SEDATIVE-HYPNOTIC DRUGS:

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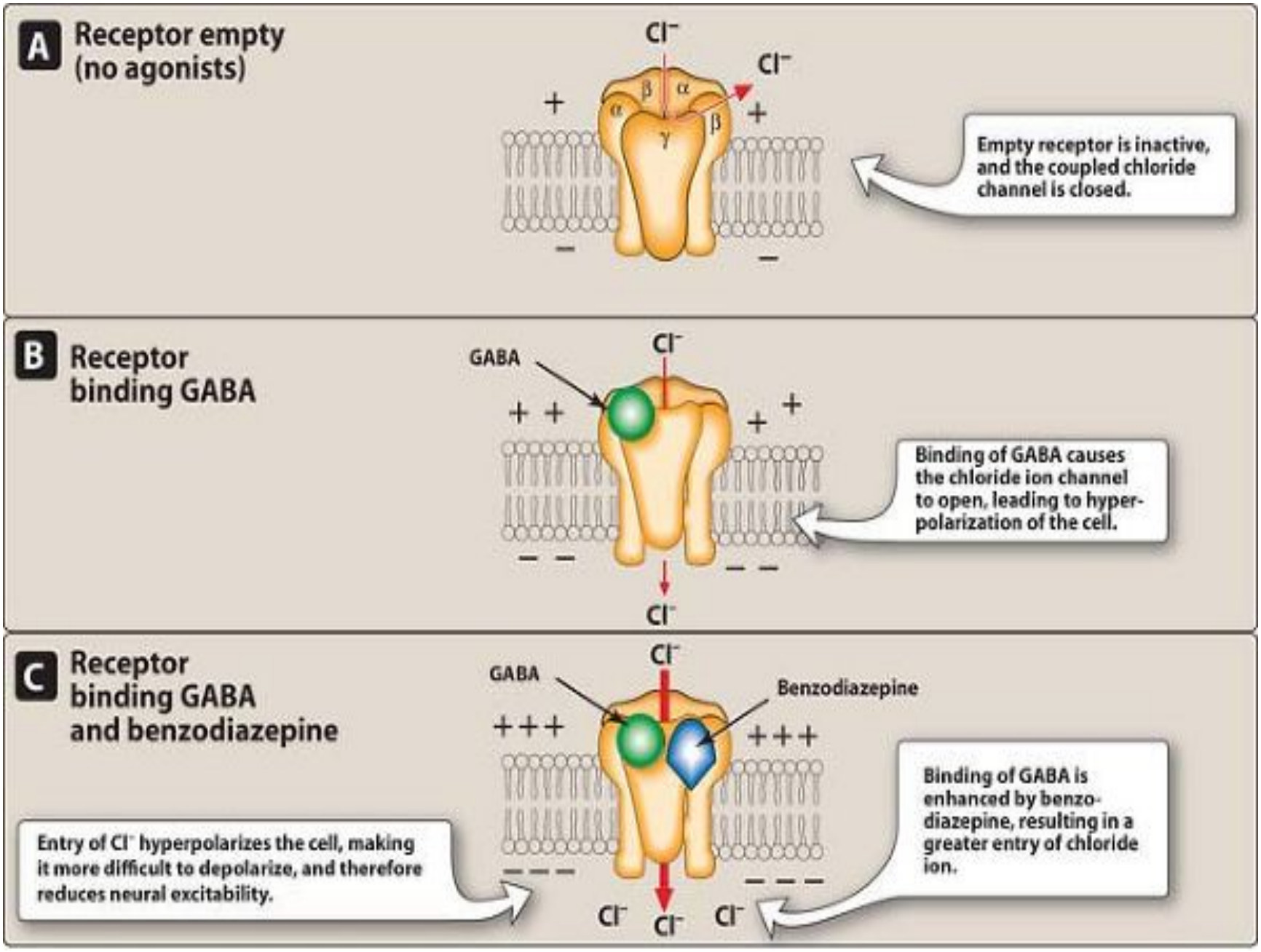
Pharmacology and therapeutics

- An effective sedative (anxiolytic) agent should reduce anxiety and exert a calming effect. A hypnotic drugs should produce drowsiness and encourage the onset and maintenance of a state of sleep.
- **Chemical Classification**

1. Benzodiazepines
2. Barbiturates.
3. Melatonin(naturally hormone that produced during sleep by pineal body) receptor agonist like Ramelteon
4. Beta blockers like propranolol
5. Certain antihistaminic agents including Diphenhydramine and doxylamine hydroxyzine and promethazine
6. Zopiclone and Zolpidem
7. Others include chlorhydrate, zaleplon, eszopiclone, Glutethimide and meprobamate.


