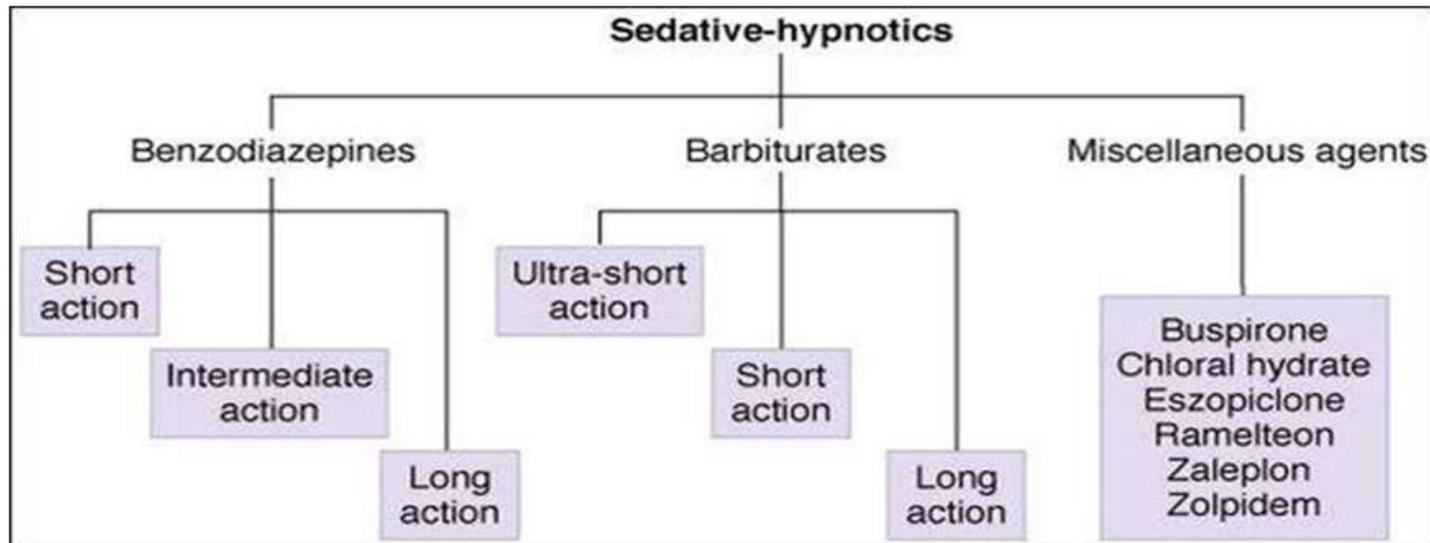


➤ **Anxiolytic agents (sedatives)** are the drugs that reduces tension, anxiety and **calms the patients** with minimum effect on the mental or motor functions.

➤ **Hypnotics** induce **sleep**.



