Sedative - Hypnotics

By

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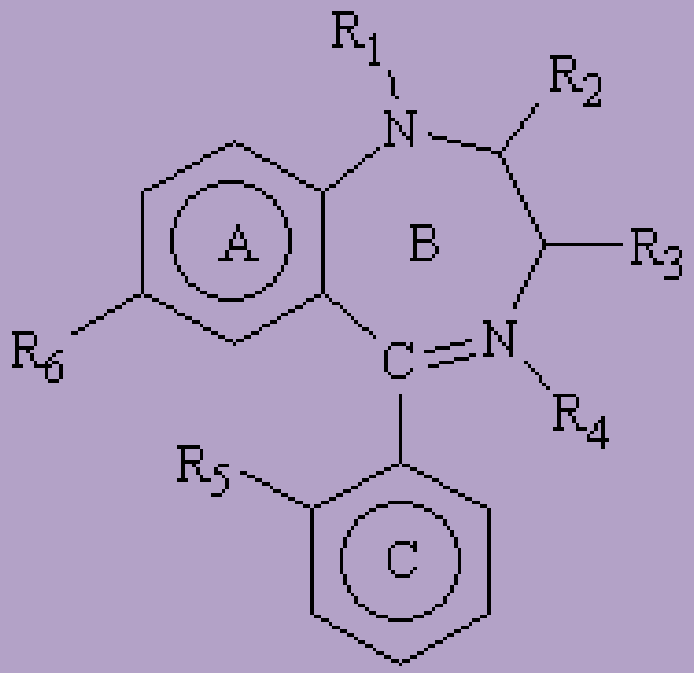
- ***Sedative*** : a drug that reduces anxiety & exerts calming effects.

- ***Hypnotic*** : a drug that produces drowsiness & encourages onset of sleep.

Sedative - Hypnotics

1. Benzodiazepines (BDZ):-



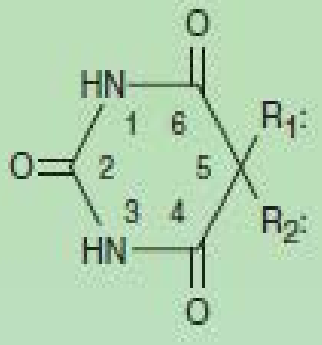
Other BDZ :

Nitrazepam, Clonazepam, Midazolam.

