Lec 3 Anxiolytic & Hypnotic drugs

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4th stage/ 1st course

- **Anxiety:**
- An unpleasant state of **tension, apprehension, fear from unknown source**.
- **Symptoms:** tachycardia, sweating, trembling, palpitation (sympathetic activity). Mild anxiety common life experience.
- **Treatment:**
- 1. Anxiolytic (minor traquilizers) &/or psychotherapy.
- 2. Hypnotic
- 3. Some antidepressants.
- 4. SSRI

- **Anxiolytic drugs**
- **1. Benzodiazepine (BZD):**
- widely used, differ in duration of action, no difference in terms of actions.
- **BNZ Actions:** They have no antipsychotic, analgesic, not affecting the autonomic NS.

➢1. Reduction of **anxiety** : GABA-A α2 subunit.

➢2. **Sedative & hypnotic actions**. GABA-A α1 subunit.

➢3. **Anterograde amnesia**: GABA-A α1 subunit.

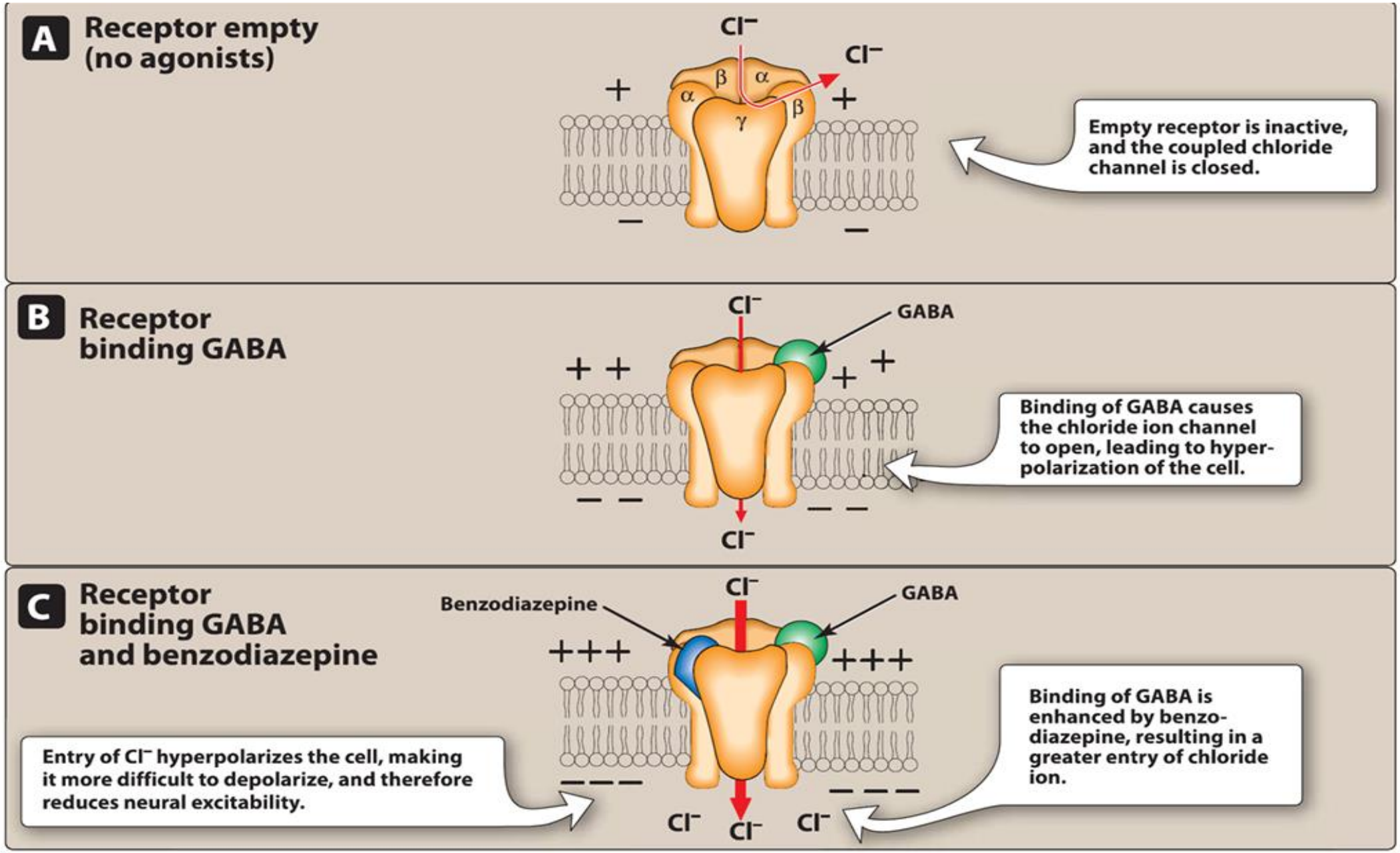
➢4. **Anticonvulsants**: GABA-A α1 subunit.

