	Benzodiazepines (BDZ)	Barbiturates
Examples	**Short Acting (<5 hrs):** Midazolam **Intermediate acting (5-24 hrs):** Lorazepam, Temazepam **Long acting (>24 hrs):** Diazepam	**Ultrashort acting:** Thiopental (15-20 min) **Long acting:** Phenobarbital (6-8 hrs)
Pharmacokinetics	**Absorption:** rapid orally **Distribution:** -well distributed to all tissues -Redistributed from CNS to blood (contribute to its action termination in CNS). **Metabolism (in liver):** -**Long acting** drugs by **oxidation**→ **active** metabolites→ long duration of action -**Short acting** drugs by **conjugation**→ **inactive** metabolites→ cleared by kidney→ short duration of action	**Absorption:** rapid orally, Thiopental IV **Distribution:** -well distributed to all tissues -**Thiopental**, a short-acting, highly soluble barbiturate, is rapidly absorbed, redistributed, and metabolized into an inactive form. -**Phenobarbital**, less soluble, is slowly absorbed and redistributed. **-Induce CYP450 enzymes.**
MOA	-Binds to **another site** on GABA receptor and **enhances GABA action** on **GABA A receptor**→↑Cl- influx→ Hyper-polarization & inhibition -↑**Frequency** of Channel opening -There are 16 subtypes of these protein subunits, which is composed of α, β, γ subunits, GABA A receptors mediate the effects of drugs that bind to them	**-Enhance GABA action** (similar to BDZ), or **acts directly on GABA receptor** →↑Cl influx → Hyper-polarization & inhibition -↑**Duration** of Channel opening -**Non-selective**→ In high doses cause CNS and Medullary depression
Pharmcological effects	-Anxiolytic (low dose) -Hypnotic (higher doses) -Muscle relaxant -Anti-convulsant -**Anterograde amnesia:** amnesia from the onset of action to termination	Anxiolytic -Hypnotic (+++) -Muscle relaxant -**Anesthetic** (Thiopental) -**Anti-convulsant** (Phenobarbital): in tonic clonic convulsions -Generalized CNS depression
Uses	**-Anxiety disorders:** GAD, panic attacks and phobia **-Insomnia** (temazepam) -**Anesthetic** (Midazolam): in cases of surgery and endoscopy **-Anti-convulsant** (Diazepam): IV for status epilepticus & drug-induced seizures **-Muscle spasms** (Diazepam)	**Phenobarbital:** -TTT of Grand mal epilepsy -TTT of **physiological jaundice** in neonates (CYP450 Inducer)→ Activate hepatic **glucuronyl-transferase** and **fasten metabolism.** **Thiopental:** IV Anesthetic
S/E	-Sedation, **amnesia** and dull attention **(interfere with learning ability)** -**Tolerance** and **dependance** (↓GABA sensitivity and ↑excitatory glutamate) -**Rebound insomnia** after discontinuation **-Hungover** with long acting drugs -**Apnea** after **rapid IV** injection **(flumazenil is the antidote)** **Flumazenil:** -Competitive antagonist at BDZ receptors. -Reverses the CNS effects from BDZ overdose. -Speeds recovery from BDZ effects in anesthetic & diagnostic procedures.	-Drowsiness, impaired concentration -Dependence. -Respiratory and myocardial depression -CYP450 induction→ drug interaction

	Other anxiolytic drugs	Other hypnotic drugs			
		Z-Drugs	Ramelteon	Orexin receptor antagonist	Anti-histamines
Examples	Buspirone	Eszopiclone	———	Suvorexant	Doxepin (TCA) Diphenhydramine
MOA	-partial agonist on 5-HT1A receptors -full agonist at the presynaptic 5-HT1A auto- receptors	**same as BDZ** but have a different allosteric binding site	selective agonist at melatonin MT1 and MT2 receptors **(involved in sleep)**	-**Orexins:** neuropeptides that activate orexin receptors 1 & 2 in the lateral hypothalamus, **promoting arousal and wakefulness.** -**Blocked**→ promote sleep	-**H1 receptor inhibition** blocks histamine activity, leading to sedation. -Atropine-like action
Uses/ Advantages	**-No dependance** **-Delayed onset (≥2 weeks):** used in TTT of chronic GAD **-Anxiolytic of choice in elderly**	-replaced older BDZ for the TTT of insomnia -Fewer adverse effects than the older BDZ. -Less potential for tolerance and dependence. -Shorter duration of action→ Doesn't cause hungover - Target specific subunits, especially those with α-1. -BDZ are less selective, affecting a wider range of $GABA_A$ receptors and causing more side effects	-Sleep onset-Insomnia (Difficulty falling asleep)	———	1st gen drugs (cross BBB) are used as (OTC) to treat mild insomnia.
S/E	Headache, nervousness, tachycardia.	———	dizziness and fatigue		**Atropine-like action**→ less useful than BDZ and non-BDZ

Benzodiazepines Vs Barbiturates

-BDZ work **only in the presence of GABA** released by neurons, the depth of CNS depression is limited. Therefore, the BDZ exhibit a **ceiling effect** whereby greater doses do not produce significantly greater effects and do not depress the brain to the point of anesthesia and death.

-In contrast to BDZ, the barbiturates also act to directly increase chloride influx **in the absence of GABA**. For this reason, barbiturates **do not exhibit a ceiling effect** and can produce severe respiratory depression and death after administration of a large dose.