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

Anxiolytics & Hypnotics

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Anxiety

- **Anxiety** is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source).
- The physical symptoms of severe anxiety are tachycardia, sweating, trembling, and palpitations and involve **sympathetic** activation.
- Episodes of **mild anxiety** are **common** life experiences and do **not** warrant treatment.
- However, **severe, chronic, debilitating anxiety** may be treated with **antianxiety** drugs (sometimes called anxiolytics) and/or some form of **psychotherapy**.

Anxiolytics

ANXIOLYTICS AND HYPNOTICS

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

BENZODIAZEPINES

- Benzodiazepines are **widely** used anxiolytic drugs.
- They have largely replaced **barbiturates and meprobamate** in treating anxiety and insomnia because benzodiazepines are generally considered **safer** and more **effective**.
- Certain antidepressants with **anxiolytic** action, such as **SSRIs**, are preferred in many cases
- **Nonbenzodiazepine** hypnotics and **antihistamines** may be preferable for **insomnia**.

BENZODIAZEPINES

- **Benzodiazepines** are classified according to the **duration of action** into:

1. Short acting (3-8 hours): **triazolam, Oxazepam**
2. Intermediate (10-20 hours):

Alprazolam, Lorazepam, Estazolam, Temazepam

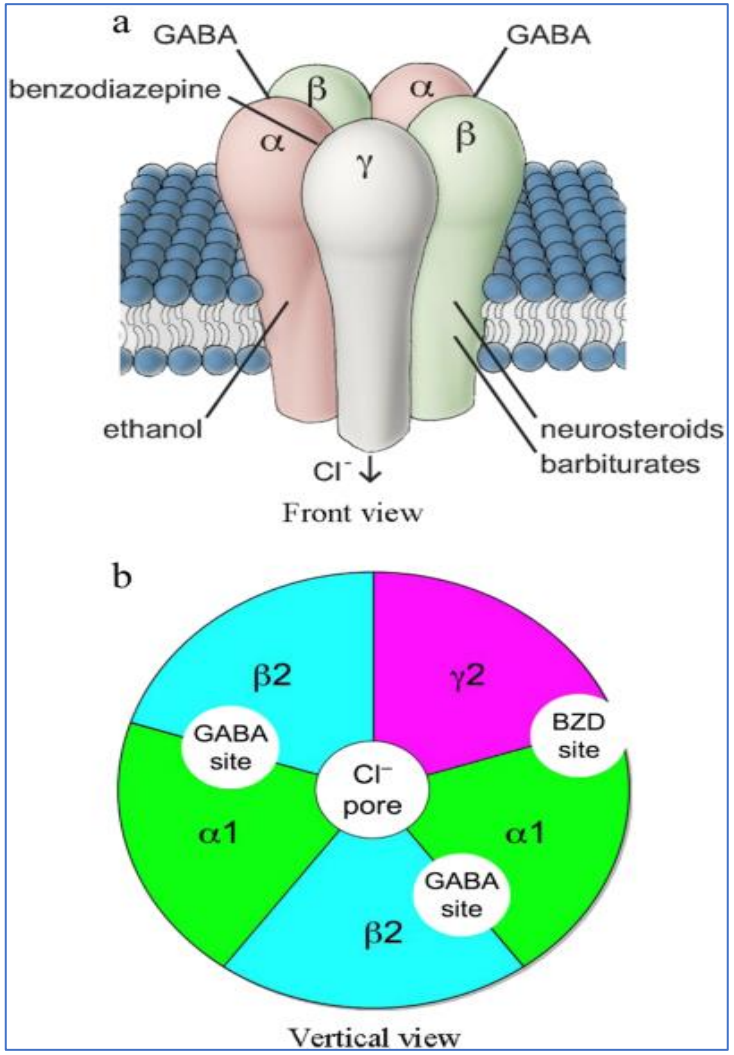
3. Long acting: (1-3 days):