➢5. **Muscle relaxant** : GABA-A α2 subunit.

➢6. **Baclofen** acts on GABA-B receptors in the spinal cord.

BENZODIAZEPINES
Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam GENERIC ONLY
Flurazepam GENERIC ONLY
Lorazepam ATIVAN
Midazolam GENERIC ONLY
Oxazepam GENERIC ONLY
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION
BENZODIAZEPINE ANTAGONIST
Flumazenil GENERIC ONLY
OTHER ANXIOLYTIC DRUGS
Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone GENERIC ONLY
Meprobamate GENERIC ONLY
BARBITURATES
Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital GENERIC ONLY
Secobarbital SECONAL
OTHER HYPNOTIC AGENTS
Antihistamines VARIOUS (SEE CHAPTER 37)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Suvorexant BELSOMRA
Tasimelteon HETLIOZ
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

- **BNZ Mechanism of action:**
- • The target for benzodiazepine actions is the γ aminobutyric acid (GABA-A) receptors, that composed of a combination of five 2α, 2β, and γ subunits.
- • BZDs bind within the interface between the α and γ subunits
- • Binding of GABA to its receptor triggers an opening of the central ion channel, allowing chloride through the pore.
- • The influx of chloride ions causes **hyperpolarization** of the neuron and decreases neurotransmission by inhibiting formation of action potentials.
- the Common BZ receptor subtypes in the CNS are BZ1 (α1 subunit) or BZ2 (α2 subunit).
- • Benzodiazepines increase the frequency of channel openings produced by GABA.



Schematic diagram of benzodiazepine–GABA–chloride ion channel complex

- **BNZ Therapeutic uses:**
- **1. Anxiety disorders:**
- • Benzodiazepines are effective for the treatment of anxiety symptoms secondary to:

✓**Panic disorder**

✓**Generalized anxiety disorder (GAD)**

✓**Social anxiety disorder**

✓**Performance anxiety**

✓**Posttraumatic stress disorder**

✓**Obsessive–compulsive disorder**

These drugs should be reserved for severe anxiety only and not used to manage the stress of everyday life.

• Because of their **addiction potential**, they should only be used for short periods of time.

• The longer-acting agents, such as **clonazepam, lorazepam, and diazepam**, are often preferred in those patients with anxiety that may require prolonged treatment.

• For **panic disorders**, alprazolam is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of patients.

- **2. Sleep disorders:**
- Decrease **latency to sleep**, ↑ stage II NREM:
- **Flurazepam, Quazepam (long),**
- **Temazepam, Estazolam (intermediate),**
- **Triazolam (short) treatment of insomnia.**
- **Flurazepam**: rarely used, extended t1/2-day time.

- **Temazepam:**
- for patients with frequent wakening, given 1-2 hr. before bed time.
- **Triazolam:**

• Short duration, induce sleep in **recurrent insomnia**, tolerance , withdrawal (**rebound insomnia**), for intermittent & not for daily use.

• A few benzodiazepines are useful **as hypnotic agents**.

• These agents decrease the latency to sleep onset and increase stage II of non–rapid eye movement (REM) sleep.

• Commonly prescribed benzodiazepines for sleep disorders include intermediate-acting temazepam and short-acting triazolam.

• Long-acting flurazepam is rarely used, due to its extended half-life, which may result in excessive daytime sedation.