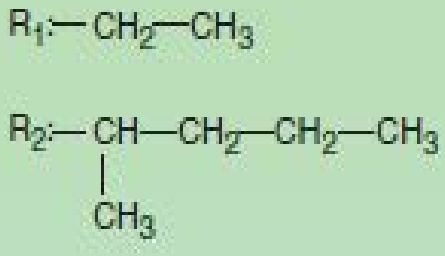

Valium
Diazepam
10 mg
50 comprimidos
Roche


VALIUM
5

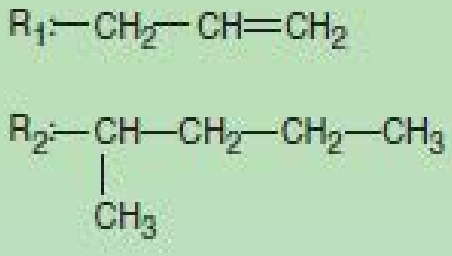
2. Barbiturates (barb.) :-



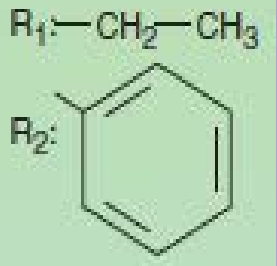
Barbiturate nucleus



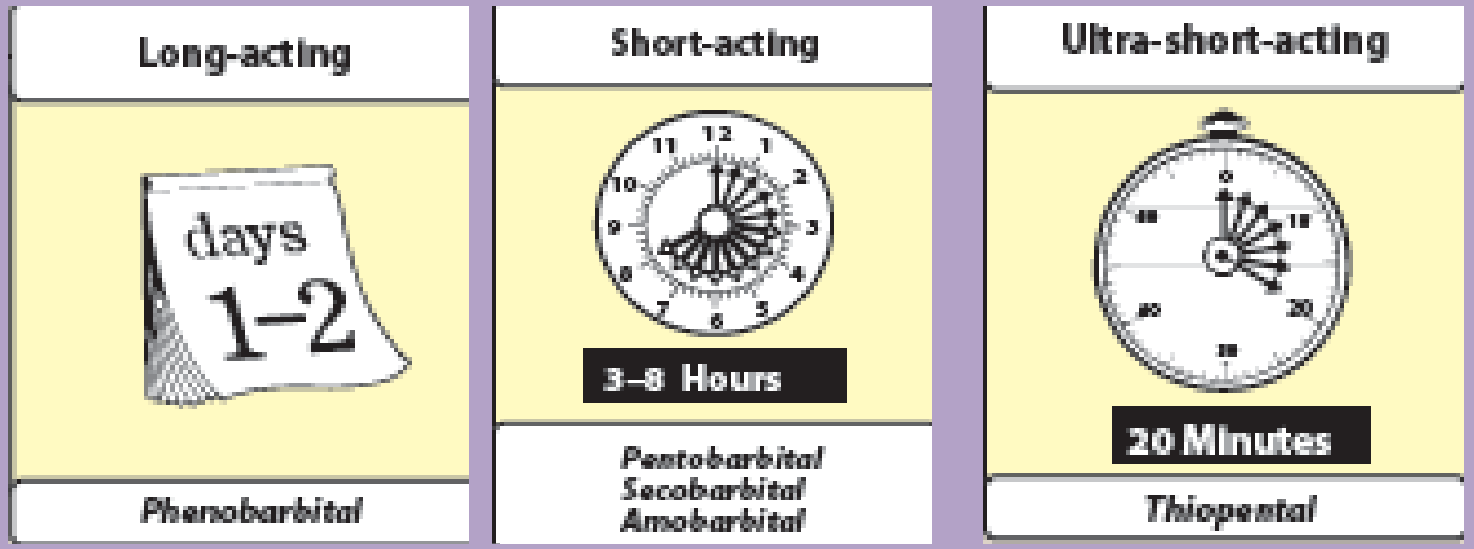
Pentobarbital



Secobarbital



Phenobarbital



Other barb. : Thiamylal and Methohexital (GA).

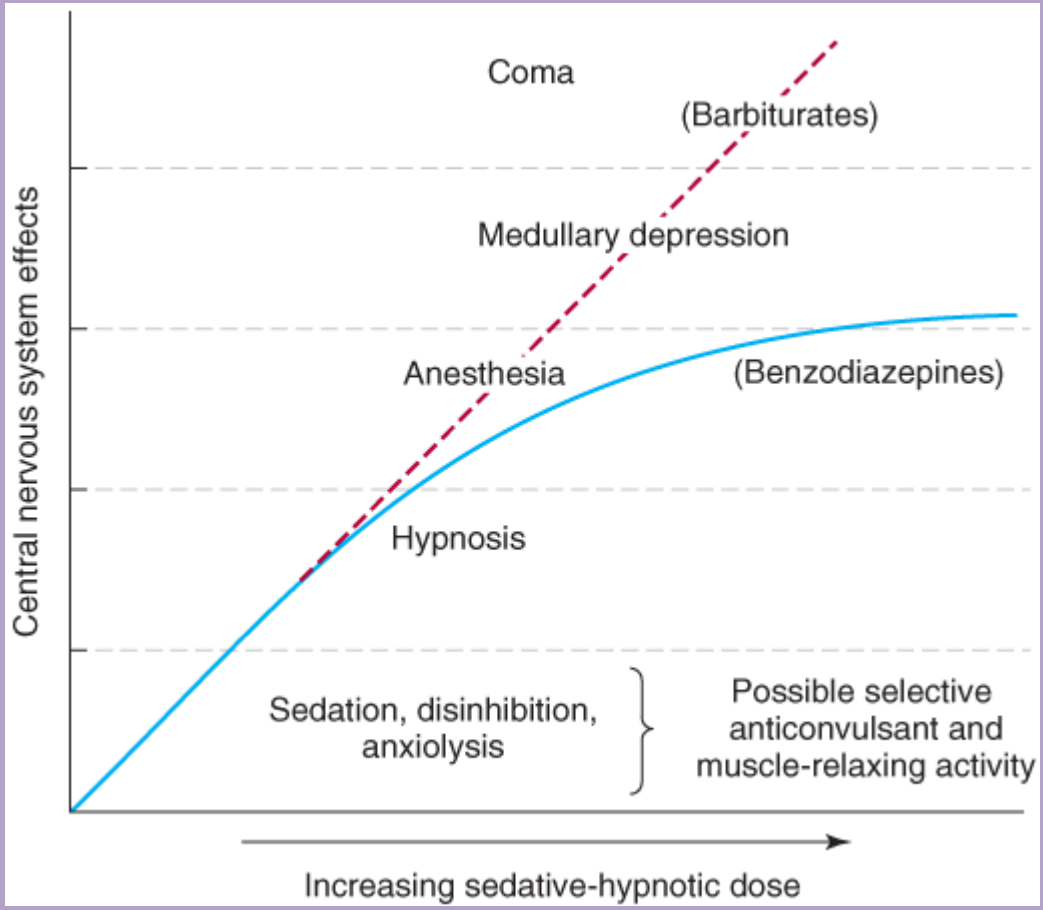
3. Non-BDZ that have similar mechanism of action to BDZ :-

e.g. ***Zolpidem, Zaleplon and Eszopiclone***.