Diazepam, Chlordiazepoxide, Flurazepam, Quazepam, Clorazepate

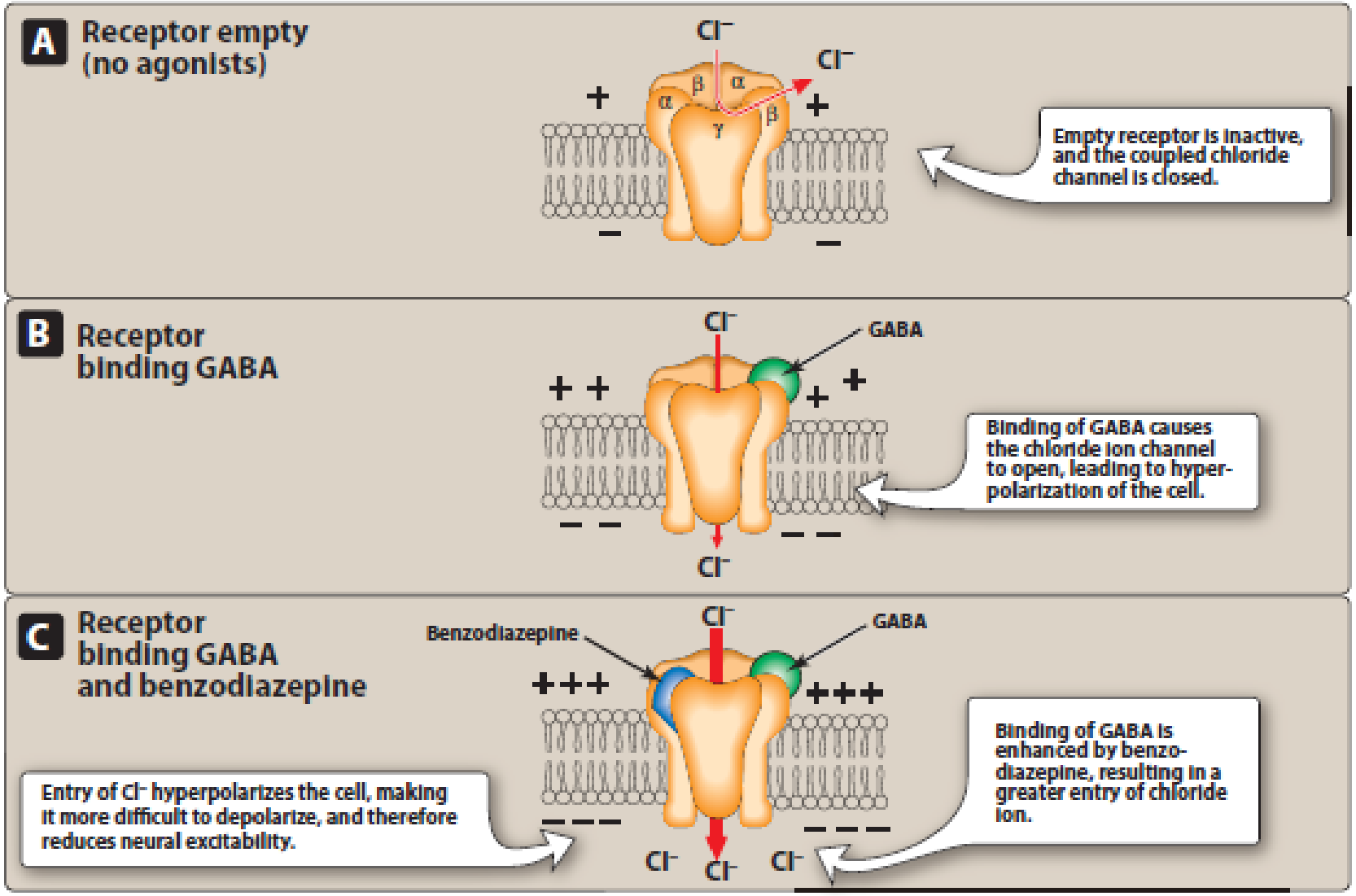
BENZODIAZEPINES

Mechanism of action:

- The target for benzodiazepine actions is the **γ-aminobutyric acid** (GABAA) 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 the formation of action potentials.
- 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.



