Al-Mustaqbal University
College of Pharmacy
4th stage
Pharmacology II
Lecture: 3

Anxiolytics & Hypnotics

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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**.

OTHER ANXIOLYTIC AGENTS

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 and muscle-relaxant properties of benzodiazepines.
- Sedation and psychomotor and cognitive dysfunction are **minimal**, and dependence is **unlikely**.
- Buspirone does **not potentiate** the CNS depression of alcohol.

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**.

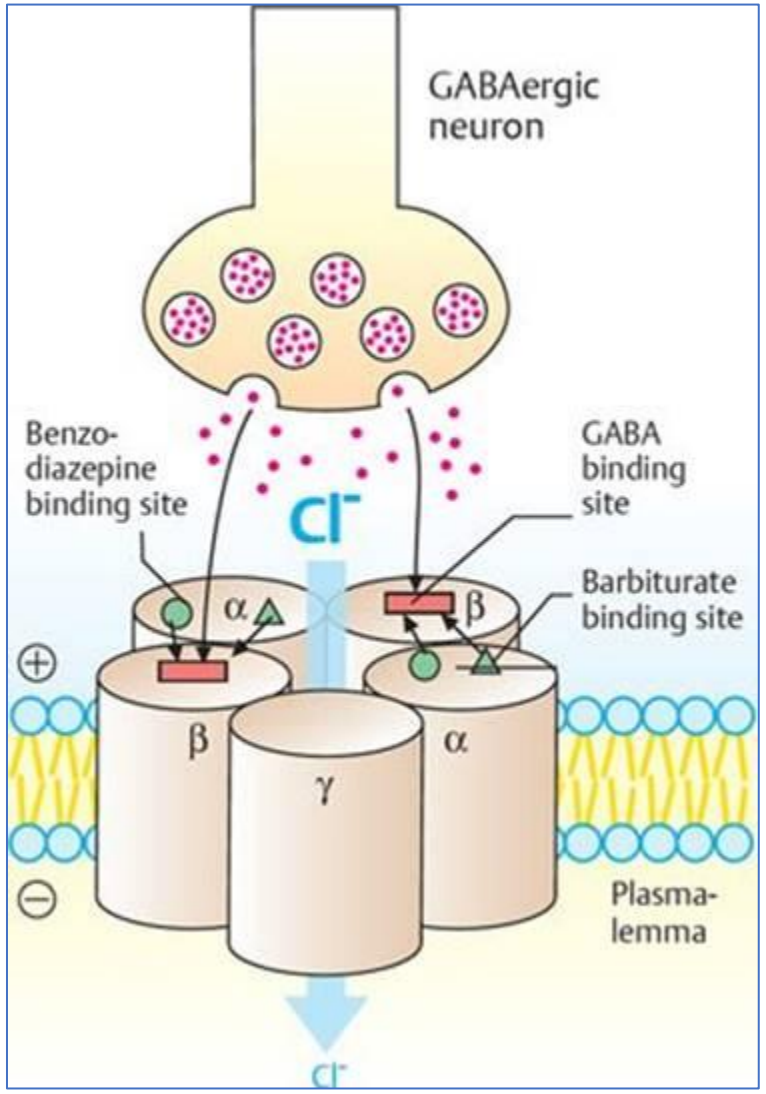
BARBITURATES

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

B. Actions

- Barbiturates are **classified** according to their **duration of action** into:

Long-acting

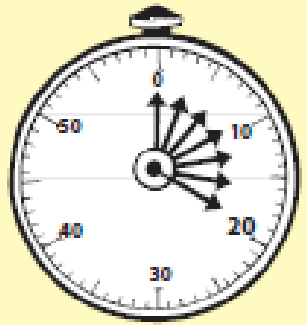
Phenobarbital

Short-acting

3–8 Hours

Pentobarbital
Secobarbital
Amobarbital

Ultra-short-acting



20 Minutes

Thiopental

BARBITURATES

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.

