Sedative: A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced.

Hypnotic: A drug that induces and/or maintains sleep, similar to normal arousable sleep.

- The sedatives and hypnotics are more or less general CNS depressants with somewhat differing time-action and dose-action relationships.
- Those with quicker onset, shorter duration are preferred as hypnotics while more slowly acting drugs are employed as sedatives.

- Differentiate between sedative and hynotics.

Classification

1. *Barbiturates*

Long acting	*Short acting*	*Ultra-short acting*
Phenobarbitone	Butobarbitone	Thiopentone
	Pentobarbitone	Methohexitone

2. *Benzodiazepines*

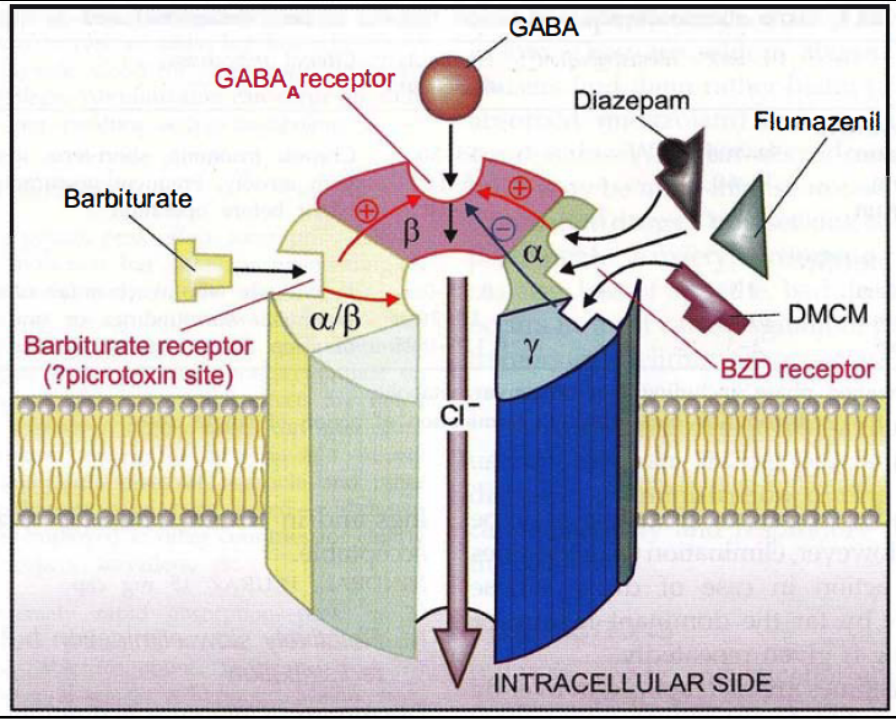
Hypnotic	*Antianxiety*	*Anticonvulsant*
Diazepam	Diazepam	Diazepam
Flurazepam	Chlordiazepoxide	Lorazepam
Nitrazepam	Oxazepam	Clonazepam
Alprazolam	Lorazepam	Clobazam
Temazepam	Alprazolam	
Triazolam		

3. *Newer nonbenzodiazepine hypnotics*

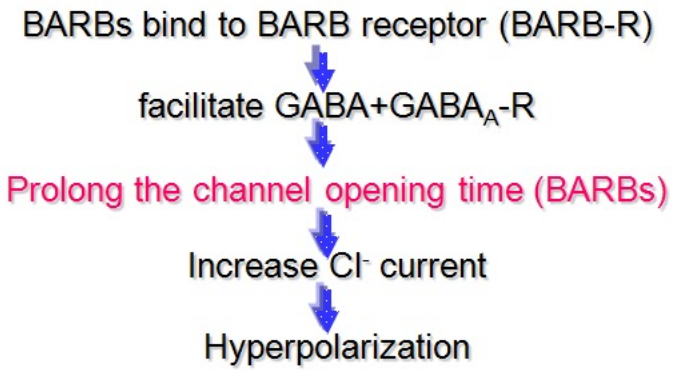
Zopiclone,	Zolpidem	Zaleplon

Barbiturates: Mechanism of Action

- Barbiturates appear to act primarily at the GABA:BZD receptor-Cl^- channel complex and potentiate GABAergic inhibition by increasing the lifetime of Cl^- channel opening induced by GABA.
- They do not bind to the BZD receptor, but bind to another site on the same macromolecular complex to exert the GABA-facilitatory action.