BENZODIAZEPINES



Schematic diagram of benzodiazepine–GABA–chloride ion channel complex

BENZODIAZEPINES

Actions:

1. Reduction of anxiety:

- At **low doses**, benzodiazepines are **anxiolytic**.
- The **anxiolytic** effects are mediated by the **α2-GABAA** receptors

2. Sedative/hypnotic:

- **All** benzodiazepines have **sedative** and **calming** properties, and **some** can produce **hypnosis** (artificially produced sleep) at **higher** doses.
- The **hypnotic** effects are mediated by the **α1-GABAA** receptors.

3. Anterograde amnesia:

- **Temporary** impairment of memory with the use of benzodiazepines is also mediated by the **α1-GABAA** receptors.
- The ability to learn and form **new memories** is also **impaired**.

BENZODIAZEPINES

Actions:

4. Anticonvulsant:

- **Several** benzodiazepines have **anticonvulsant** activity.
- This effect may be mediated by **α1-GABAA** receptors.

5. Muscle relaxant:

- **At high doses**, the benzodiazepines **relax** the spasticity of skeletal muscle, probably by **increasing presynaptic inhibition** in the spinal cord, where the **α2-GABAA** receptors are largely located.
- **Baclofen** is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord.

BENZODIAZEPINES

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

BENZODIAZEPINES

Therapeutic uses:

1. Anxiety disorders:

- 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.

BENZODIAZEPINES

Therapeutic uses:

2. Sleep disorders:

- 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.**

BENZODIAZEPINES

Therapeutic uses:

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.

BENZODIAZEPINES

Therapeutic uses:

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**.

Muscular disorders:

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

1. **Skeletal muscle spasms**, such as occur in muscle strain
2. **Spasticity** from degenerative disorders, such as multiple sclerosis and cerebral palsy

BENZODIAZEPINES

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.

BENZODIAZEPINES

Pharmacokinetics:

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.

BENZODIAZEPINES

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**.

BENZODIAZEPINES

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.

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 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**.

