بسم الله الرحمن الرحيم

Sedative hypnotics (part one)

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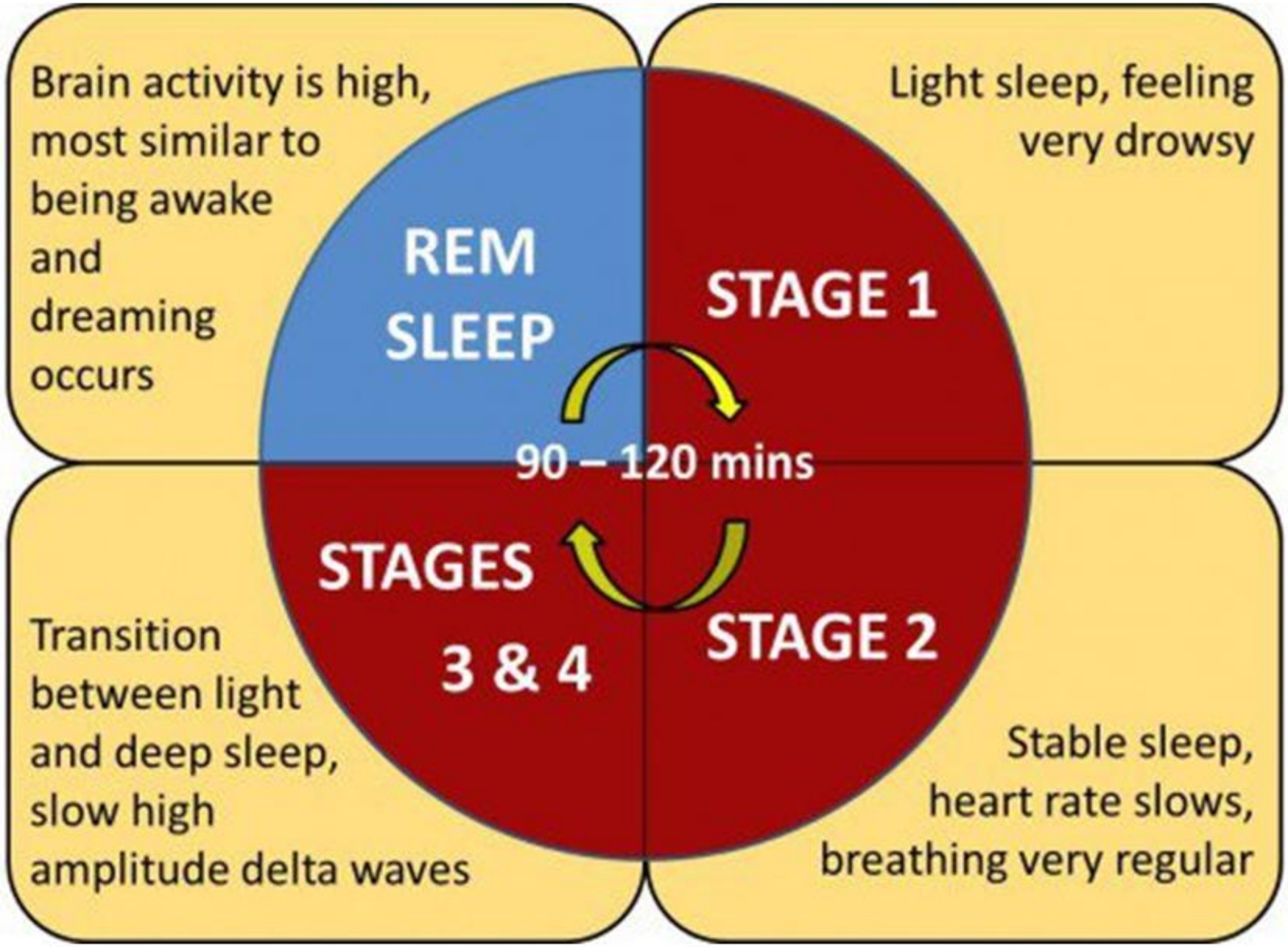
Normal sleep



Stages of sleep:

Stage	Definition
Stage 1:	**Drowsiness**; small wave freq. (4-7hz), on EEG, NREM Sleep
Stage 2:	**Asleep**; EEG dominated by **theta** waves but hz increases, high energy bursts on EEG (sleep spindles), NREM Sleep
Stage 3:	**Delta** waves, (1-4hz), less sleep spindles, NREM Sleep
Stage 4:	Deepest stage of NREM, **delta** waves, hard to wake, growth **hormone** released here, SWS (slow wave sleep)
REM Sleep (paradoxical sleep)	Fast desynchronised EEG, body effectively paralysed, dreaming more likely to occur
Move back to stage 2 (approx 20 mins):	Move back into REM, repeat pattern, approx every 90 minutes, 4/5 a night

Sedative Hypnotics

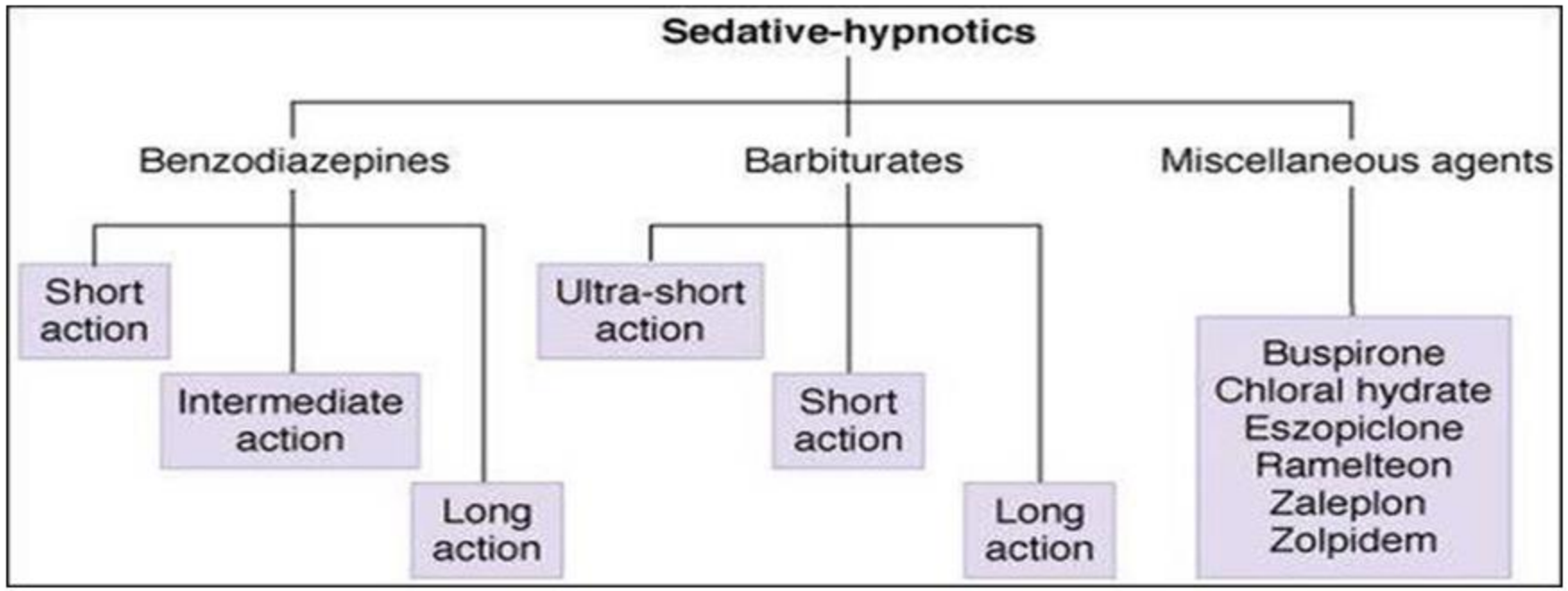
- **Sedatives** are the drugs that decreases the activity, moderates the excitement & calms the recipient. It decreases the responsiveness of stimulation & decreases motor activity.
- **Hypnotics** are the drugs that produce drowsiness & facilitate the onset & maintenance of sleep that resembles natural sleep.
- Sedative & Hypnotics are CNS depressants differing in time & action.
- Hypnotics at low dose acts as Sedative.
- Hypnotics at high dose acts as General anaesthetic.