Barbiturates: MOA



Pharmacological action

CNS

- Produces dose dependent effects on CNS
- Sedation→ Sleep →Anaesthesia→ Coma

CVS

- Hypnotic dose (100-200 mg) slight fall in BP and HR

Respiration- depressed

Skeletal Muscle: reduce muscle contraction

Smooth muscle: decreased bowel tone and motility

Kidney: reduce urine flow

Use: Except for phenobarbitone in epilepsy and thiopentone in anaesthesia, barbiturates are seldom used now. As hypnotic and anxiolytic they have been superseded by BZDs.

Adverse Effect

- hangover (common when used as hypnotic)
- Mental confusion, impaired performance and traffic accidents may occur.
- Hypersensitivity
- Tolerance and dependence

Contraindication

- Liver and kidney disease.
- Severe pulmonary insufficiency, e.g. emphysema.
- Obstructive sleep apnoea.

Benzodiazepines

- Gained popularity over barbiturates as hypnotic and sedative. Why?
- BZDs have a high therapeutic index. Ingestion of even 20 hypnotic doses does not usually endanger life- there is no loss of consciousness (though amnesia occurs) and patient can be aroused; respiration is not so depressed as to need assistance.

Table 29.1: Some pharmacokinetic and clinical features of benzodiazepines used as hypnotics

Drug	*t½ (hr)**	*Redistribution\$*	*Hypnotic dose (mg)*	*Clinical indications*
I. LONG ACTING				
Flurazepam	50–100	–	15–30	Chronic insomnia, short-term insomnia
Diazepam	30–60	+	5–10	with anxiety; Frequent nocturnal awakening;
Nitrazepam	30	±	5–10	Night before operation
II. SHORT ACTING				
Alprazolam	12	+	0.25–0.5	Individuals who react unfavourably to
Temazepam	8–12	+	10–20	unfamiliar surroundings or unusual timings
Triazolam	2–3	±	0.125–0.25	of sleep. Sleep onset difficulties.

* t½ of elimination phase, including that of active metabolite
\$ + indicates that redistribution contributes to termination of action of single dose

MOA

BDZs bind to BDZ receptor

↓

facilitate GABA+$GABA_A$-R

↓

Cl^- channel open frequency ↑ (BDZs)

↓

↑ Cl^- current

↓

Hyperpolarization

Uses

- As hypnotic
- As anxiolytic and for day-time sedation
- As anticonvulsant (Clonazepam, diazepam, nitrazepam and Flurazepam)
- As centrally acting muscle relaxant (clonazepam, diazepam)
- For preanaesthetic medication, i.v. anaesthesia and conscious sedation
- Alcohol withdrawal in dependent subjects.

Adverse Effect

- dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time-impairment of psychomotor skills (should not drive).
- Weakness, blurring of vision, dry mouth and urinary incontinence are sometimes complained.

Chlordiazepoxide

- **Chlordiazepoxide**, trade name **Librium**, is a sedative and hypnotic medication of the benzodiazepine class.
- is a long-acting benzodiazepine drug.
- The drug has amnestic, anticonvulsant, anxiolytic, hypnotic, sedative and skeletal muscle relaxant properties.

MOA
Same as benzodiazepine

Uses:
Anxiety
Alcohol withdrawal syndrome

Flumazenil

- Benzodiazepine antagonist

Uses

- To reverse BZD anaesthesia- 0.3-1mg IV
- BZD overdose- 0.2 mg/min may be injected i.v. till the patient regains consciousness.

Adverse Effect

Agitation, discomfort, tearfulness, anxiety, coldness and withdrawal seizures are the occasional side effects.

Zolpidem

- a short-acting non benzodiazepine, It works quickly, usually within 15 mins, and has a short half-life of 2- 3 hrs.

MOA: increases the activity of GABA by binding to $GABA_A$ receptors at the same location as benzodiazepines.

Adverse Effect

Common side effect: drowsiness, dizziness, diarrhea, dry mouth, allergy , back pain, chest pain, heart palpitations, lethargy, sleep disorder

Indication

Insomnia (induces but not maintain sleep)

Dose: 5-10 mg /d po

*Flumazenil- also reverse zolpidem's sedative/hypnotic