- **4. Seizures:**

- **Clonazepam** is occasionally used as adjunctive therapy for certain types of seizures.
- **Lorazepam and diazepam** are the drugs of choice in terminating status epilepticus.
- **Chlordiazepoxide, clorazepate, oxazepam, diazepam**: acute treatment of alcohol withdrawal .
- **5. Muscular disorders:**

- **Diazepam** is useful in the treatment of:

➢1. Skeletal muscle spasms, such as occur in muscle

➢2. Spasticity from degenerative strain disorders, such as multiple sclerosis and cerebral palsy

- **3. Amnesia:**

- The shorter-acting agents are often employed as premedication for anxiety provoking and unpleasant procedures, such as endoscopy, dental procedures, and angioplasty.
- They cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures.
- **Midazolam** is a benzodiazepine used to facilitate amnesia while causing sedation prior to anesthesia.
- **BNZ Pharmacokinetics:**
- **1. Absorption and distribution:**
- • They are **lipophilic**, so they are rapidly and completely absorbed after oral administration, distribute throughout the body and penetrate the CNS.
- **2. Duration of action:**
- • Their half-lives are important clinically, because the duration of action may determine the therapeutic usefulness.
- • Sometimes the clinical duration of action does not correlate with the actual half-life, this may be due to receptor dissociation rates in the CNS and subsequent redistribution to fatty tissues and other areas.

- **3. Fate:**

- Drug effects are terminated not only by excretion but also by redistribution .
- The benzodiazepines are excreted in the urine as glucuronides or oxidized metabolites.
- They are not recommended for use during pregnancy.
- Nursing infants may also be exposed to the drugs in breast milk.

BNZ Dependence

- Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given for a prolonged period.
- All benzodiazepines are controlled substances.
- Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including **confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures.**
- Benzodiazepines with a short elimination half-life, such as triazolam, **induce more abrupt and severe withdrawal reactions** than those seen with drugs that are slowly eliminated such as flurazepam.

- **BNZ Adverse effects**

- **Drowsiness and confusion** are the most common side effects of benzodiazepines.
- **Ataxia** occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile.
- **Cognitive impairment** (decreased long-term recall and retention of new knowledge) can occur with the use of benzodiazepines.
- **Triazolam** often shows the rapid development of tolerance, early morning insomnia, and daytime anxiety, as well as amnesia and confusion.
- Drug overdose is seldom lethal unless other central depressants, such as **alcohol**, are taken concurrently .

- **BENZODIAZEPINE ANTAGONIST**

- **Flumazenil** is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines.
- The drug is available for **intravenous (IV)** administration only.
- Onset is **rapid**, but the duration is **short**, with a half-life of about 1 hour.
- **Frequent administration** may be necessary to maintain the reversal of a long-acting benzodiazepine.
- Dizziness, nausea, vomiting, and agitation are the most common side effects.
- May ppt. withdrawal symptoms independent patient.
- May ppt. seizure if BZD used to control seizure.

- **OTHER ANXIOLYTIC AGENTS**
- **A. Antidepressants**

•**SSRIs**, such as **escitalopram or paroxetine** or **SNRIs** such as **venlafaxine or duloxetine** may be used alone or prescribed in combination with a low dose of a benzodiazepine during the first weeks of treatment.

- After 4-6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered.

•SSRIs and SNRIs have a **lower potential for physical dependence** than benzodiazepines and have become the first-line treatment for GAD (generalize anxiety disorder).

• B. Buspirone

• Buspirone is useful for the **chronic treatment of GAD** and has an efficacy comparable to that of benzodiazepines.

• Its action is mediated by **5-HT1A and 5-HT2A** receptors, although it also displays some affinity for **D2 dopamine receptors.**

• It lacks the anticonvulsant benzodiazepines.

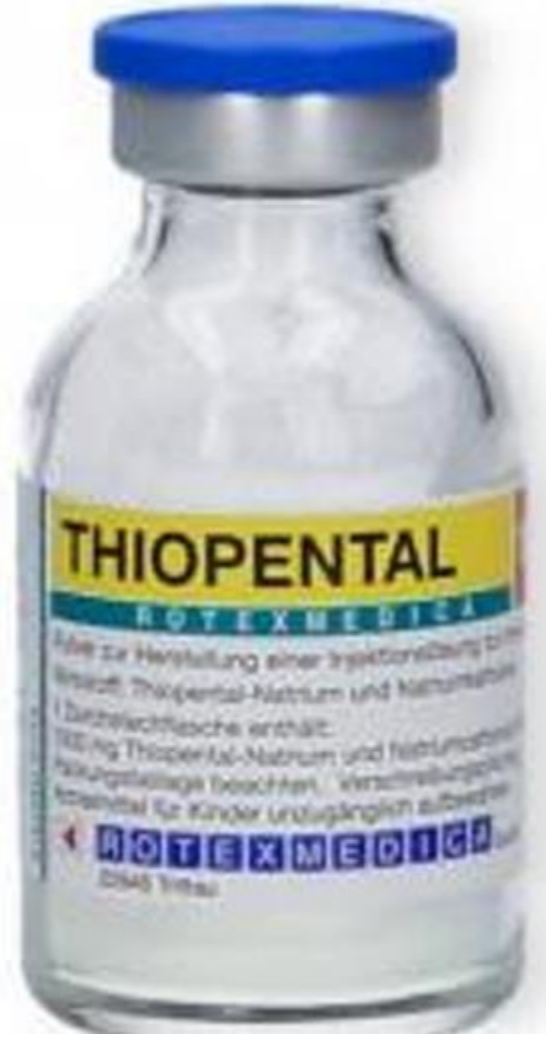
• Sedation and psychomotor dysfunction are muscle-relaxant properties of and cognitive minimal, and dependence is unlikely.