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
α
β
α
β
γ
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
GABA
Cl⁻
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
Cl⁻
C
Receptor binding GABA and benzodiazepine
GABA
Cl⁻
Benzodiazepine
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.
Cl⁻
Cl⁻
Cl⁻

- **Benzodiazepines:** are the most widely used anxiolytic drugs include Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Lorazepam, Quazepam, Estazolam, Flurazepam and Triazolam.
- **Mode of action**:
- The benzodiazepine receptors are found only in the central nervous system (CNS), and their location parallels that of the $GABA_1$ neurons. The binding of benzodiazepines enhances the affinity of GABA receptors for this neurotransmitter, resulting in a more frequent opening of adjacent chloride channels causes hyperpolarization.
- **Actions:**

1. Reduction of anxiety: At low doses.
2. Sedative and hypnotic actions: At higher doses all of the benzodiazepines used to treat anxiety have some sedative properties.
3. Anticonvulsant: Several of the benzodiazepines have anticonvulsant activity and are used to treat epilepsy and other seizure disorders. Clonazepam is useful in the chronic treatment of epilepsy, whereas diazepam is the drug of choice in terminating grand mal epileptic seizures and status epilepticus

1. Muscle relaxant: disorders: Diazepam is useful in the treatment of skeletal muscle spasms such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.
2. Anterograde amnesia (for recent events).

- **Flurazepam**: This **long-acting** benzodiazepine significantly increases the duration of sleep. Flurazepam has a long-acting effect and causes little rebound insomnia.
- **Triazolam:** This benzodiazepine has a relatively short duration of action and is therefore used to induce sleep in patients with recurring insomnia. **Pharmacokinetics**
- The benzodiazepines are lipophilic and are well absorbed orally. The half-lives of the benzodiazepines are very important clinically, since the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate- and long-acting groups. Most benzodiazepines are metabolized in the liver.