## 1. *Barbiturates*

*Long acting*

Phenobarbitone

*Short acting*

Butobarbitone

Pentobarbitone

*Ultra-short acting*

Thiopentone

Methohexitone

## 2. *Benzodiazepines*

*Hypnotic*

Diazepam

Flurazepam

Nitrazepam

Alprazolam

Temazepam

Triazolam

*Antianxiety*

Diazepam

Chlordiazepoxide

Oxazepam

Lorazepam

Alprazolam

*Anticonvulsant*

Diazepam

Lorazepam

Clonazepam

Clobazam

## 3. *Newer nonbenzodiazepine hypnotics*

Zopiclone,

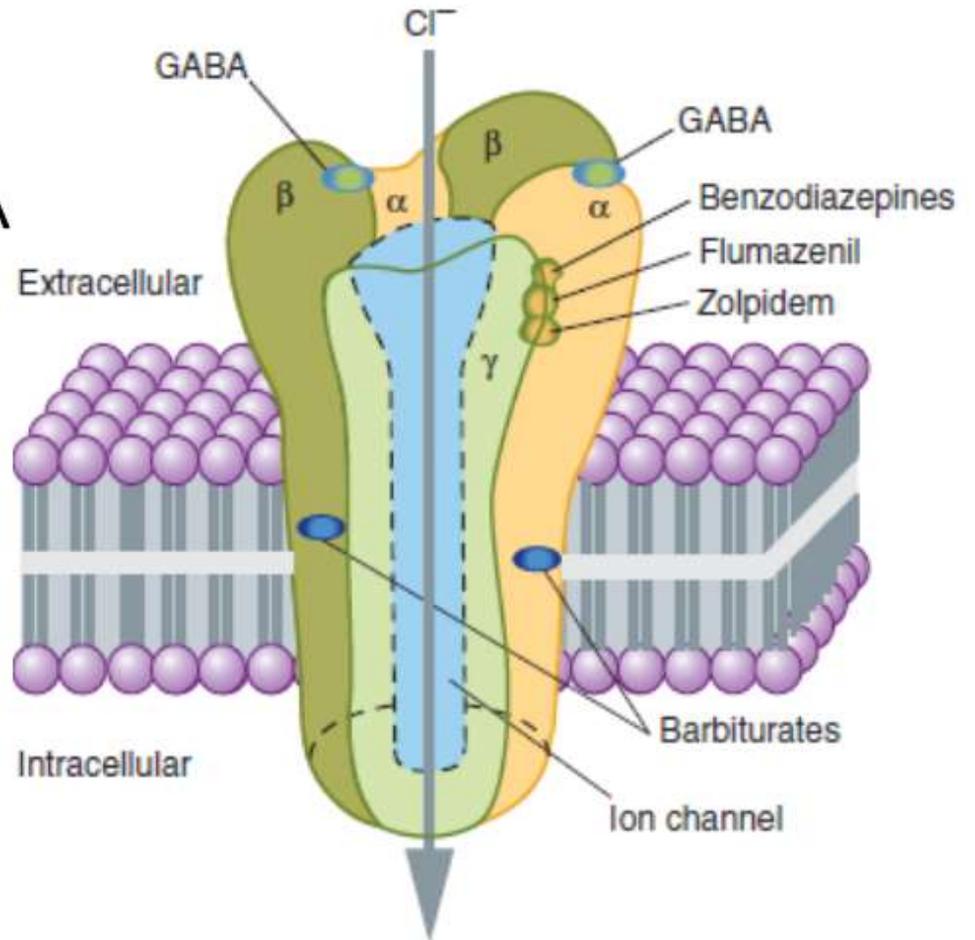
Zolpidem

Zaleplon

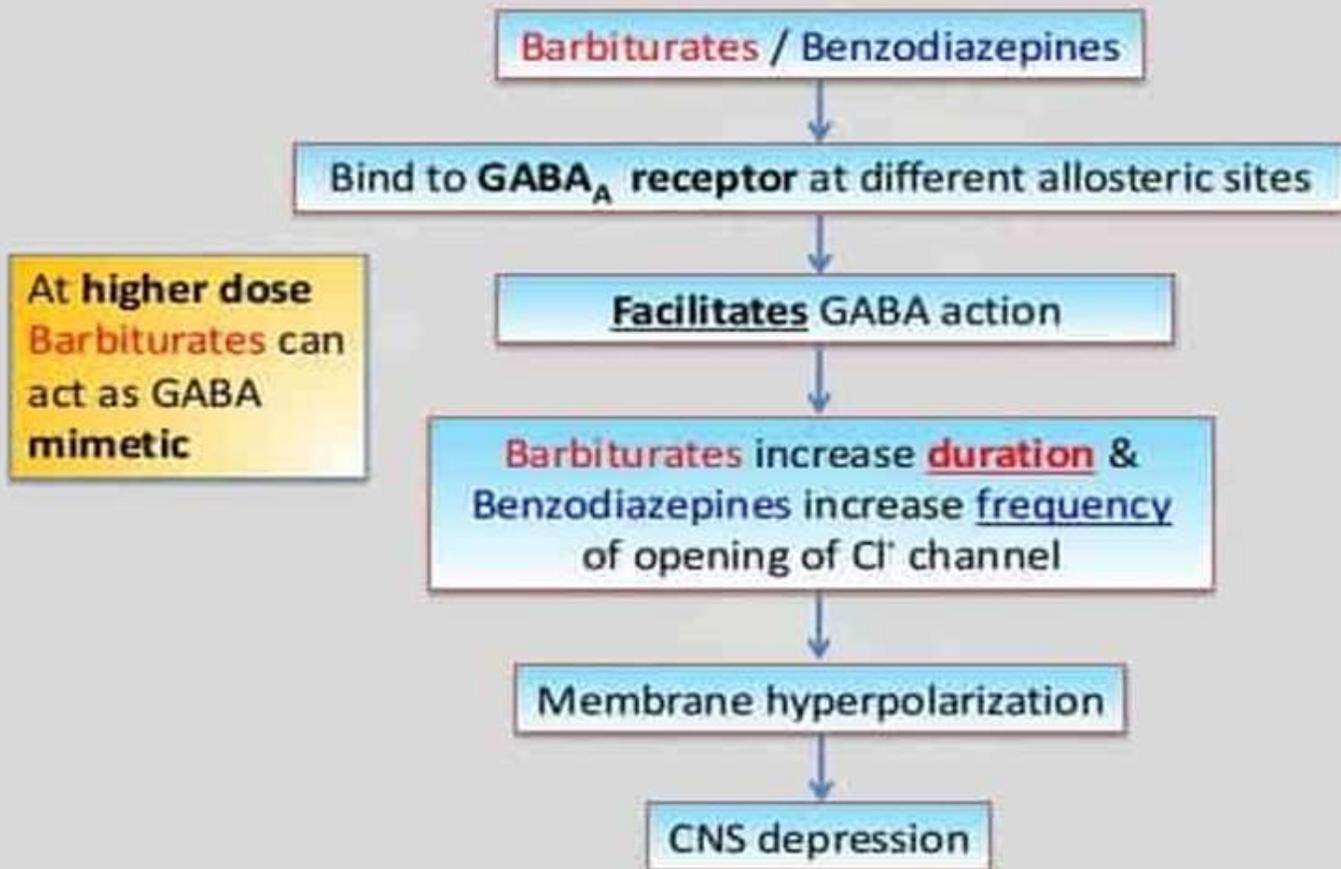
# Barbiturates

**Barbiturates** Bind to a specific **barbiturate receptor** on the **GABA<sub>A</sub>** 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<sup>+</sup> channels, & block the excitatory NMDA receptors of glutamate.**



