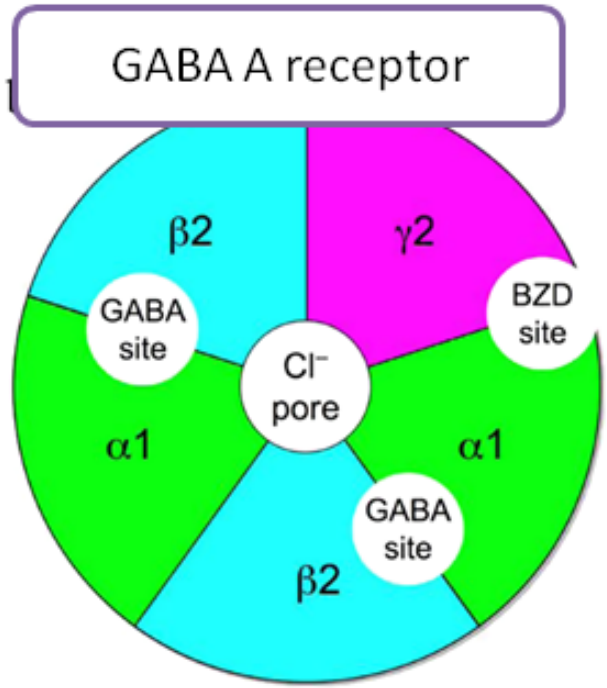
Pharmacodynamics of benzodiazepines

GABA :-
ماسك بـ تلك الـ Synapse
في الدماغ

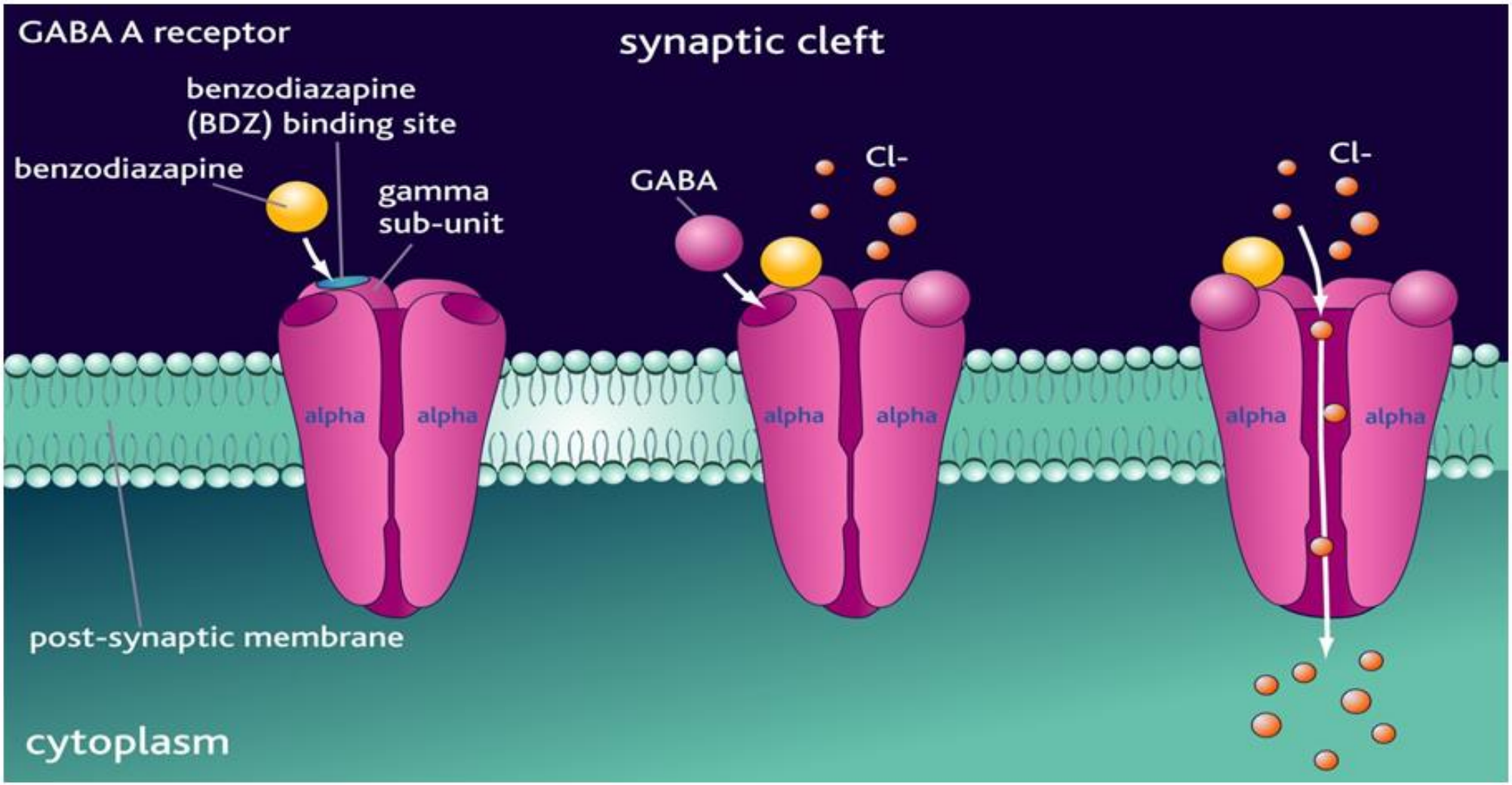
Mechanism of action :

