Sedative- Hypnotics Drugs Pharmacology

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Sedative- Hypnotics

Sedatives:

- Drugs which reduce the excitement, anxiety and calm the patient without inducing the sleep and it may produce drowsiness. (Reduce the CNS activity)
- At large dose it may produce hypnotics
- Mainly act on limbic system which regulate the thought and mental functions

Hypnotics:

- Drugs which induce and maintain the normal sleep
- At high dose it may induce General Anesthesia
- Mainly act on Mid brain and Reticular Activating System which maintain the wakefulness.

Sedative- Hypnotics Classii=

Classification

1. Barbiturates

- Long Acting: Phenobarbitone
- Short Acting: Butobarbitone, Pentobarbitone
- Ultra Short Acting: Thiopentone, Methohexitone

2. Benzodiazepines:

- **Hypnotics:** Diazepam, Flurazepam, Nitrazepam, Alprazolam, Temazepam, Triazolam
- **Antianxiety:** Diazepam, Chlordiazepoxide, Oxazepam, Lorazepam, Alprazolam
- **Ant convulsion:** Diazepam, Lorazepam, Clonazepam, Clobazam

3. Newer nonbenzodiazepine hypnotics:

- Zopiclone, Zolpidem, Zaleplon

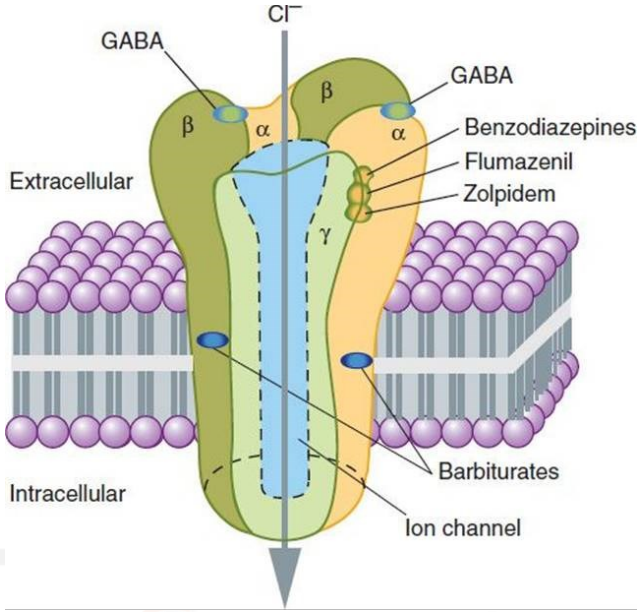
Sedative- Hypnotics

Barbiturates

- Gaba Mimetic action
- More neurological depression
- Low margin of safety
- respiratory and cardiovascular depression
- Suppression of REM sleep