Increasing grades of CNS depression:

Sedation ⟹ Hypnosis ⟹ General Anaesthesia

➢ **Anxiolytic agents (sedatives)** are the drugs that reduces tension, anxiety and calms the patients with minimum effect on the mental or motor functions.

➢ **Hypnotics** induce sleep.



Benzodiazepines

Members:

a) Drugs used for anxiety:

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

(b) Drugs used for insomnia:

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

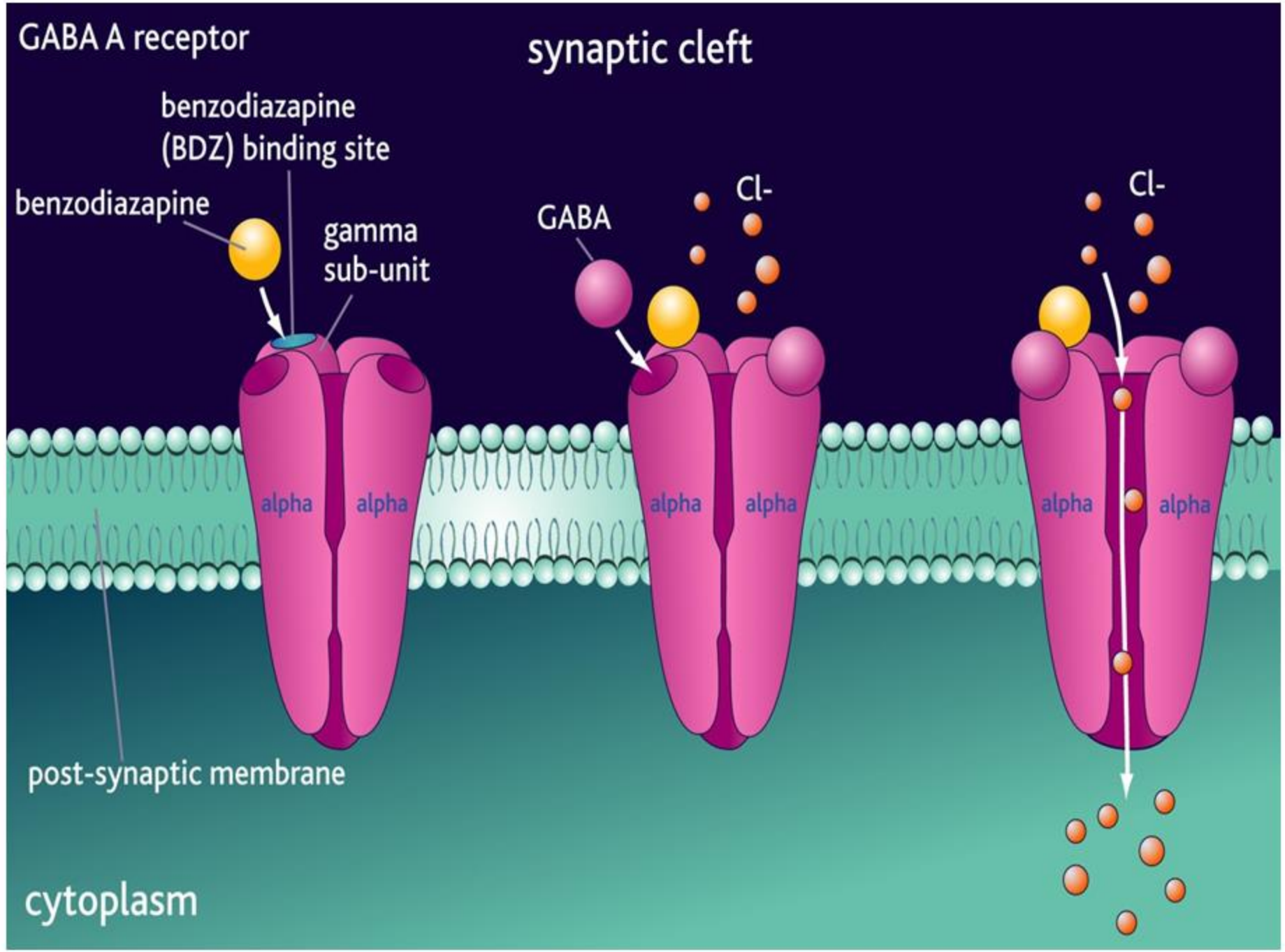
Water soluble (slow onset) **Lipid soluble** (rapid onset)

