بسم الله الرحمن الرحيم

Sedative hypnotics (part two)

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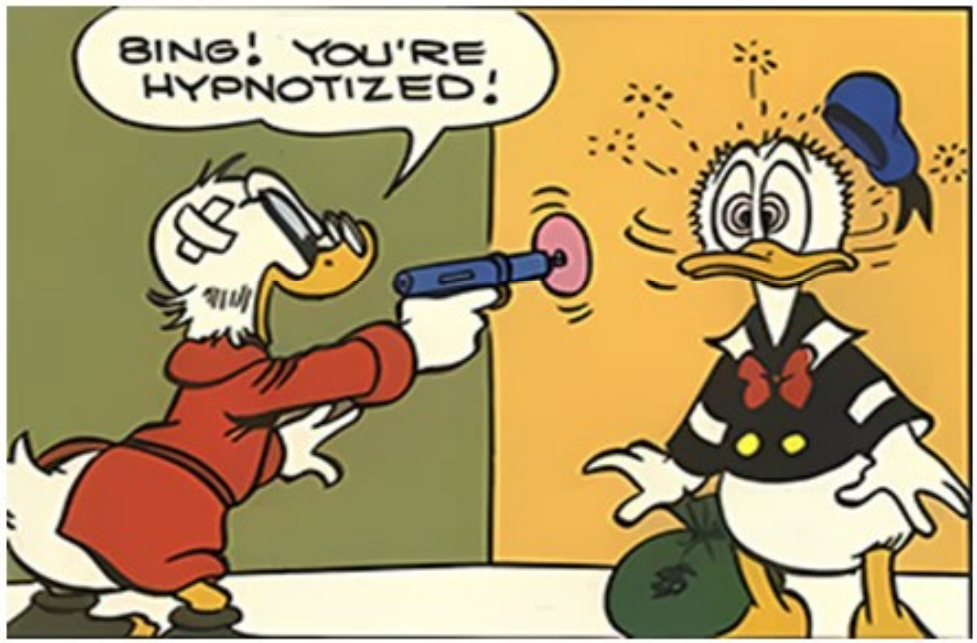
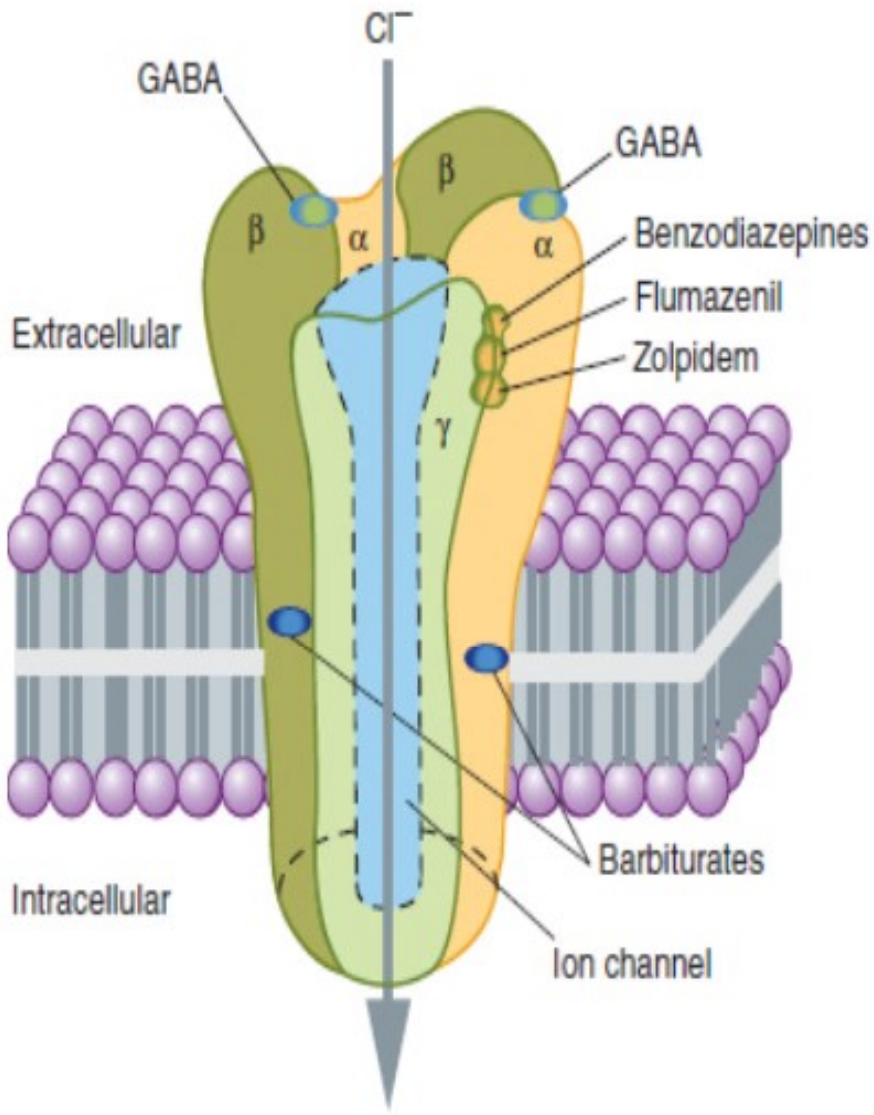