BZD act by **potentiating the inhibitory effect of GABA**

- Benzodiazepines bind to **specific benzodiazepine receptors** (type I & II) on **GABAA - Chloride channel complex.**
- This leads to **augmentation** (allostric effect) of the binding of GABA to its receptor (GABA-A receptor).
- Binding of GABA to its GABA-A receptors leads to **increase** (2) in the **frequency** of opening of Chloride channels causing more hyperpolarization of the neurons and decreasing their excitation.



- The **existence of GABA is essential for the action of BZD**
- The effects of BZD are prevented by GABA receptor antagonists (as bicuculline) or a GABA synthesis inhibitor (e.g., L-Allylglycine).
- Both BZD & 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 β-carboline** and useful in treatment of their toxicities.

Pharmacological actions of BZD

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

Antianxiety effect:

BZD (small dose): calm the patient, ↓anxiety, tension & aggression

Hypnotic effect:

- BZD in enough high doses can induce sleep
- The latency of sleep onset is reduced.
- BZD ↑ total sleeping time by ↑ duration of **stage 2 of NREM sleep.**
- BZD ↓ the nightmares and night terrors by decreasing the duration of slow wave sleep (stages 3 & 4 of NREM sleep), but if the reduction is marked, **day mares** may occur.
- REM sleep duration is ↓ 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).

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Anticonvulsant effect:

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

Skeletal muscle relaxation:

BZD can ↓ muscle tone & ↓ 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) Respiratory system:

- In high doses, BZD cause slight respiratory depression (versus barbiturates), and **acidosis** occurs due to ↓ alveolar ventilation.
- This effect is critical in asthmatics or in patients using morphine or other respiratory depressants like **alcohol**.
- N.B. Respiratory and CVS effects are more marked when sedative-hypnotics are given **intravenously.**

C) CVS:

In **high doses** (used for pre-anesthetic medication) or at toxic doses, myocardial contractility and vascular tone both may be **depressed** by central (vasomotor depression) and peripheral effects (via **facilitation** of the actions of **adenosine**), leading to **circulatory collapse**.

D) GIT:

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

Tolerance to BZD versus barbiturates

- An increase in the rate of drug metabolism (pharmacokinetic tolerance) may be partly responsible in tolerance to barbiturates.
- In the case of **BZD**, the development of tolerance has been associated with **down-regulation of brain benzodiazepine receptors (Pharmacodynamic tolerance)**

Pharmacokinetics of BZD

absorbed in small intensine ∴ ابسوربد

Absorption

- 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. Contraindicating during Pregnancy.

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.

