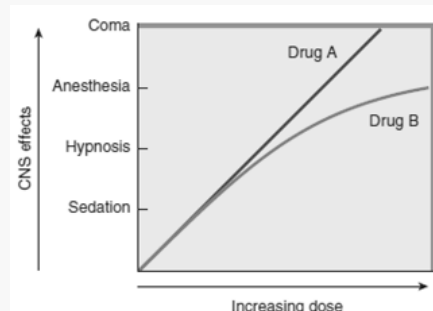


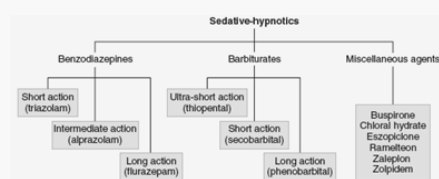
Introduction:

Sedation:	Reduction of anxiety
Hypnosis:	Induction of sleep
Sedative:	Synonym=anxiolytic, Reduces anxiety and has a calming effect
Hypnotic:	Produces drowsiness, Induces and maintains sleep

Dose-Responsive Curve for S-H Agents:



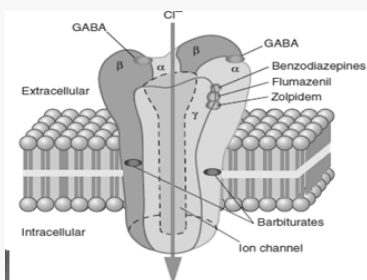
Classification:



Benzodiazepines:

- > **Short-acting:** Triazolam
- > **Intermediate-acting:** alprazolam, lorazepam, oxazepam, temazepam
- > **Long acting:** pentobarbitone, phenobarbitone, secobarbitone

Mechanism of Action:



MOA: Benzodiazepines

Receptors for BZ present = Thalamus, limbic structures, cerebral cortex
BZ receptors =
 > Part of GABA^A receptor chloride ion channel macromolecular complex
 > Major GABA^A receptor isoform
 > Five subunits: 2α1, 2β2, and 1γ2

Benzodiazepines bind between **α1 and γ2 subunits**

Increase the **FREQUENCY** of GABA-mediated chloride ion opening

MOA: Barbiturates:

> Depress neural activity in midbrain reticular formation
 > Bind to **α and β subunits of the GABA^A receptor**
 > Prolong the action of GABA and glycine

Increase the **DURATION** of GABA-mediated chloride ion channel opening

> may also block glutamate receptors and sodium channels at higher doses

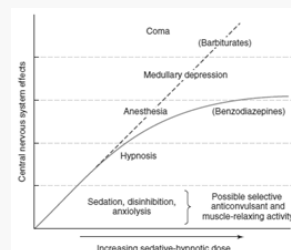
MOA: Other Agents:

Zolpidem, Zaleplon, Eszopiclone = **not Benzodiazepines**
 > Bind to benzodiazepine receptor (BZ1 or ω1)
 More selective to GABA^A isoforms that contain α1 subunits
 - Fewer adverse effects than benzodiazepines
 - Minimal effects on sleep patterns, less likely to cause dependence
 > Increase the **FREQUENCY** of GABA-mediated chloride ion opening

Effects:

Sedation	Anticonvulsant actions	Tolerance
Hypnosis	Muscle relaxation	Psychological dependence - Compulsive use
Anaesthesia	Medullary depression	Physiological dependence - withdrawal symptoms if drug is discontinued

CNS Effects:



Clinical Uses:

- > Anxiety states
- > Sleep disorders
- > Anesthesia
- > Epilepsy
- > Alcohol withdrawal state

Adverse Effects:

Psychomotor Dysfunction:	Cognitive impairment, decreased psychomotor skills, daytime sedation
Additive CNS Depression:	Alcohol, antihistamines, antipsychotic agents, opioids, tricyclic antidepressants
Overdose:	CVS and respiratory depression, Antidote: Flumazenil

Pharmacokinetics:

> Most are lipid soluble, absorbed well from GIT

> May cross the placental barrier during pregnancy - may depress neonatal vital functions

> Detectable in breast milk - may exert depressant effects in nursing infant

> Metabolism by hepatic enzymes - renal function = no significant effect on elimination

Pharmacokinetics:

Benzodiazepines:

-Converted to active metabolites with long half-lives

--Potential for accumulation

-Lorazepam and oxazepam do not form active metabolites

-Metabolized mainly by CYP3A4

Barbiturates:

-Extensively metabolized

--Except pentobarbital

---Excreted partly unchanged in urine

Zolpidem: No active metabolites

Drug Interactions:

-Inducers/inhibitors of CYP3A4 interact with sedative hypnotics

--E.g. rifampicin (inducer), ketoconazole, cimetidine (inhibitors)

-Barbiturates induce metabolic enzymes

Atypical Sedative-Hypnotics:

Buspirone:

>Partial agonist at 5-HT^{1A} receptors

>Selective anxiolytic effects:

-Minimal CNS depressant effects = No anticonvulsant or muscle relaxation effect

>Minimal tolerance, dependence, and abuse potential

Ramelteon, Tasimelteon:

> Melatonin receptor agonists

>Minimal rebound or withdrawal symptoms

>Minimal abuse potential