DURATION OF ACTION OF BENZODIAZEPINES

Long-acting

Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam

Intermediate-acting

10–20 Hours

Alprazolam
Estazolam
Lorazepam
Temazepam

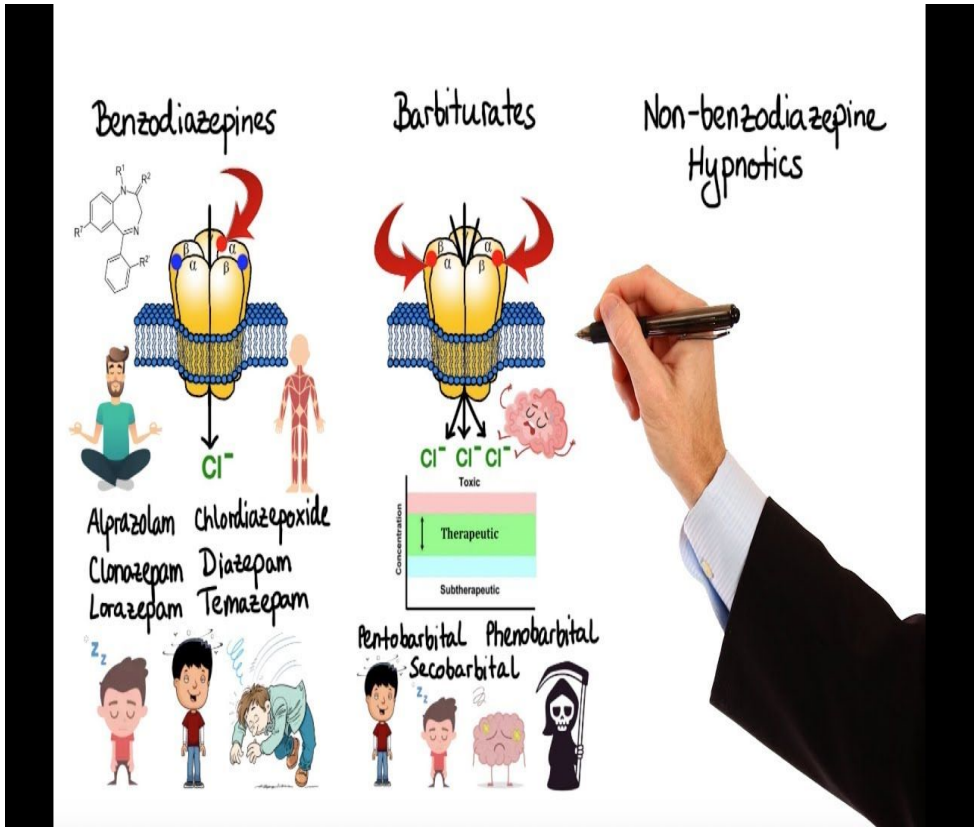
Short-acting

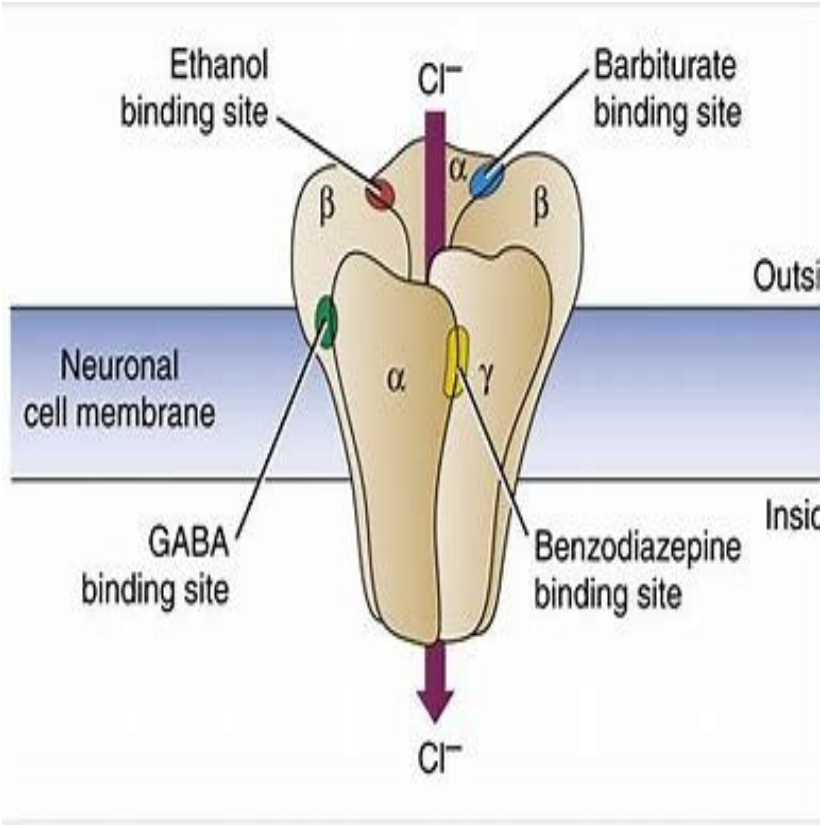
3–8 Hours

Oxazepam
Triazolam

- **Dependence**
- Psychological and physical dependence on benzodiazepines can develop if high doses of the drug are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, and tension.
- **Adverse effects**
- Drowsiness and confusion, ataxia, cognitive impairment, development of tolerance, and early morning insomnia.
- **OTHER ANXIOLYTIC AND HYPNOTIC AGENTS**
- **Zolpidem:** It acts on a subset of the benzodiazepine receptor family, **has no anticonvulsant or muscle relaxing properties**. It shows no withdrawal effects, exhibits minimal rebound insomnia and little or no tolerance occurs. It is rapidly absorbed from the GIT, and has a rapid onset of action and short elimination half-life (about 3 hours).