- Sedatives slow the brain activity, and **calm** the patient.
- **Hypnotics**: drugs which **induce sleep.**

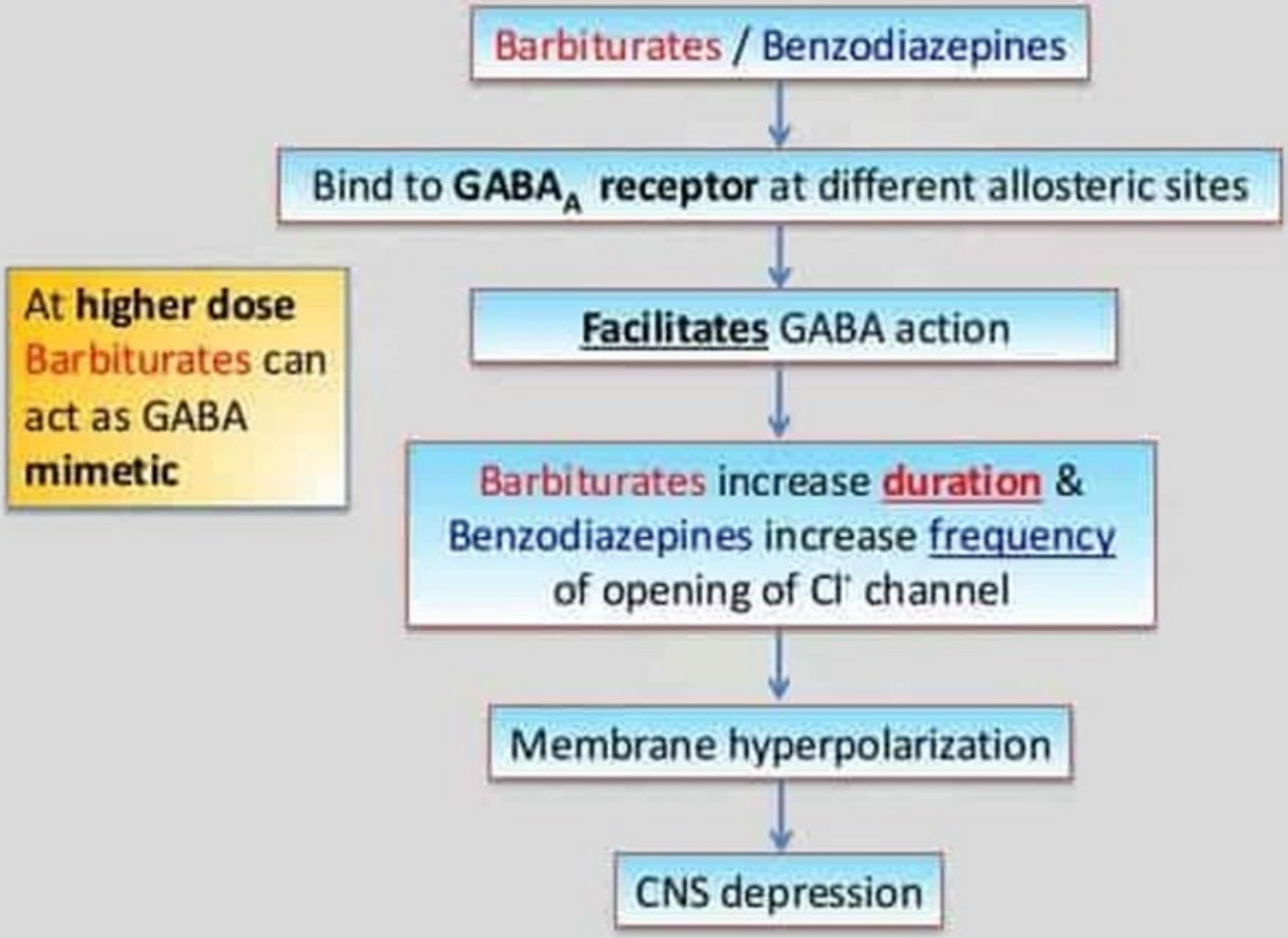
Barbiturates

Barbiturates Bind to a specific barbiturate receptor on the **$GABA_A$** Chloride channel complex and facilitate GABA-mediated chloride ion channel opening(increasing duration), membrane hyperpolarization and CNS depression occur.