# Mechanism of Action



## Barbiturates

Pharmacokinetics	<p>1-They are weak acidic drugs, absorbed orally.</p> <p>2- redistribute in the body</p> <p>3- metabolized in the liver</p> <p>4- induce P450 microsomal enzymes</p> <p>5- inactive metabolites are excreted in the urine.</p> <p>6- Alkalinization of urine helps their excretion (IV sodium bicarbonate is used for management of acute barbiturate toxicity)</p> <p>7- readily cross the placenta and can depress the respiratory center of the fetus.</p>
Therapeutic uses	<p><b>1- Anesthesia :</b>(The ultra-short acting barbiturates, such as thiopental, are used intravenously to induce general anesthesia.)</p> <p><b>2- Treating anxiety and insomnia (BZD are preferred now):</b></p> <p>a- used as mild sedatives to relieve anxiety, nervous tension, and insomnia (amobarbital).</p> <p>b- Barbiturates suppress REM sleep significantly.</p> <p><b>3- Anticonvulsant: (phenobarbital, mephobarbital):</b></p> <p>a- Phenobarbital is used in long-term management of tonic- clonic seizures, status epilepticus, and eclampsia.</p> <p>b- Primidone is also used for seizure disorders and tremors.</p> <p>c- The anticonvulsant doses are less than hypnotic doses and doses used for anaesthesia.</p> <p><b>4- Treatment of young children with recurrent febrile seizures:</b></p> <p>a- phenobarbital can depress cognitive performance in children</p> <p>b- drug should be used cautiously.</p> <p><b>5- Treatment of neonatal jaundice:</b>(Stimulation of microsomal hepatic enzymes by phenobarbital can accelerate bilirubin metabolism.</p> <p><b>6- Methohexital</b></p> <p>a- is used for procedural sedation of short duration</p> <p>b- e.g. cardioversion and pediatric outpatient surgery, fracture reduction for elective intubation).</p> <p><b>7- Butalbital:</b>( is used for the treatment of headache disorders.)</p>
Adverse effects of barbiturates	<p><b>1- Dose dependent CNS depression:</b>(Barbiturates cause drowsiness, vertigo, impaired concentration, etc.)</p> <p><b>2- Drug hangover:</b> (Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes.)</p> <p><b>3- In toxic doses</b> ( respiratory depression, Cardiovascular collapse, and coma. Death occurs due to respiratory failure)</p> <p><b>4- induce the P450 system</b> (affect metabolism of many drugs (drug-drug interactions)).</p> <p><b>5- increase porphyrin synthesis</b> (C.I : in patients with porphyria)</p> <p><b>6- behaviour change in children</b></p> <p><b>7- tolerance , dependence, addiction</b> (more than BZD)</p> <p><b>8- Abrupt withdrawal</b> (anxiety, restlessness, delirium, seizures, weakness, vomiting , cardiac arrest )</p>

## **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	Melatonin and Ramelteon	Orexin receptor antagonists
	<p>1-It selectively binds to SHT1A (serotonin) receptor acting as a partial agonist.</p> <p>2- It has no relation to BZD receptor or GABA inhibitory neurotransmitter.</p> <p>3- Ipsapirone:</p> <p>a- one is a selective 5-HT1A receptor partial agonist.</p> <p>b- It has both antidepressant and anxiolytic effects</p>	<p>1- Both melatonin and Ramelteon are agonists at MT 1 and MT 2 melatonin receptors located in the brain.</p> <p>2- The drug has no direct effects on GABAergic neurotransmission in the CNS (Little CNS depression).</p> <p>3- Ramelteon (Synthetic tricyclic analog of melatonin)</p>	<p>1- orexin receptor antagonists), which include Almorexant and suvorexant.</p>
	<p>1- Its anxiolytic effect does not appear before 2-4 weeks of its administration.</p> <p>2- it is highly bound to plasma protein</p> <p>3- metabolized in the liver by CYP 3A4</p> <p>4- Tolerance to its effect does not occur, little potential to abuse and no withdrawal symptoms develop after abrupt withdrawal.</p>	<p>1-Melatonin is used orally or sublingual</p> <p>2- It is safe for children.</p> <p>3- It has no rebound insomnia or significant withdrawal symptoms.</p> <p>4- Ramelteon has minimal potential for abuse, and regular use does not result in dependence</p>	<p>1- Orexin A and B are peptides that are involved in the control of wakefulness and that are silent during sleep.</p> <p>2- Orexin levels increase in the day and decrease at night.</p> <p>3- Loss of orexin neurons is associated with narcolepsy (daytime sleepiness).</p> <p>4- Animal studies show that orexin receptor antagonists have sleep-enabling effects.</p>
	<p>1- suitable for chronic anxiety</p> <p>2- <u>not</u> effective in severe anxiety like panic attacks</p> <p>3- <u>not</u> effective in acute anxiety states.</p> <p>4- It has <u>no</u> hypnotic or anticonvulsant effects.</p>	<p>1- novel hypnotic drug specifically useful for patients who have difficulty in falling asleep.</p>	<p>1- A new class of hypnotics (orexin receptor antagonists)</p> <p>2- Suvorexant was approved for use as hypnotic by FDA.</p>
	<p>1- CNS :headache, nausea, drowsiness but sedation is minimal.</p> <p>2- paresthesias may occur.</p> <p>3- tachycardia</p> <p>4- eye: causes a dose-dependent pupillary constriction (miosis).</p> <p>5- Other : palpitations, GI distress</p>	<p>1- dizziness</p> <p>2- fatigue</p> <p>3- endocrine changes (increases prolactin and decreases testosterone).</p>	