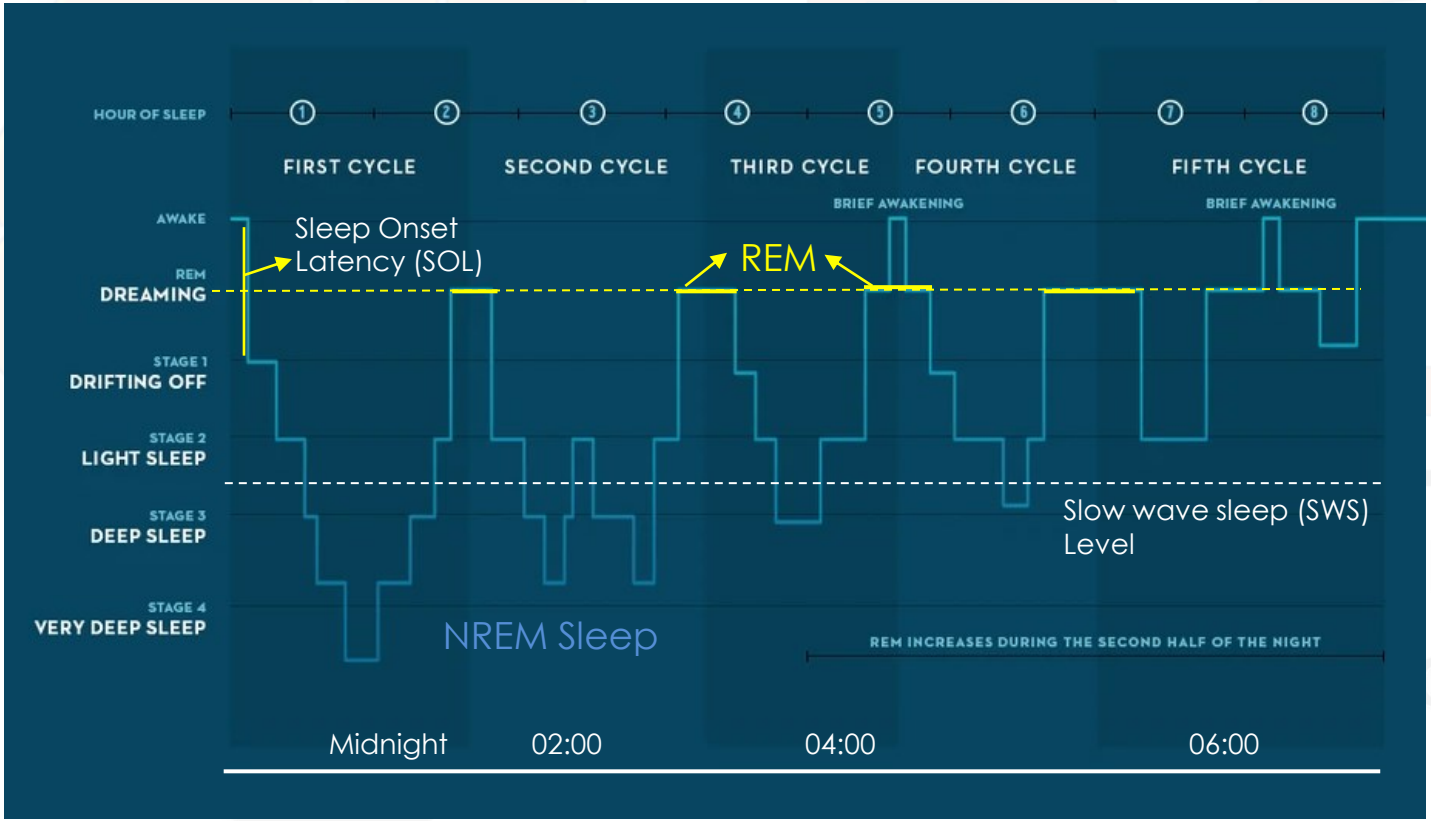
BDZs

- Gaba Facilitatory action
- Less neurological depression
- High Margin of safety
- No respiratory and cardiovascular effects on hypnotic dose
- No effect on REM Sleep



Sedative- Hypnotics

- Hypnograme



Sedative- Hypnotics

Stage 1 (Dozing)
- Lightest (1-7 min), 3-6% sleep time
- HR, Breath, eye movement slowdown
- Muscle relaxed or occasionally twitch
- EEG begin to slowdown

Stage 2 (Unequivocal Sleep)
- Light (10-25 min), 40-50 % sleep time
- HR, Breath slowdown, Muscle relaxed
- eye movement stop, Body temp drops
- Brain wave activity slow

Stage 3 (Deep Sleep)
- 20-40 min (Stage 3 & 4), 5-8% sleep time
- HR, Breath at low, Muscle relaxed
- Brain wave slowdown even more

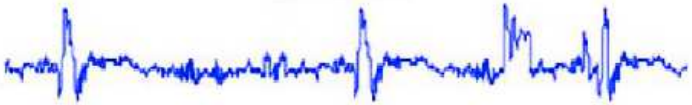
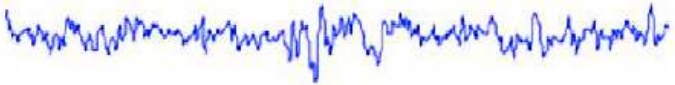
Stage 4 (Cerebral Sleep)
- Deepest sleep, mostly in 1st cycle, 10-20%
- 20-40 min, 5-8% sleep time
- HR, Breath at low, Muscle relaxed
- Brain wave slowdown even more

Stage 5 (REM)
- Rapid eye movemets
- Breathing, HR, BP increased
- Dreaming/nightmares

Sedative- Hypnotics

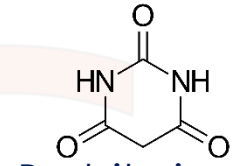
	REM (Paradoxical Sleep)	NREM (Slow Wave Sleep)
Eye Movement	Rapid	Non Rapid (Slow)
Electroencephalo-graph (EEG)	Similar to alert or awake person	Slow wave, V-wave, K-complexes
Vital function	Irregular	Normal, Stable
Body Function	Muscle Twitches	Muscle Relaxation
Dreaming	Common	Rare
Arousal	Hard to arouse but wake up spontaneously	Easily awakened
% Sleep (Adult)	20%	80%
Other		4 stages, must pass through this type of sleep first

Sedative- Hypnotics

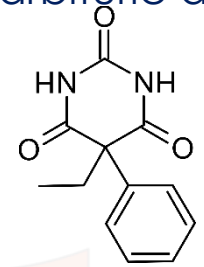
Sleep Stages (R&K)	EEG Signal
Wake	 Wake (Alpha 8-12 Hz)
Stage 1: N-REM	 N-REM S1 (Theta 4-7 Hz)
Stage 2: N-REM	 N-REM S2 (Sleep Spindles, K-complex) (12-14 Hz)
Stage 3: N-REM	 N-REM S3 (Delta 0-3 Hz)
Stage 4: N-REM	 N-REM S4 (Delta 0-3 Hz)
Stage 5: REM	 REM (Alpha, Beta, Theta)

Barbiturates

- Barbiturates are the Barbituric acid Derivatives.
- Barbituric acid as such is not a CNS depressant but its aklyl/aryl substituted at C-5 like phenobarbitone, pentobarbitone shows hypnotic effects.
- Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s, but are not used now to promote sleep or to calm patients.
- However, they are described first because they are the prototype of CNS depressants.



