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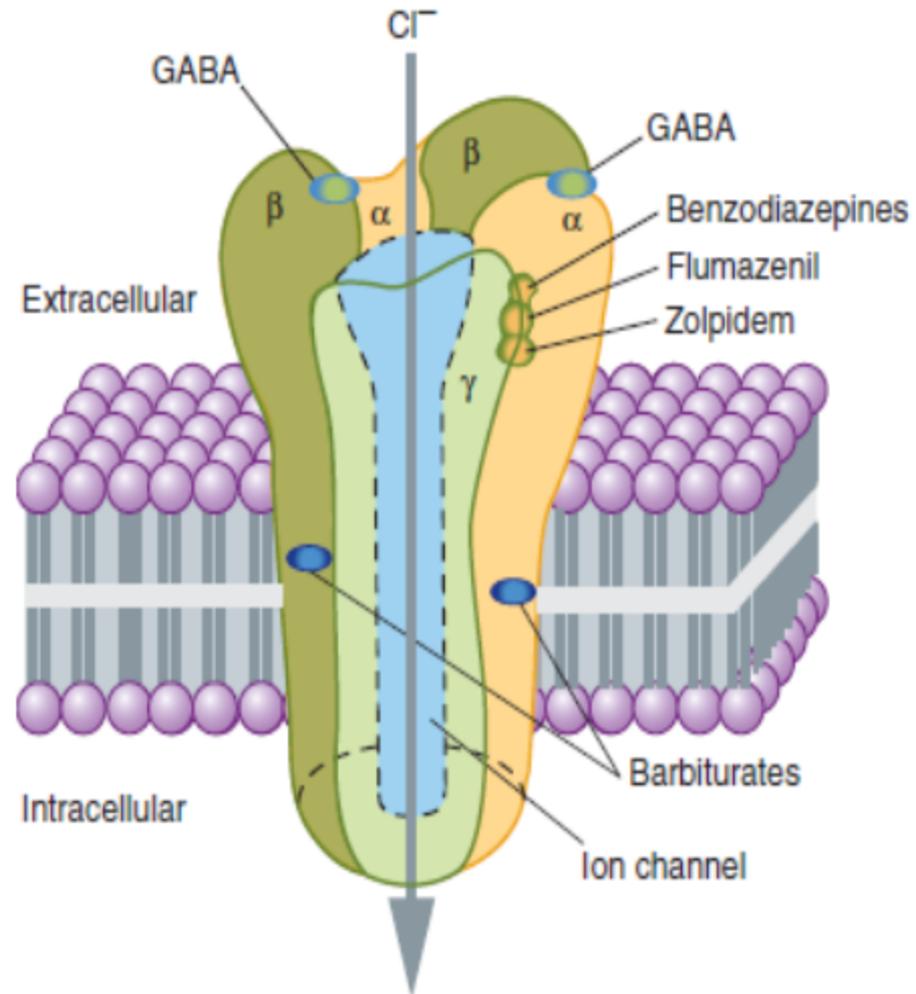
Sedatives & hypnotics (part two)

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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 & CNS depression
- **Barbiturates** also can **block** neuronal **Na⁺ channels** & block the excitatory **NMDA receptors** of glutamate.
- **Barbiturates** in high doses act as GABA mimetic.



Pharmacological actions of barbiturates

Dose-dependent CNS depression including:

1. Sedation
2. Relief of anxiety
3. Amnesia
4. Hypnosis
5. Anticonvulsant action
6. Skeletal m. relaxation
7. Anaesthesia
8. Coma
9. Respiratory depression (steeper dose-response relationship than benzodiazepines).
10. Additive CNS depression with ethanol & other CNS depressants (e.g., opioids and general anaesthetics) 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**).
- Alkalinization of urine (by I.V. sodium bicarbonate) increases urinary excretion of barbiturates . This used for management of acute barbiturate toxicity.

Therapeutic uses of barbiturates

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

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**, **fracture reduction** and elective **intubation**).

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

Adverse effects of barbiturates

1. Dose dependent CNS depression.
2. Drug hangover: feeling of tiredness in the morning.
3. In toxic doses: respiratory depression, Cardiovascular collapse, and coma. **Death** occurs due to respiratory failure.
4. Barbiturates **induce the P450 system** (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).
8. **Abrupt withdrawal** from barbiturates may cause **tremors**, **anxiety**, weakness, **restlessness**, nausea and **vomiting**, **seizures**, **delirium**, and **cardiac arrest**.

Acute Barbiturates poisoning

Manifestations:

Deep **coma** , **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 pH of the urine alkaline via using **IV. sodium bicarbonate**
- 4- In severe cases, hemodialysis is done.

Buspirone

- It is a **partial 5HT_{1A}** (serotonin) receptor **agonist**.
- It has no relation to BZD receptor or GABA.
- Its **anxiolytic** effect appear after 2-4 weeks of administration. So, it is **suitable for chronic anxiety** but not acute anxiety states.
- Buspirone is **not effective in severe anxiety** like panic attacks.
- It has **no hypnotic or anticonvulsant effects**.
- **Tolerance does not occur**, little abuse & **no withdrawal symptoms**.
- It is **highly** bound to plasma protein and metabolized by **CYP 3A4**.
- ❑ Side effects: **headache**, nausea, drowsiness, **minimal sedation**, **tachycardia**, palpitations, GI distress and **paresthesias** may occur.
- ❑ Buspirone causes a dose-dependent pupillary constriction (**miosis**).
- ❑ **Ipsapirone** is a selective 5-HT_{1A} receptor partial agonist. It has both **antidepressant** and **anxiolytic** effects.

Melatonin, Ramelteon and tasimelteon

- ❑ Ramelteon (Synthetic tricyclic analog of melatonin) is a **hypnotic drug** 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 hepatic patients.
- Ramelteon has **no rebound insomnia** & little withdrawal symptoms.
- Ramelteon has minimal potential for abuse.
- Melatonin is used **orally** or **sublingual**. It is **safe for children**.
- **Adverse effects** include **dizziness**, fatigue, **endocrine changes** (**increases prolactin** and **decreases testosterone**).
- Ramelteon is metabolized by **CYP1A2** and **CYP2C9** (drug interactions).

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 < 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. Post traumatic vertigo or headache are common.

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

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

Thank You