Pharmacodynamics of benzodiazepines

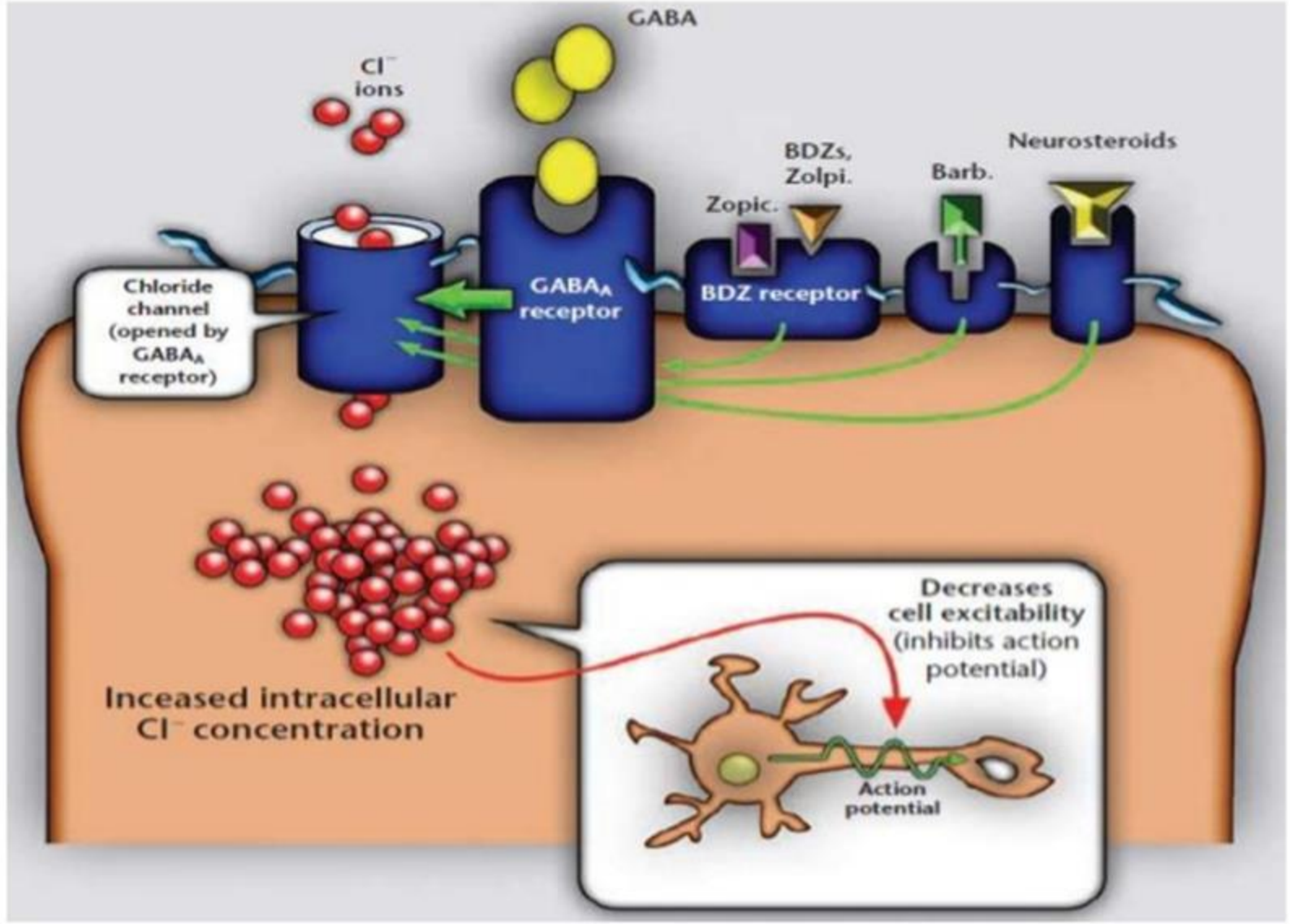
Mechanism of action :