Barbituric acid



phenobarbitone

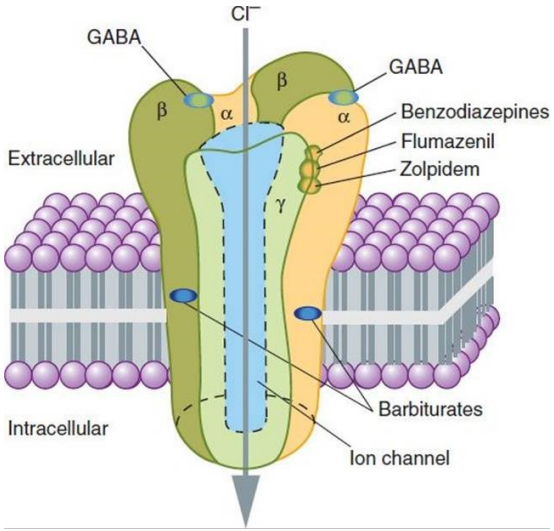
Barbiturates

- Long Acting: Phenobarbitone
- Short Acting: Butobarbitone, Pentobarbitone
- Ultra Short Acting: Thiopentone, Methohexitone

Barbiturates

Mode of Action

- Barbiturates bind with its particular site at GABA-A and potentiate the GABA-A mediated inhibitory action on CNS by increasing Cl- ion channel opening time.
- Barbiturates→GABA-A→increase Cl- conduction→hyperpolarization
- At high conc. It can directly open the channel (GABA mimetic action)
- Barbiturates also inhibit the cation conduction and inhibit the NMDA-mediated excitatory action



Barbiturates

Pharmacological Action

1. CNS:

- Dose dependent CNS depressant effects
- sedation → sleep → anaesthesia → coma.
- Barbiturates depress all areas of the CNS, but reticular activating system is the most sensitive; its depression is primarily responsible for inability to maintain wakefulness
- **At hypnotic dose-**
  - induce the sleep and duration
  - REM and stage 3, 4 sleep are decreased; REM-NREM sleep cycle is disrupted
  - rebound increase in REM sleep and nightmares
  - Hangover (dizziness, distortions of mood, irritability and lethargy) may occur in the morning after a nightly dose

Barbiturates

Pharmacological Action

1. CNS:

- **At Sedative dose-**
  - Smaller dose at daytime can produce drowsiness, reduction in anxiety and excitability.
  - Barbiturates can impair learning, short term memory and judgement.
  - They have no analgesic action; small doses may even cause hyperalgesia.
  - Euphoria may be experienced by addicts.

Barbiturates

Pharmacological Action

2. Respiratory- depressed

3. CVS- Depressed

4. Skeletal muscles- relaxed at anesthetic dose

5. **Smooth Muscles-** tone and motility decreased

6. **Kidney-** Barbiturates tend to reduce urine flow by decreasing BP and increasing ADH release. Oliguria attends barbiturate intoxication

Barbiturates

Pharmacokinetics

- Barbiturates are well absorbed from the g.i. tract. They are widely distributed in the body. The rate of entry into CNS is dependent on lipid solubility (Highly lipid soluble can easily and rapidly enters to the brain)
- They can cross the placenta and secrete in milk
- Plasma protein binding varies with the compound, e.g. thiopentone 75%, phenobarbitone 20%
- Redistribution occurs
- Primarily metabolized in liver by oxidation, dealkylation and conjugation. Their plasma t½ ranges from 12–40 hours and exreted through urine
- Low lipid soluble (Long acting) drugs excreted unchanged in urine

Barbiturates

Side Effects

- Idiosyncrasy
- Hypersensitivity Rashes, swelling of eyelids, lips
- Tolerance and dependence
- **Acute barbiturate poisoning** Mostly suicidal, sometimes accidental- Highly CNS depressant, CVS depressed, Respiratory Depressed
  - Treatment: Gastric lavage (Activated Charcoal)
  - Supportive measures
  - **Alkaline diuresis**: with sodium bicarbonate 1 mEq/kg i.v. with or without mannitol is helpful only in the case of long acting barbiturates which are eliminated primarily by renal excretion.
  - Haemodialysis and haemoperfusion (through a column of activated charcoal or other adsorbants) is highly effective in removing long-acting as well as short-acting barbiturates