Barbiturates also can block neuronal Na^+ channels & block the excitatory NMDA receptors of glutamate.



Mechanism of Action



Pharmacological Effects of barbiturates:

Dose-dependent CNS depression including:

1. Sedation
2. Relief of anxiety
3. Amnesia
4. Hypnosis
5. Anaesthesia
6. Coma
7. Respiratory depression (steeper dose-response relationship than benzodiazepines). Additive CNS depression with ethanol and other CNS depressants occur.

Pharmacokinetics of barbiturates

- They are weak acidic drugs, absorbed orally.
- All barbiturates redistribute in the body.
- Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.
- They readily cross the placenta and can depress the respiratory center of the fetus.
- **Barbiturates induce P450 microsomal enzymes in the liver and affect the metabolism of several drugs (**drug induction).
- Barbiturates are excreted in urine. **Alkalinization of urine helps their excretion** (IV sodium bicarbonate is used for management of acute barbiturate toxicity)

Therapeutic uses

1- Anesthesia

The ultra-short acting barbiturates, such as **thiopental**, are used intravenously to induce general anesthesia.

2- Treating anxiety and insomnia (BZD are preferred now)

Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia (amobarbital). Barbiturates suppress REM sleep significantly.

3- Anticonvulsant: (phenobarbital, mephobarbital)

Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. Primidone is also used for seizure disorders and tremors.

The anticonvulsant doses are less than hypnotic doses and doses used for anaesthesia.

4- Treatment of young children with recurrent febrile seizures: However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.

5- Treatment of neonatal jaundice: Stimulation of microsomal hepatic enzymes by phenobarbital can accelerate bilirubin metabolism.

6- Methohexital: is used for procedural sedation of short duration (e.g. cardioversion and pediatric outpatient surgery, fracture reduction for elective intubation).

7- Butalbital: is used for the treatment of headache disorders.

Adverse effects of barbiturates

1. **Dose dependent CNS depression:** Barbiturates cause drowsiness, vertigo, impaired concentration, etc.
2. **Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes.**
3. **In toxic doses: respiratory depression, Cardiovascular collapse, and coma. Death occurs due to respiratory failure.**
4. **Barbiturates induce the P450 system and affect metabolism of many drugs (drug-drug interactions).**

5. **Barbiturates** increase **porphyrin synthesis** (contraindicated in patients with porphyria).
6. **Behavioural changes in children**.
7. **Tolerance, dependence, and addiction** (more than BZD do).
8. **Abrupt withdrawal** from barbiturates may cause **tremors**, **anxiety**, **weakness**, **restlessness**, **nausea** and **vomiting**, **seizures**, **delirium**, and **cardiac arrest**.

Acute Barbiturates poisoning

causes deep coma with marked respiratory depression & hypotension.

Treatment includes :

1- support respiration and circulation.

2- gastric lavage followed by charcoal and cathartics.

3-increase renal excretion of phenobarbital by making urine pH alkaline with IV. sodium bicarbonate

4- In severe cases, hemodialysis is done.

Buspirone

- It selectively binds to 5HT1A (serotonin) receptor acting as a partial agonist.
- It has no relation to BZD receptor or GABA inhibitory neurotransmitter.
- Its anxiolytic effect does not appear before 2-4 weeks of its administration. So, it is **suitable for chronic anxiety** but not acute anxiety states. Also, it is not effective in severe anxiety like panic attacks.
- It has **no hypnotic or anticonvulsant effects.**
- Tolerance to its effect does not occur, little potential to abuse and no withdrawal symptoms develop after abrupt withdrawal.

Buspirone is highly bound to plasma protein and metabolized in the liver by **CYP 3A4.**

Side effects of Buspirone may include headache, nausea, drowsiness but sedation is minimal. Tachycardia, palpitations, GI distress and paresthesias may occur. Buspirone causes a dose-dependent pupillary constriction (miosis).

Ipsapirone is a selective 5-HT1A receptor partial agonist. It has both antidepressant and anxiolytic effects

Melatonin and Ramelteon

- Ramelteon (Synthetic tricyclic analog of **melatonin) is a novel hypnotic** drug specifically useful for patients who have difficulty in falling asleep.