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

- This means the **presence of GABA is essential for the action of benzodiazepines** and the effect of benzodiazepines is prevented by pretreatment with either GABA receptor antagonists (as bicuculline) or GABA synthesis inhibitors.
- Both benzodiazepines and GABA have <u>independent</u> sites on the same receptor Cl^- channels complex .



GABA$_A$ receptor

Benzodiazepine receptors exist in two different conformations:

- Form (A) that can bind to GABA and open Cl- channels
- Form (B) that can't bind to GABA and does not open Cl- channels

So there are 3 types of drugs interacting with benzodiazepine receptors

1-Agonists: as benzodiazepines and Z compounds, bind to the form (A) and potentiate GABA action and useful as anxiolytic agents.

2-Inverse agonists: as β-carboline binds to the form (B) and produce effect opposite to benzodiazepines (causes anxiety, insomnia and convulsions).

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 toxicity.

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 clearer in patients with asthma 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

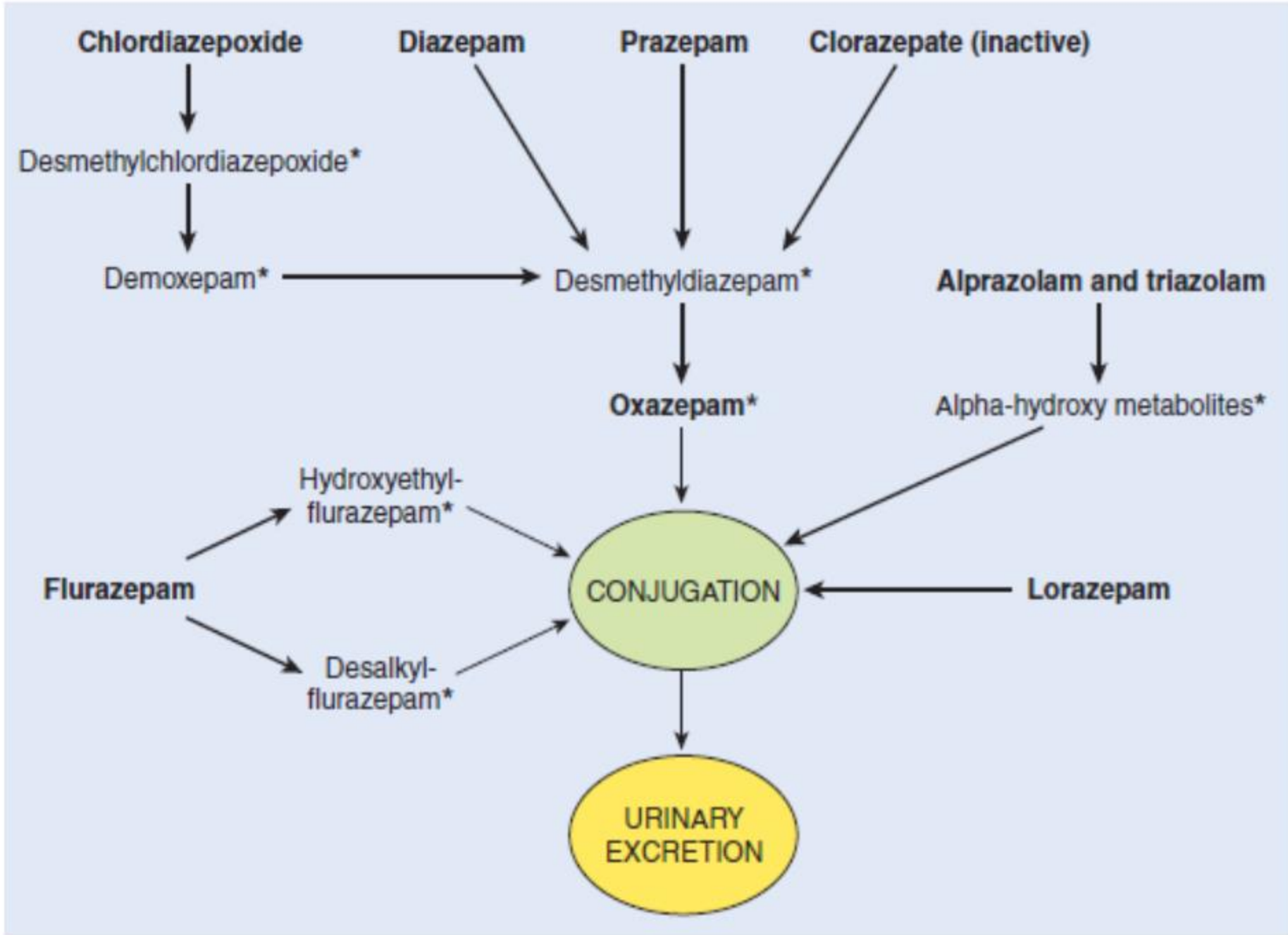
- BZD have high lipid solubility, so they cross blood brain barrier easily. This property allows **redistribution** where the effect of single dose of diazepam is terminated quicker due to re-distribution from brain to muscle and fat by blood flow.
- Plasma protein binding (**60-90%**) and they can displace 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 similar to 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**.