4. Non-barb. that have similar mechanism of action to barb. :-

e.g. ***Meprobamate, Chloralhydrte and Glutethimide.***

Graded dose-dependent CNS depression

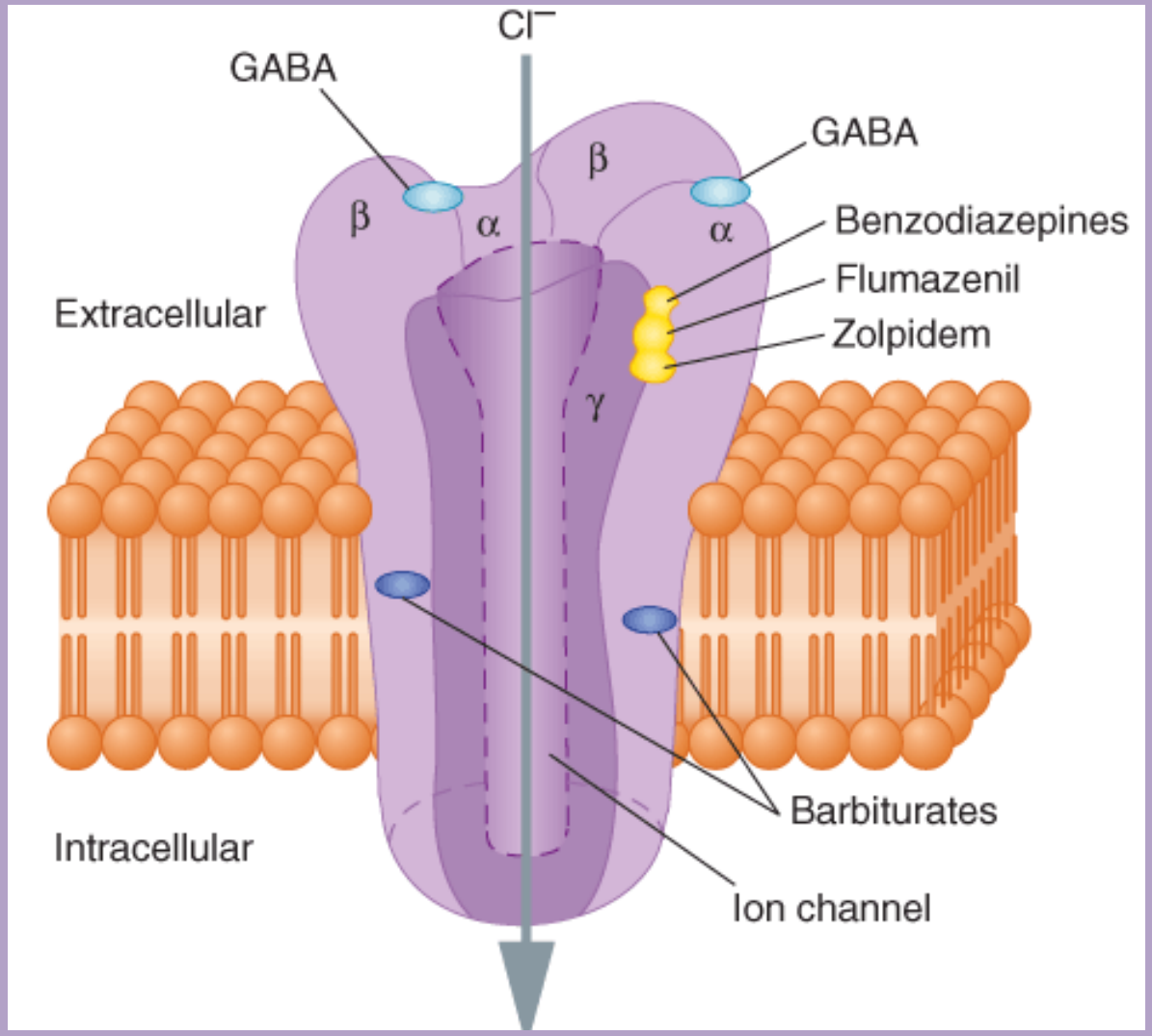


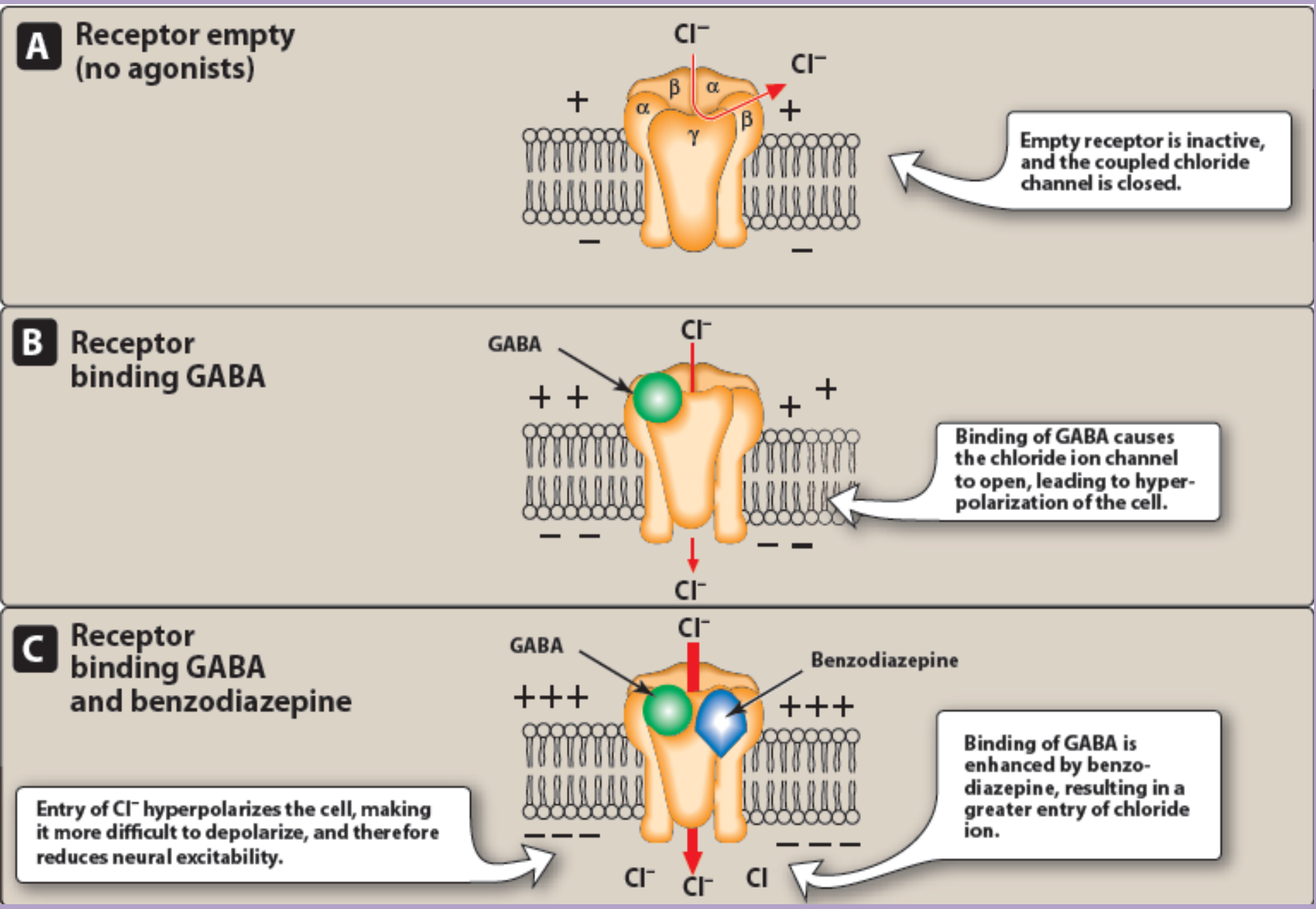
Pharmacokinetics

- Lipid solubility is a major factor in determining rate of oral absorption & onset of action.

- $t_{½}$ of parent d. may have little contribution to the duration of action of the drug, why?

Pharmacodynamics




A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
+
+
−
−
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
GABA
Cl⁻
+ +
+ +
− −
− −
Cl⁻
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
C
Receptor binding GABA and benzodiazepine
Cl⁻
GABA
Benzodiazepine
+++
+++
− − −
− − −
Cl⁻
Cl⁻
Cl
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.

- Will BDZ and related d. compete with GABA for GABA-R ?