• Buspirone does **not potentiate** the CNS depression of alcohol.

- (Hypnotic drugs)
- BARBITURATES

The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep.

- Today, they have been largely replaced by the **benzodiazepines**.
- Barbiturates induce tolerance and physical dependence and are associated with very severe withdrawal symptoms.
- All barbiturates are controlled substances.
- Certain barbiturates, such as the very short-acting **thiopental**, have been used to induce **anesthesia.**



- **A. Mechanism of action**

- The sedative-hypnotic action of them is due to that:

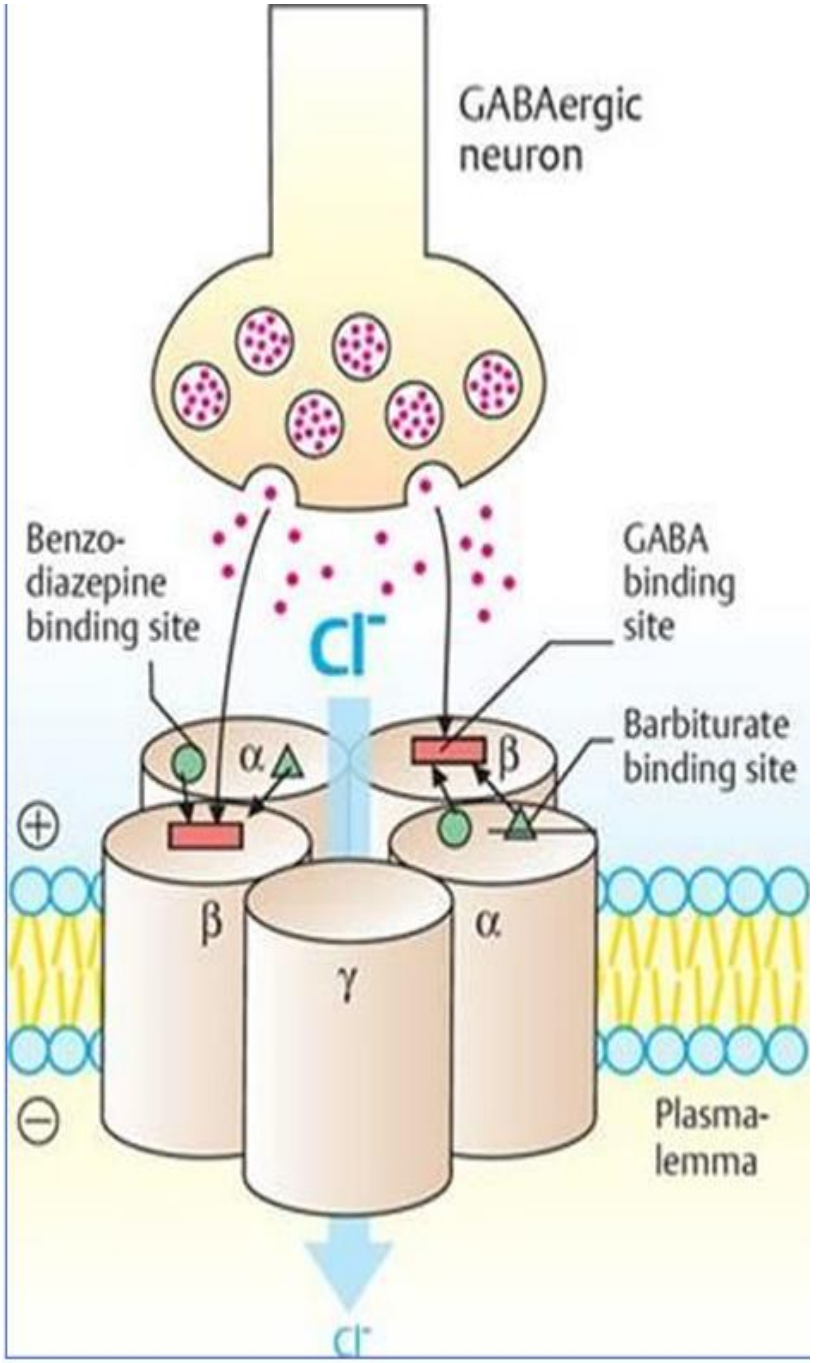
➢1. Barbiturates potentiate **GABA action** on **chloride** entry into the neuron by prolonging the duration of the chloride channel openings.