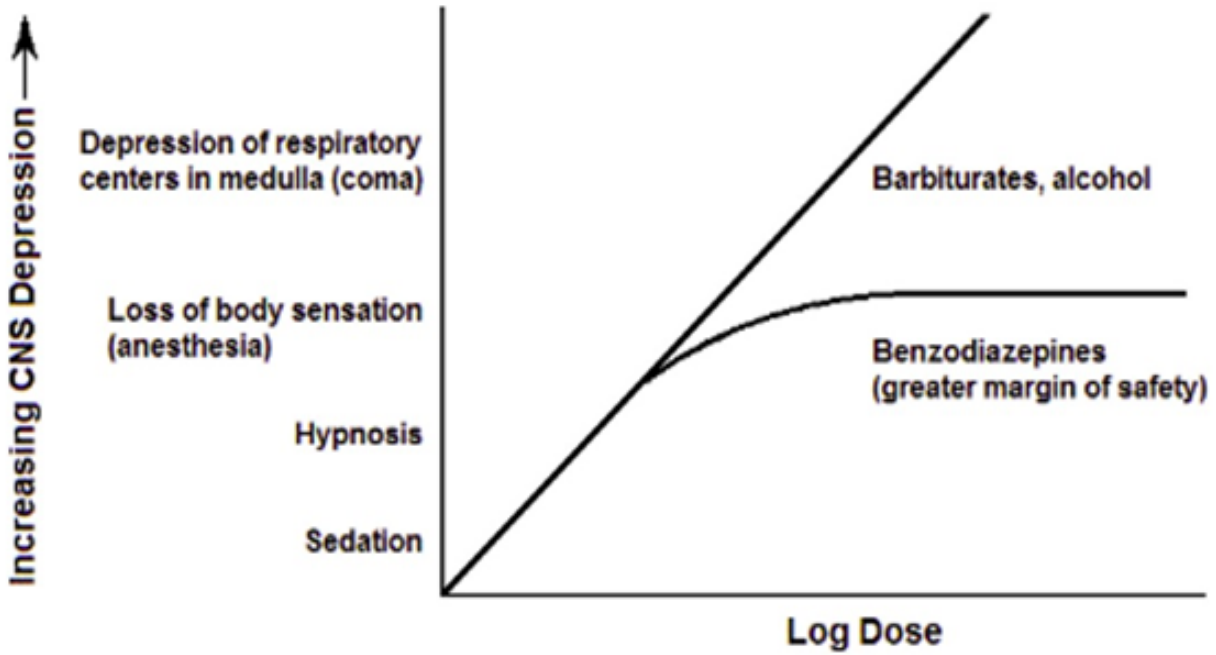
Excretion

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

BDZ have the following advantages **over barbiturates:**

1. **Less depressant** effect on **respiration**.
2. **Less** tendency for abuse & **dependence.**
3. **Less** drinduction of liver microsomal enzymeug **interaction**
   - ❑)
4. **Little** effects of **rapid eye movement** stage of **sleep.**
5. Have **wider therapeutic index.**
6. Have **available pharmacological antagonist (flumazenil)**

REM



Therapeutic uses of Benzodiazepines

1-Anxiety disorders:

- **Diazepam & lorazepam** are often preferred (longer acting)
- The antianxiety effects of BDZ are less subject to tolerance than the anticonvulsant and hypnotic effects.
- **BZD** are used for management of generalized anxiety disorders.
- **Alprazolam** is also effective in **panic disorder.**
- **Alprazolam** is useful in **chemotherapy related vomiting.**

2- Sleep disorders:

- **Triazolam** (short acting) is useful in initial insomnia (difficult to enter sleep).
- **Temazepam** (intermediate acting) & flurazepam (long acting) 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).

7- As diagnostic aids or for treatment in psychiatry disorders.

Adverse effects of BZD

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 (hangover) 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 effects 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.

Cause of death.

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

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

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7- Tolerance for the **anticonvulsant** and **hypnotic** effects.

8- Abrupt withdrawal may cause rebound insomnia

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BZD abuse & 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. Flu-like 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.**

Contraindications and precautions of BZD

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 **major depression**, BZD may precipitate suicidal tendencies and may be 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**: risk of BZD abuse is greatest.

8- Hepatic disease (may precipitate hepatic coma).

Acute BZD toxicity

Manifested by Coma , Respiratory depression and Hypotension.

Treatment

1- A specific pharmacological BDZ receptor antagonist (Flumazenil) should be used to reverse the respiratory depression and coma.

Flumazenil is short-acting and repeated doses may be needed.

Flumazenil is given IV.

2- Mechanical ventilation may be needed.

Novel BZD receptor agonists (Z compounds)

- 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.**
- They cause **less hangover** in the morning.
- 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.
- **Zolpidem, Eszopiclone and zaleplon are examples**

اشخص واحد عالي

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

Zolpidem

- Oral, Sublingual and oral spray formulations exist for zolpidem.
- **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, visual problems, **headache** and **diarrhea**.

Eszopiclone

- t½ is longer than zolpidem (about 6 hours)
- It 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 the 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 BZD receptors antagonist.
- 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.


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Thank
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