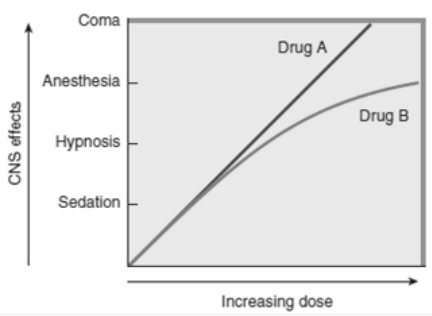
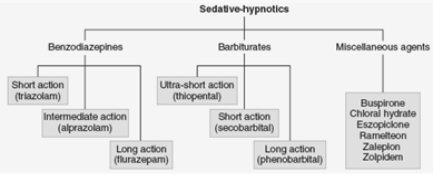
Introduction:

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

Dose-Responsive Curve for S-H Agents:



Classification:



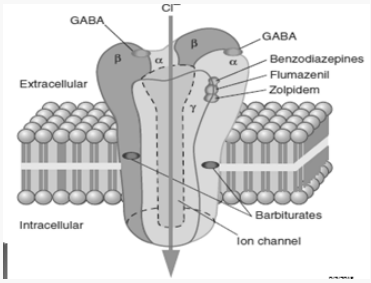
Benzodiazepines:

>**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 1Y2

Benzodiapines bind between **α1 and Y2 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 Benzaodiazepines**

>Bind to benzodiazepine receptor (BZ1 or ω1)

More selective to $GABA^A$ isoforms that contain α1 subunits

-Fewer adverse effects than benzodiazepines

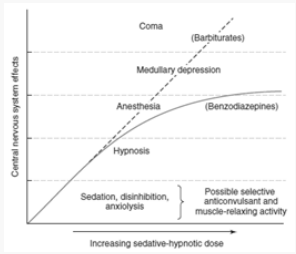
-Minimal effects on sleep patterns, less likely to cause dependence

>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 - withdrawl 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

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Pharmacokinetics:

> Most are lipid soluble, absorbed well from GIT

> May cross the placental barrier during pregnancy - may depressed 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

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