Barbiturates

Drug Interaction

- Barbiturates are the metabolic enzyme inducer – induce the metabolism of warfarin, steroids (including contraceptives), tolbutamide, griseofulvin, chloramphenicol, theophylline
- Additive action with other CNS depressants —alcohol, antihistamines, opioids, etc.
- Sodium valproate increases plasma concentration of phenobarbitone.
- Phenobarbitone decreases absorption of griseofulvin from the g.i.t

Uses

- Phenobarbitone in epilepsy
- Thiopentone- General Anaesthesia

Benzodiazepines

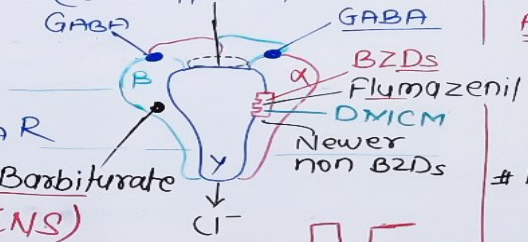
BENZODIAZEPINES (BZDs) PHARMACOLOGY

↳ BzDs → CNS Depressant → Sedative, Anxiolytics, Facilitate Sleep, Antiepileptics, & Reduction in muscle tone

Site of Action: - Midbrain (RAS), Limbic System, Medullary Site, & Cerebellum

MOA: → BZDs → BZD Site ($GABA_A$ Receptor)

GABA Facilitatory
↑ Frequency of opening of Cl^- channel
↑ GABA binding to $GABA_A$ R



PHARMACOLOGICAL ACTION (CNS)

Sedation
Anti-Anxiety → Limbic System
Hypnotic (sleep) → Quick Sleep, ↑ Sleep duration, Time spent in Stage-2 ↑ but ↓ Stage 3 & 4, ↓ REM Time but ↑ frequency (*Except Nitrazepam)
Centrally Acting muscle relaxant → Diazepam and Clonazepam have marked action
Anti-Convulsant – Reduce the Excessive neuronal Firing (Diazepam, Clonazepam, Nitrazepam, Lorazepam, etc)

PKINETIC PROFILE

Oral Active, Abs ∝ Lipid Solubility
Protein binding → Lorazepam – 10 %, Diazepam – 99 %
Widly distributed in body
Metabolized by Liver (CyP3A4 & CyP2C19) → Dealkylation & Hydroxylation

ADR

Safer than Barbiturates

At hypnotic dose → Dizziness, Vertigo, Ataxia, disturbed in psychomotor skill
Mild withdrawal Symptoms - Anxiety, restlessness, insomnia, etc
Teratogenic toxicity

INTERACTION

+ Alcohol → ↑↑ CNS Depression
+ Sod Valproate → Psychotic Action
+ Metabolic Inhibitors (ketoconazole, etc) → ↓ Metabolism of BZDs

PC
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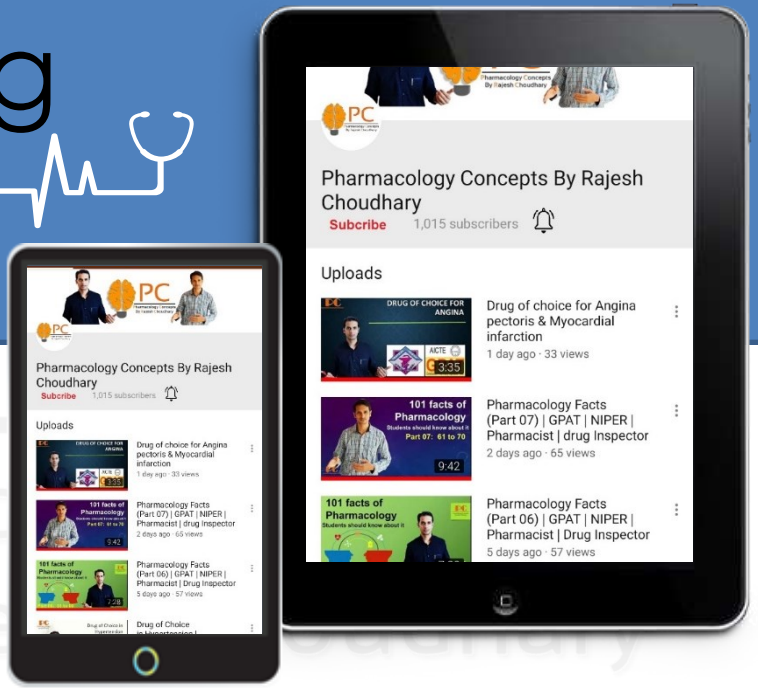
By Rajesh Choudhary

Thanks for Watching



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