- How can you explain the ability of barb. To induce full surgical anesthesia while BDZ and related compounds lack this property ?

Pharmacological actions

1. ***Sedation***: Reduce anxiety and have calming effects, they may impair psychomotor & cognitive functions (BDZ may produce amnesic effects).

2. ***Hypnosis:*** ↓ latency of sleep onset

↑ duration of sleep

3. Anesthesia: thiopental, thiamylal and methohexital.

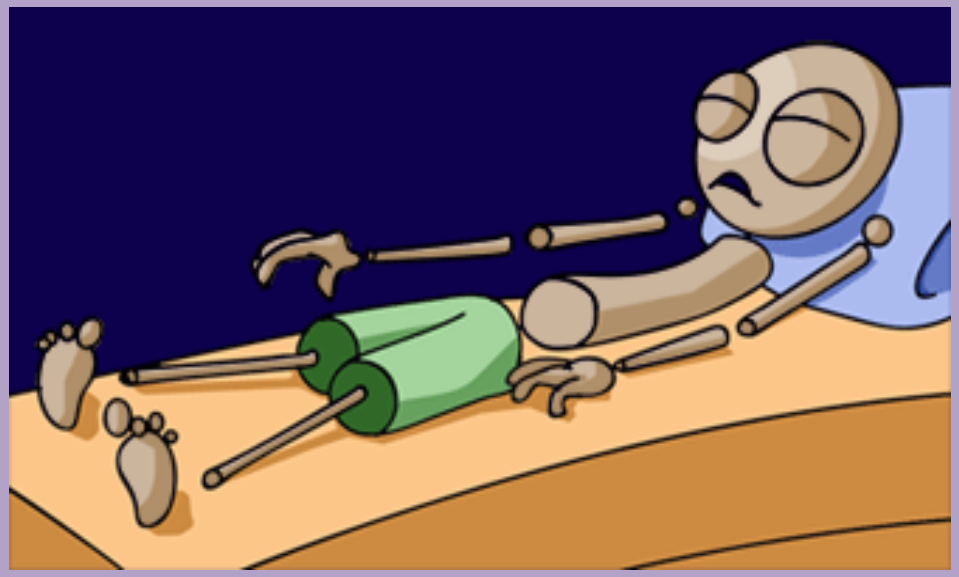
4. Anti-convulsant effects:

BDZ: Clonzepam, Nitrazepam , Dizepam and Lorazepam.

Barb.: Phenobarbital.

- Zolpidem, Zaleplon & Eszopiclone lack anticonvulsant effects.

5. Muscle relaxation: BDZ, Meprobamte have muscle relaxing activity.



- Zolpidem, Zaleplon & Eszopiclone lack muscle relaxing effects.

Tolerance and Dependence

Tolerance and Dependence

- ***Tolerance:*** is decreased responsiveness to drug following repeated exposure.
- Then what ???
- Tolerance is very common with Sedative-Hypnotics use which occurs mostly in long treatment courses.
- Why does tolerance occur?
- Minimal tolerance has been observed with Zolpidem, Zaleplon & Eszopiclone.

- ***Physiologic dependence:*** is altered physiologic state that requires continuous drug administration to prevent withdrawal symptoms.

- What are withdrawal symptoms associated with discontinuation of Sedative-Hypnotics?

- When do withdrawal symptoms appear?

- Does drug's half life possess any effect on development of withdrawal syndrome?

Respiratory depression induced by Sedative-Hypnotics

- Which carries a greater risk for induction of respiratory depression BDZ or barb.?

- Is there a specific antidote for overdose of:

- BDZ
- Zolpidem, Zaleplon & Eszopiclone

} Flumazenil

- Barbiturates. → Sorry , No.

Buspirone

- An anxiolytic without causing marked sedation, hypnosis or euphoria.

- Buspirone is $5HT_{1A}$ partial agonist.

Ramelteon

- Is MT_1 and MT_2 (melatonin) receptor agonist.
- No withdrawal symptoms (promotes natural cycle of sleep).
- AE: ↓ testosterone
  ↑ prolactin

Suvorexant

- Orexin receptors antagonist.
- Orexin is a neuropeptide that promotesc wakefulness.
- Suveroxant was recently approveinsd by FDA for treatment of insomnia.

Clinical uses of Sedative-Hypnotics

- Anxiety.
- Insomnia.
- Epilepsy.
- Anesthesia.
- Control of ethanol withdrawal states.

Thank you

References

-Basic & Clinical Pharmacology , Bertram G. Katzung 12th edition .

-Lippincott’s Illustrated Reviews: Pharmacology , 5th edition .

-Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. .