➢2. Barbiturates also can **block excitatory glutamate receptors.**

➢3. Anesthetic concentrations of pentobarbital also block high-frequency **sodium channels**.

- The binding site of barbiturates on the GABA receptor is distinct from that of benzodiazepines .

- All of these molecular actions lead to decreased neuronal activity.



- Barbiturates are classified according to their duration of action

Long-acting

Phenobarbital

Short-acting

3–8 Hours

Pentobarbital
Secobarbital
Amobarbital

Ultra-short-acting

20 Minutes

Thiopental

- **B. Action**

➢1. Depression of CNS:

- At low doses, the barbiturates produce **sedation.**
- At higher doses, the drugs cause **hypnosis**, followed by **anesthesia** (loss of feeling or sensation), and, finally, **coma and death**.
- Barbiturates do not raise the pain threshold and have no analgesic properties; they may even exacerbate pain.
- Chronic use leads to tolerance.

➢2. Respiratory depression:

- Barbiturates suppress the **hypoxic and chemoreceptor response to CO2.**
- Overdosage is followed by respiratory depression and death.

- **C. Therapeutic uses**
- **1. Anesthesia:**
- **Thiopental** (ultra–short-acting), has been used IV to induce anesthesia.

❖2. Anticonvulsant:

- **Phenobarbital** has specific anticonvulsant activity and it is used in the long-term management of **tonic-clonic seizures**.
- Similarly, phenobarbital may be used for the treatment of **refractory status epilepticus.**

❖3. Sedative/hypnotic:

- Barbiturates have been used as **mild sedatives** to relieve anxiety, nervous tension, and insomnia.
- However, the use of barbiturates for insomnia is no longer generally accepted.
- Butalbital is commonly used in combination products (with acetaminophen and caffeine or aspirin and caffeine) as a sedative to assist in the management of **tension-type or migraine headaches.**

D. Pharmacokinetics

- Barbiturates are well absorbed after **oral** administration and distribute throughout the body.
- All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue (short duration of action ?)
- Barbiturates readily **cross the placenta** and can **depress the fetus**.
- These agents are metabolized in the liver , and inactive metabolites are excreted in urine .

E. Adverse effects

- Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness, and occasionally, nausea and dizziness occur.
- Barbiturates **induce cytochrome P450** (CYP450) microsomal enzymes in the liver?
- Barbiturates are contraindicated in patients with **acute intermittent porphyria**.
- **Abrupt withdrawal** from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.

- **OTHER HYPNOTIC AGENTS**
- **A. Zolpidem**

• **Zolpidem** is not structurally related to BZ, but it selectively binds to BZ1 receptor subtype .

• Zolpidem has **no anticonvulsant or muscle-relaxing** properties.

• It shows few withdrawal effects, exhibits minimal rebound insomnia, and little tolerance.

• Zolpidem has rapidly absorbed from the GIT, and it has a rapid onset of action and short elimination half-life (2-3 hrs).

• It provides a hypnotic effect for approximately 5 hours.

• **Adverse effects** of zolpidem include nightmares, agitation, anterograde amnesia, headache, GI upset, dizziness, and daytime drowsiness

- **B. Zaleplon**

• **Zaleplon** is an oral non benzodiazepine hypnotic similar to zolpidem.

• However, zaleplon causes **fewer residual effects** on psychomotor and cognitive function compared to zolpidem or benzodiazepines.