- Both melatonin and Ramelteon are agonists at MT 1 and MT 2 melatonin receptors located in the brain.

- The drug has no direct effects on GABAergic neurotransmission in the CNS (Little CNS depression).

- Ramelteon should be used with caution in patients with liver dysfunction

- It has no rebound insomnia or significant withdrawal symptoms.
- Ramelteon has minimal potential for abuse, and regular use does not result in dependence .
- Melatonin is used orally or sublingual. It is safe for children.
- **Adverse effects** include dizziness, fatigue, **endocrine changes** (increases prolactin and decreases testosterone).

Orexin receptor antagonists

- A new class of hypnotics (orexin receptor antagonists) , which include Almorexant and suvorexant.
- Orexin A and B are peptides that are **involved in the control of wakefulness** and that are silent during sleep.

- Orexin levels increase in the day and decrease at night.
- Loss of orexin neurons is associated with narcolepsy (daytime sleepiness).

- Animal studies show that orexin receptor antagonists have sleep-enabling effects.

- Suvorexant was approved for use as hypnotic by FDA.

Treatment of anxiety disorders

A- Stress anxiety disorder : treated by BDZs: for short-term relief; resolve < 1 month. Beta blockers can be used.

B- Social anxiety and situational anxiety disorder

1. **Beta-adrenergic blockers e.g. propranolol**
2. **Long term benefit from SSRIs.**

C- Panic attacks : There is a feeling of impending doom with tachycardia, sweating, tremor, and diarrhea.

a. **BDZs (Alprazolam) for short-term relief**
b. **SSRIs antidepressants e.g. paroxetine or TCAs e.g. clomipramine for long-term control**

SSRIs = Selective Serotonin Reuptake Inhibitors.
TCAs = Tricyclic antidepressants.

D- Phobias : Patient fears a particular situation, fear of public places, fear of objects (dogs, spiders, snakes).

Phobias are treated by Behavioral therapy and drugs like Alprazolam (acute), or SSRIs (long-term).

E-Generalized anxiety disorder is treated by :-

a. BDZs : for acute symptoms or for chronic use.

b. Buspirone : for chronic control esp. in elderly.

c. Antidepressants esp. SSRIs are also helpful

F- Obsessive-compulsive disorder (OCD) is treated by :-

a. Psychotherapy

b. Antidepressants e.g Clomipramine or SSRIs.

BDZs are not helpful in OCD

G- Post-traumatic stress disorder (PTSD) :

- follows characteristically exposure to very traumatic stress event. The patient has re-experience of this event & develops symptoms of insomnia with anxiety & tension; and tries to avoid any stimuli associated with the event.

Drugs employed in treatment include :

1. BDZs : should be used early to promote sleep and minimize mental re-experience of the stress trauma which can lead to its persistence . May be used long-term for 6 months.

2. SSRIs : paroxetine for long term control .
3. Other antidepressants TCAs may also be used.

Miscellaneous sedative hypnotics

1- Chloral hydrate :

It is a **gastric irritant** ; it is metabolized in liver to active metabolite Trichloroethanol (which is also a microsomal hepatic enzyme inducer). Little used now as hypnotic.

It displaces warfarin from plasma protein binding sites.

2. Chlormethiazole :

- It may be used as hypnotic in elderly.
- It may also be used IV for status epilepticus.
- It is a thiamine analogue.
- It enhances GABA actions.

3-Alpha 2-Adrenoreceptor Agonists

1- Clonidine

- Antihypertensive.
- Was used for the treatment of panic attacks.
- Has been useful in suppressing anxiety during the management of withdrawal from nicotine and opioid analgesics.
- Withdrawal from clonidine, after long use, may lead to a life-threatening hypertensive crisis.

2- Dexmedetomidine

It is used for sedation in mechanically ventilated adults, and it may reduce time needed for extubating patients, and reduce the time of ICU stay.

4- β-Adrenoreceptor Antagonists

(e.g., Propranolol)

- Used to treat some forms of **anxiety**, particularly when physical (autonomic) symptoms (sweating, tremor, tachycardia) are severe.
- Adverse effects of propranolol may include lethargy, vivid dreams, hallucinations, bronchospasm, **bradycardia**, **hypoglycemia** with insulin, and hyperlipidemia.

5- Antihistaminic drugs (H1 receptor blockers)

❑ Certain antihistaminic agents including diphenhydramine, hydroxyzine, & promethazine are **sedating.**

➢ Diphenhydramine is used as over-the-counter sleep aids (for **children** with insomnia).

Thank You