Chlordiazepoxide
Diazepam
Prazepam
Clorazepate (inactive)
Desmethylchlordiazepoxide*
Demoxepam*
Desmethyldiazepam*
Alprazolam and triazolam
Oxazepam*
Alpha-hydroxy metabolites*
Hydroxyethyl-
flurazepam*
Flurazepam
CONJUGATION
Lorazepam
Desalkyl-
flurazepam*
URINARY
EXCRETION

Duration of action of BZD

BDZs are classified according to the t½ and duration of action of parent drug and their active metabolites, if present :

BDZ useful to control anxiety (sedatives)

Long t½ and duration of action > 24 hours

e.g. Diazepam, Chlordiazepoxide

Intermediate or short t½ and duration of action

< 24 hours e.g. Lorazepam , Alprazolam, oxazepam

BDZ useful for treating insomnia (hypnotics).

Long t½ and duration of action :

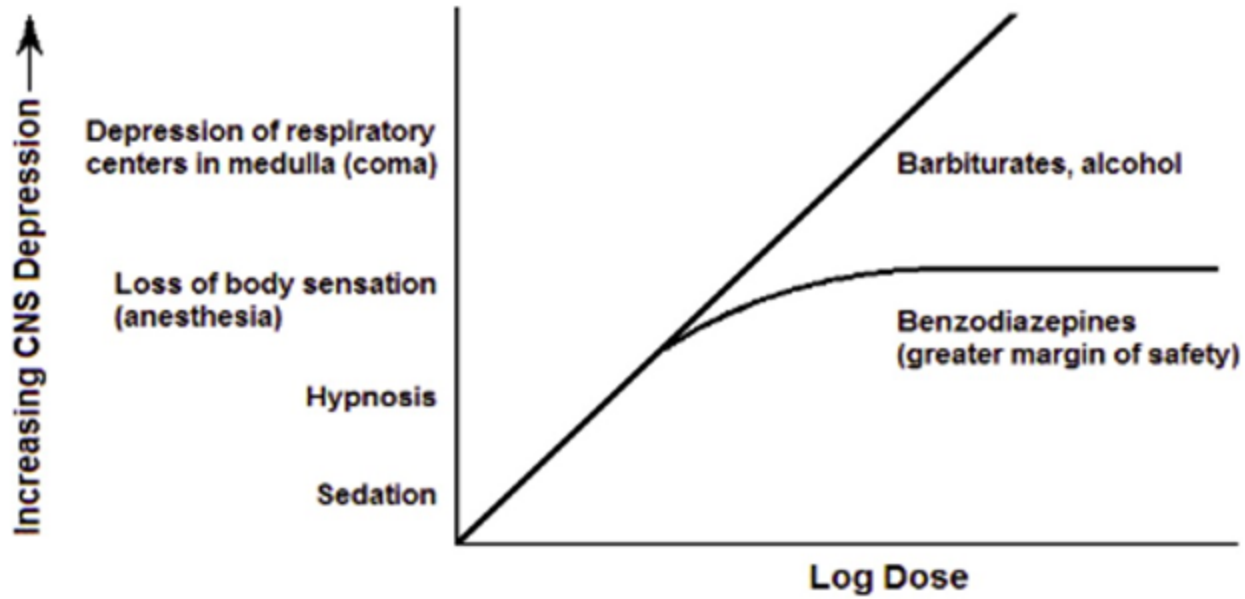
Diazepam (large dose), Nitrazepam, Flurazepam