• This may be due to its rapid elimination, with a half life of 1 hour.

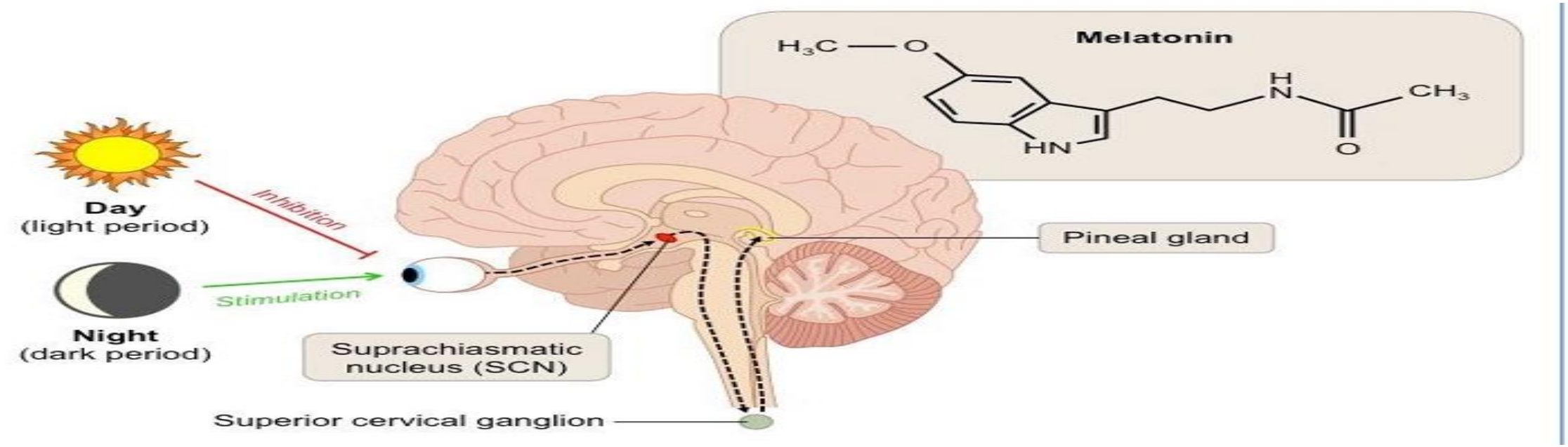
• The drug is metabolized by **CYP3A4**

C. Eszopiclone

- It is an oral non benzodiazepine hypnotic, and acts on the **BZ1 receptor**.
- It has been shown to be effective for **insomnia for up to 6 months.**
- Eszopiclone is rapidly absorbed (peak 1 hr), extensively metabolized **by oxidation and demethylation** via the CYP450 system, and mainly excreted in urine .
- Elimination half-life is approximately 6 hours.
- **Adverse events** with eszopiclone include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste.

- **D. Ramelteon**

- Ramelteon is a selective agonist at the **MT 1 and MT2** subtypes of **melatonin** receptors.
- Melatonin is a hormone secreted by the pineal gland that helps to maintain the circadian rhythm underlying the normal sleep-wake cycle.
- Stimulation of MT1 and MT2 receptors by ramelteon is thought to **induce and promote sleep.**



Ramelteon is indicated for the treatment of **insomnia characterized by difficulty falling asleep (increased sleep latency).**

- It has minimal potential for abuse , and no evidence of dependence or withdrawal effects has been observed.
- Therefore, ramelteon can be administered long-term
- Common adverse effects of ramelteon include dizziness, somnolence .
- Ramelteon may also **increase prolactin** levels.

E. Antihistamines

- Some antihistamines with **sedating** properties, such as **diphenhydramine, hydroxyzine, and doxylamine**, are effective in treating mild types of **situational insomnia.**
- However, they have undesirable side effects (such as anticholinergic effects) that make them less useful than benzodiazepines and nonbenzodiazepines.
- Some sedative antihistamines are marketed in **numerous OTC products.**

- **F. Antidepressants**

- The use of sedating antidepressants with strong antihistamine profiles has been ongoing for decades.
- **Doxepin**, an older TCA agent with SNRI mechanisms of antidepressant and anxiolytic action, was recently approved at low doses for the management of **insomnia**.
- Other antidepressants, such as **trazodone, mirtazapine**, and other older TCA with strong antihistamine properties are used off-label for the treatment of insomnia