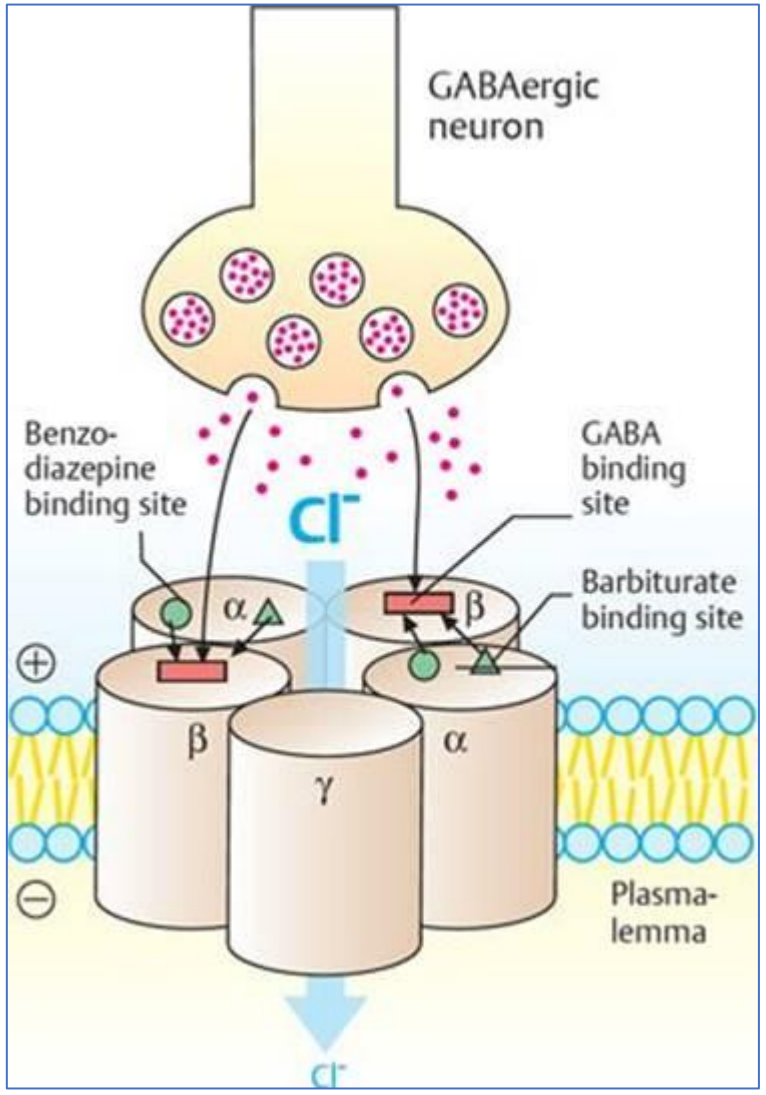
BARBITURATES

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

Long-acting

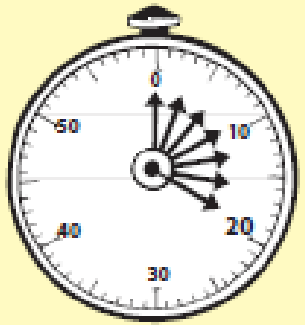
Phenobarbital

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.

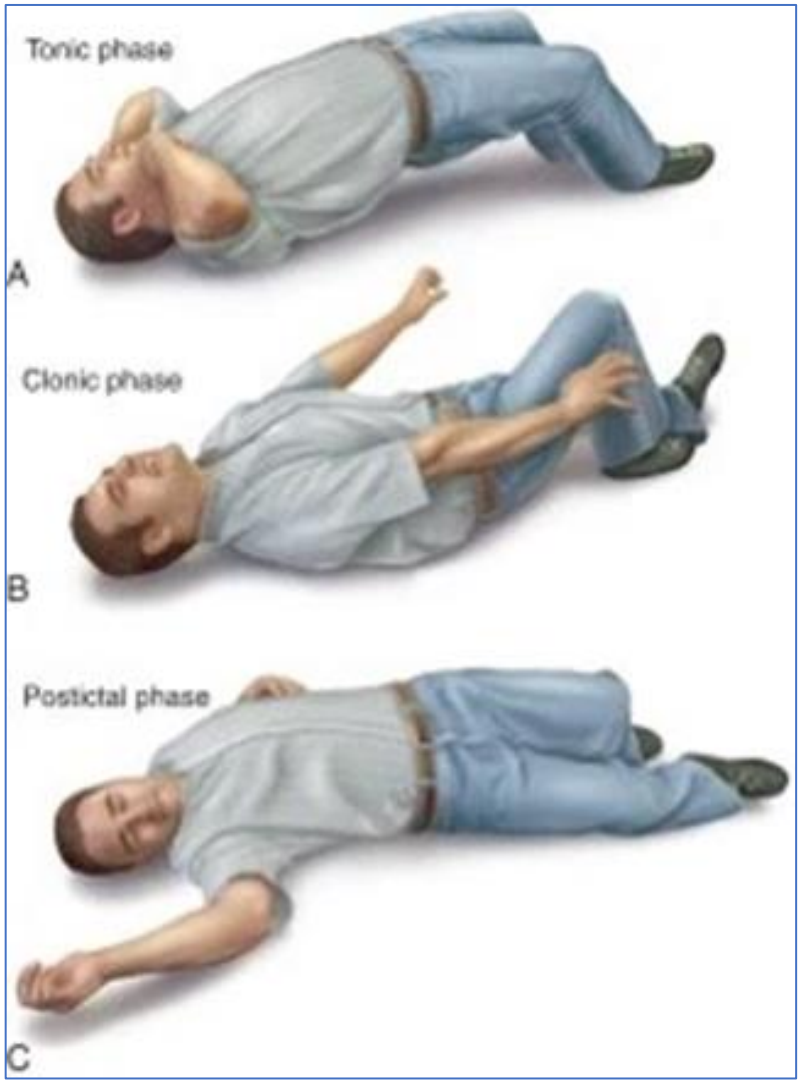
C. Therapeutic uses

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) as a **sedative** 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.