Intermediate duration of action : Temazepam.

Short duration of action : Triazolam.

Benzodiazepines are the most used anxiolytic hypnotics now 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 as patients with anxiety may require treatment for prolonged period of time.

The antianxiety effects of BDZ are less subject to tolerance than the anticonvulsant and hypnotic effects

2- Sleep disorders:

Not all BZD are useful as hypnotic agents, although all have sedative and calming effect. Commonly used BZD as hypnotic are:

1- **triazolam** (short acting useful in initial insomnia i.e. difficult to enter into sleep).

2- **temazepam** (intermediate acting) and flurazepam (long acting) which both are suitable in latent insomnia (early awakening) or intermittent sleep.

3- Seizures:

BZD which have a long half-life and 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 varying degrees of: drowsiness, increased reaction time, motor incoordination, impairment of mental & motor functions and anterograde amnesia.

All these effects can impair driving and other psychomotor skills. If the BZD is given at sleep time, these residual effects may persist at the waking hours.

2- Dis-inhibition (paradoxical) reaction: Sometimes, BZD may produce bizarre behavior like nightmares, anxiety, irritability, restlessness & excitement. Such paradoxical reactions are rare and appear as dose related.

3- Chronic use of BZD carries the risk of dependence and abuse (but still not to the same extent as seen with 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 develops for the anticonvulsant and hypnotic effects.

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. 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.

Acute BDZ toxicity

1. **coma**
2. **Respiratory depression**
3. **Hypotension.**

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

Contraindications of benzodiazepines

1- In severe asthma, bronchitis, and COPD (benzodiazepines 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 frequent **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: benzodiazepines are FDA category (D or X) meaning potential for harm in the unborn has been demonstrated.
7- The benefits of benzodiazepines are least and the risks are greatest in the **elderly.**
8- Hepatic disease (may precipitate hepatic coma).

Novel BZD receptor agonists (Z compounds)

Zolpidem, Eszopiclone and zaleplon

- They are chemically unrelated to BZD, but they are **hypnotics**.
- They bind selectively to the **omega-1 part of the BZD receptor**, which could explain their lack for the anxiolytic, muscle relaxant and anticonvulsant effects.
- They are used only as hypnotics.
- They have sustained hypnotic efficacy without occurrence of rebound insomnia on abrupt discontinuation (an advantage in comparison with BZD) with less or even **no tolerance** to their hypnotic effect.
- They have **shorter half-life** when compared to commonly prescribed benzodiazepines.
- Zaleplon has a shorter half-life (1 h), so it is effective in reducing sleep latency and treat initial insomnia.
- Z compounds are FDA **category C** for use during pregnancy.

Eszopiclone

- t½ is longer, about 6 h , and gives better sleep time (7-8 h) .
- It is the only Z-drug approved for long term use 6-12 months without 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 (eg, 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.
4. symptoms of the common cold, such as sneezing or runny nose, even fever and chills could occur.
5. Urination problems.
6. 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).
- They are used effectively in treating hepatic encephalopathy especially following exposure to BZD.
- Its half-life is shorter than most of BZD, so, repeated i.v doses (series of small injections than single bolus injection) are preferred.
- Administration of flumazenil may precipitate withdrawal symptoms in BZD dependent patients.


THANK YOU!