Miscellaneous sedative hypnotics

	1- Chloral hydrate	2.Chlormethiazole	Alpha 2-Adrenoreceptor Agonists		β-Adrenoreceptor Antagonists	5- Antihistaminic drugs
			1- clonidine	2- 2- Dexmedetomidin		
<b>Note</b>	<p>1- it is metabolized in liver to active metabolite Trichloroethanol (which is also a microsomal hepatic enzyme inducer).</p> <p>2- It displaces warfarin from plasma protein binding sites.</p>	<p>1- It is a thiamine analogue.</p> <p>2- It enhances GABA actions.</p>			e.g., Propranolol)	H1-blockers as diphenhydramine
<b>Use</b>	<p>1-Little used now as hypnotic.</p>	<p>1- It may be used as hypnotic in elderly.</p> <p>2- It may also be used IV for status epilepticu</p>	<p>1- Antihypertensive</p> <p>2- Has been used for the treatment of panic attacks.</p> <p>3- Has been useful in suppressing anxiety during the management of withdrawal from nicotine and opioid analgesics</p>	<p>1- It is used for sedation in mechanically ventilated adults</p> <p>2- it may reduce time needed for extubating patients</p> <p>3- reduce the time of ICU stay.</p>	<p>Used to treat some forms of anxiety, particularly when physical (autonomic) symptoms (sweating, tremor, tachycardia) are severe.</p>	<p>1- can be used as sleep aids for children with insomnia.</p>
<b>•Adverse effects</b>	<p>1- It is a gastric irritant</p>		<p>Withdrawal from clonidine, after long use, may lead to a life-threatening hypertensive crisis.</p>		<p>1- lethargy,</p> <p>2- vivid dreams</p> <p>3- hallucinations</p> <p>4- bronchospasm,</p> <p>5- bradycardia</p> <p>6- hypoglycemia with insulin</p> <p>7- hyperlipidemia.</p>	

## Treatment of anxiety disorders

<b>A- Stress anxiety disorder:</b>	1- treated by BDZs: for short- term relief; resolve < 1 month. 2- Beta blockers can be used
<b>B- Social anxiety and situational anxiety disorder</b>	1- Beta-adrenergic blockers e.g. propranolol 2- Long term benefit from SSRIs
<b>C-Panic attacks</b>	1- BDZs (alprazolam) for short-term relief 2- <b>SSRIs</b> antidepressants e.g. paroxeti or <b>TCA</b> s e.g. clomipramine for long-term control
<b>D- Phobias</b>	1-Phobias are treated by Behavioral therapy 2- drugs like Alprazolam (acute), or SSRIs (long-term).
<b>E-Generalized anxiety disorder</b>	1-BDZs: for acute symptoms or for chronic use. 2- Buspirone : for chronic control esp. in elderly. 3- Antidepressants esp. SSRIs are also helpful
<b>F- Obsessive-compulsive disorder (OCD)</b>	1- Psychotherapy 2-Antidepressants e.g Clomipramine or SSRIs. 3- <b>BDZs are not helpful in OCD</b>
<b>G- Post-traumatic stress disorder (PTSD):</b>	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  2- SSRIs: paroxetine for long term control .  3- Other antidepressants TCAs may also be used.

قف دُونَ رأيك  
ففي الحياة  
مُجاهدا  
إلى الحياة عقيده  
وجهاد