- **BENZODIAZEPINE ANTAGONIST**
- **Flumazenil:** It is a GABA receptor antagonist that can rapidly **reverse the effects of benzodiazepines.** Given IV only. Onset is rapid but duration is short, with a half-life of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. It may precipitate seizures if a benzodiazepine is used to control seizure activity. Dizziness, nausea, vomiting, and agitation are the most common side effects.
- **BARBITURATES**
- They are largely replaced by the benzodiazepines, mainly because barbiturates induce tolerance, drug-metabolizing enzymes, physical dependence, and very severe withdrawal symptoms.
- **Mode of action**
- Barbiturates are thought to interfere with sodium transport across cell membranes. in all areas of the CNS. Barbiturates also potentiates GABA action on chloride entry into the neuron.


Benzodiazepines
Barbiturates
Non-benzodiazepine Hypnotics
Cl⁻
Cl⁻ Cl⁻ Cl⁻
Toxic
Therapeutic
Subtherapeutic
Concentration
Alprazolam
Chlordiazepoxide
Clonazepam
Diazepam
Lorazepam
Temazepam
Pentobarbital
Phenobarbital
Secobarbital


Ethanol binding site
Cl⁻
Barbiturate binding site
α
β
β
Outsi
Neuronal cell membrane
α
γ
Insid
GABA binding site
Benzodiazepine binding site
Cl⁻

DURATION OF ACTION OF BARBITURATES

Long-acting

Phenobarbital

Short-acting

3–8 Hours

Pentobarbital
Secobarbital
Amobarbital

Ultra-short-acting

20 Minutes

Thiopental

- **Effect of barbiturates:**
- **Depression of CNS**: At low doses produce sedation but at higher doses, the drugs cause hypnosis, followed by anesthesia, and finally coma and death.
- **Respiratory depression**: over dosage is followed by respiratory depression and death.
- **Enzyme induction**: Barbiturates **induce P-450** microsomal enzymes in the liver and diminish the action of many drugs that are dependent on P-450 metabolism.

- **Therapeutic uses**
- 1- *Anesthesia:* thiopental, are used intravenously to induce anesthesia.
- 2- *Anticonvulsant*
- 3- *Anxiety:* it has been replaced by the benzodiazepines.
- **Pharmacokinetics**
- Barbiturates are absorbed orally and distributed widely throughout the body. They are metabolized in the liver, and inactive metabolites are excreted in the urine.
- **Adverse effects**
- 1. *CNS:* drowsiness, impaired concentration.
- 2. *Drug hangover*: Hypnotic doses produce a feeling of tiredness after the patient awakes.
- 3- *Drug interaction*: (oral contraceptive pills, warfarine, antifungal, other CNS depressants).
- *4- Addiction*: (dependace)
- 5- *Poisoning:* may cause severe depression of respiration is coupled with central cardiovascular depression. Treatment includes artificial respiration. Hemodialysis may be necessary if large quantities have been taken.

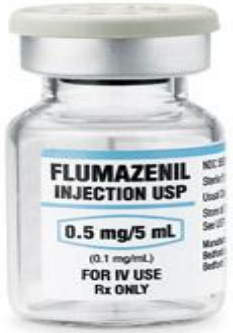
Treatment of toxicity

Barbiturates

- **Mechanical ventilation** ❖
- **IV fluids** ❖
- **Alkalinization of urine** ❖

Benzodiazepines

FLUMAZENIL is the specific antagonist



Melatonin receptors agonists :

Avtivates MT1 & MT2 receptors in suprachiasmatic nuclei in the CNS.

It show rapid onset of sleep with minimal rebound insomnia or withdrawal symptoms. Orally active forms active metabolite via CYP1A2.

Toxicity: Dizziness, fatigue and endocrine changes.

Interactions: Fluvoxamine inhibits metabolism.

Clinical use : sleep disorders, especially those characterized by difficulty in falling asleep.

- **NONBARBITURATE SEDATIVES**

A. Chloral hydrate

- Chloral hydrate is a trichlorinated derivative of acetaldehyde. The drug is an effective **sedative and hypnotic** (binds to ethanol binding site at cl channels) that induces sleep in about 30 minutes and lasts about 6 hours. Chloral hydrate is **irritating to the GIT .tract**. It also produces an unusual, unpleasant taste sensation

A. Antihistamines

- **Diphenhydramine and doxylamine** are effective in treating mild types of insomnia. They have numerous undesirable side effects that make them less useful than the benzodiazepines.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