BARBITURATES

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.
- Barbiturates **induce cytochrome P450** (CYP450) microsomal enzymes in the liver.

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

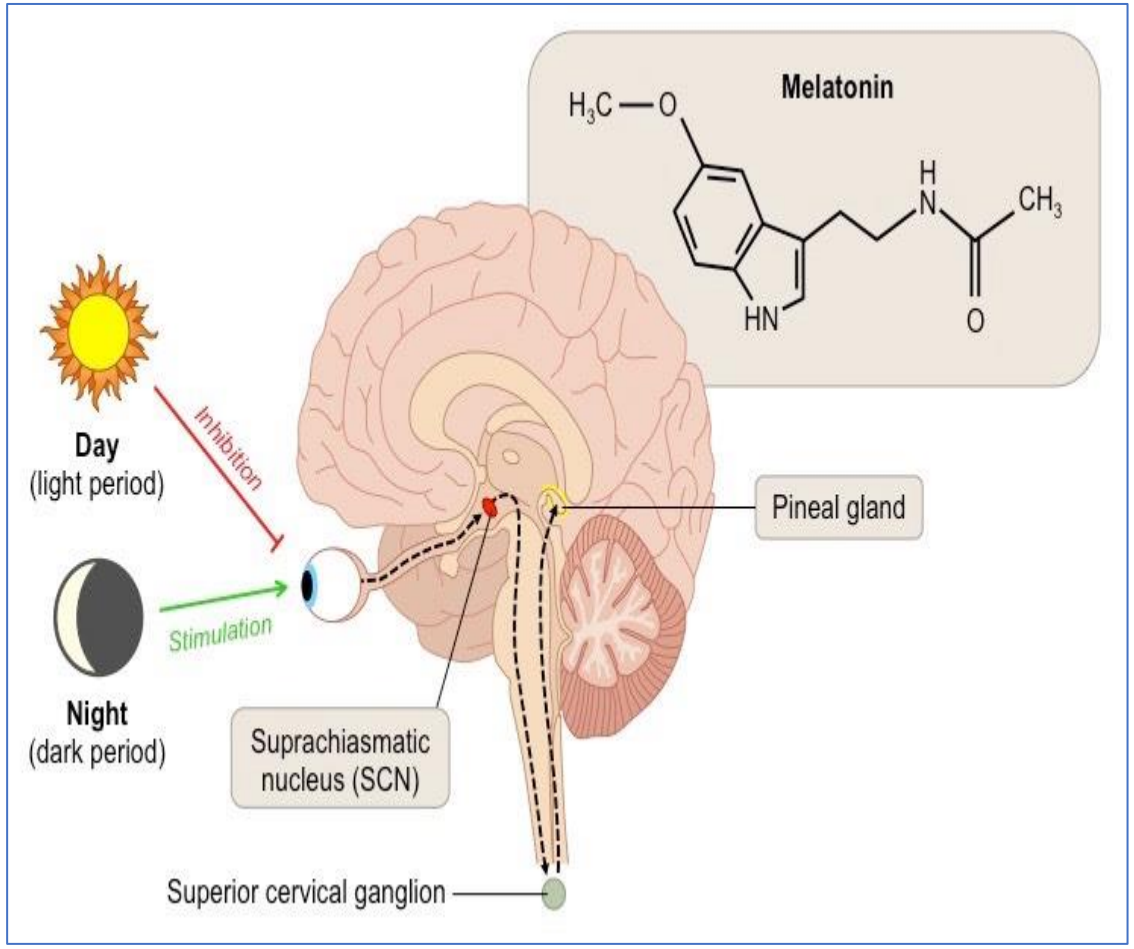
C. Eszopiclone

- 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