BARBITURATES

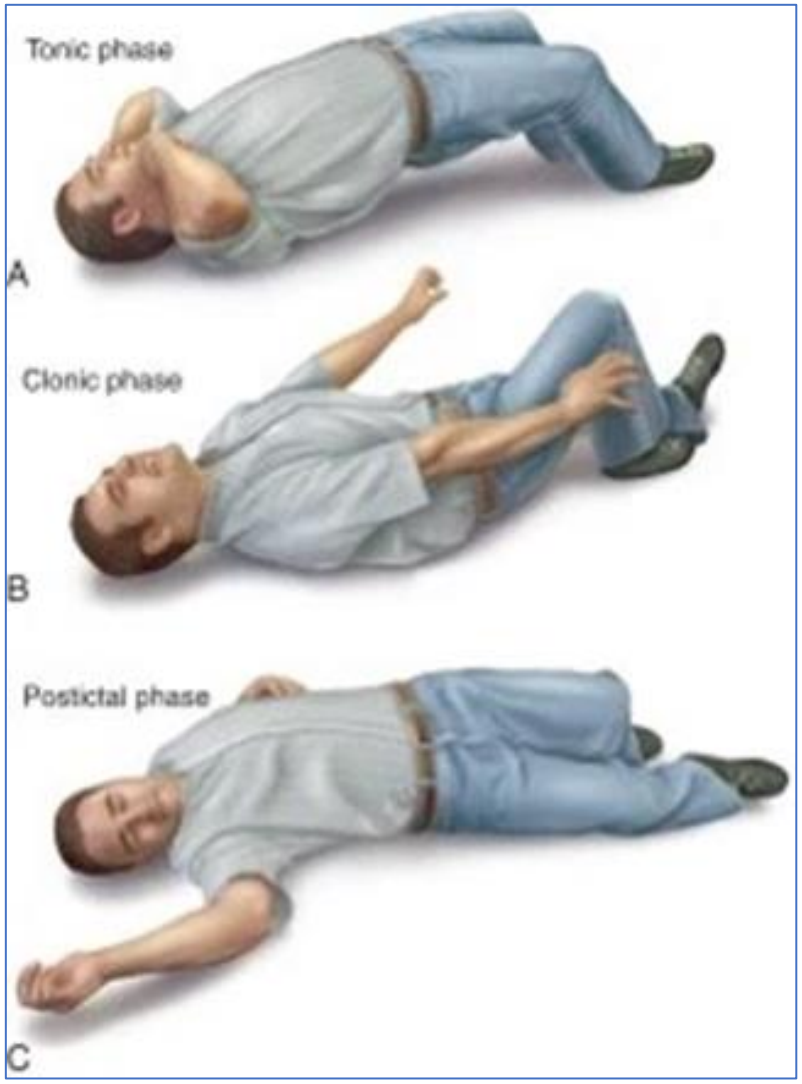
C. Therapeutic uses

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**.



BARBITURATES

C. Therapeutic uses

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) to **assist** in the management of tension-type or migraine headaches.

BARBITURATES

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

OTHER HYPNOTIC AGENTS

B. Zaleplon

- Zaleplon is an **oral nonbenzodiazepine** 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.

OTHER HYPNOTIC AGENTS

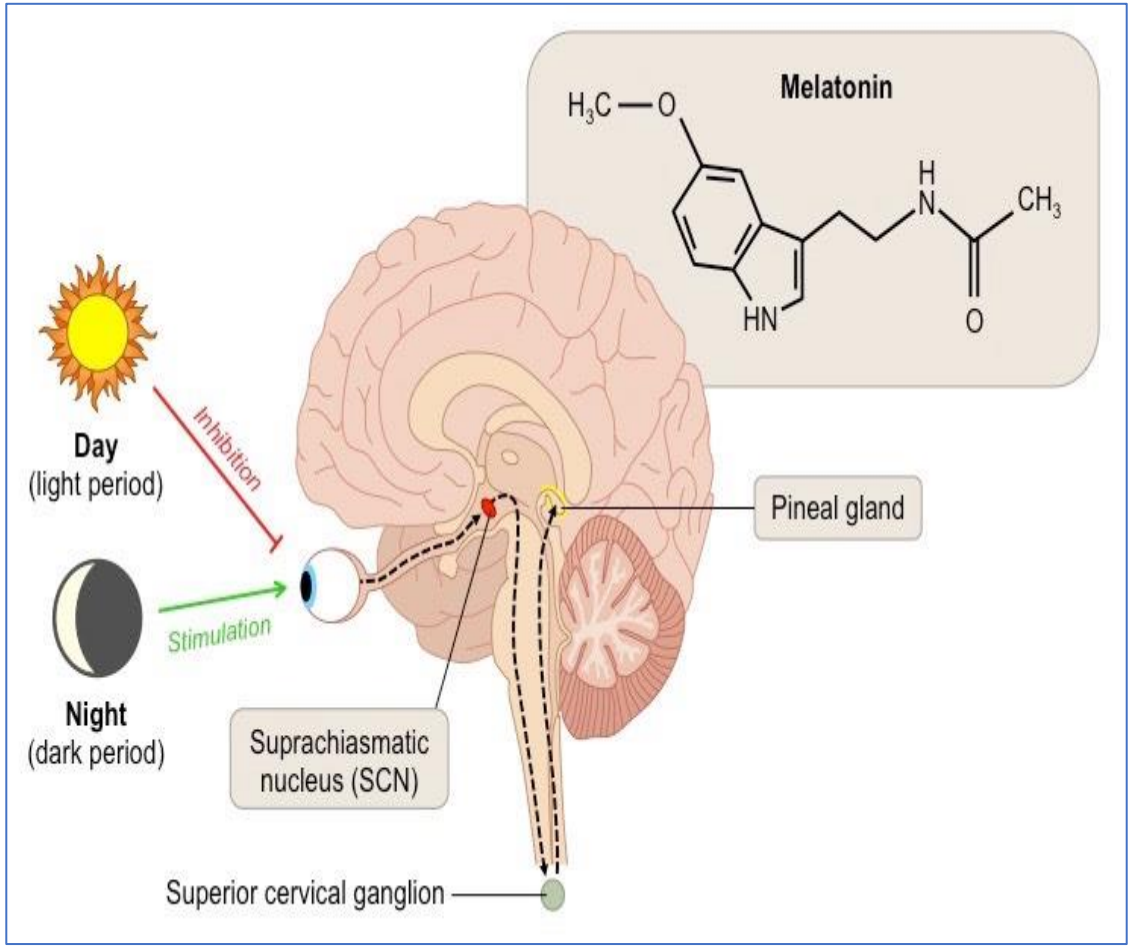
C. Eszopiclone

- It is an **oral nonbenzodiazepine** 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.

OTHER HYPNOTIC AGENTS

D. Ramelteon

- Ramelteon is a **selective agonist** at the MT1 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**.



OTHER HYPNOTIC AGENTS

D. Ramelteon

- 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, fatigue, and somnolence.
- Ramelteon may also **increase prolactin levels.**

OTHER HYPNOTIC AGENTS

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.

OTHER HYPNOTIC AGENTS

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**

THANK YOU FOR YOUR ATTENTION