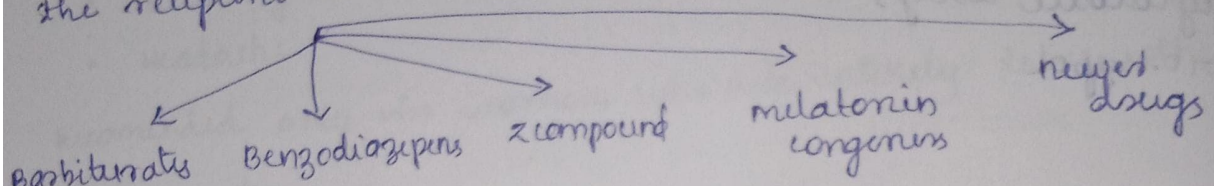
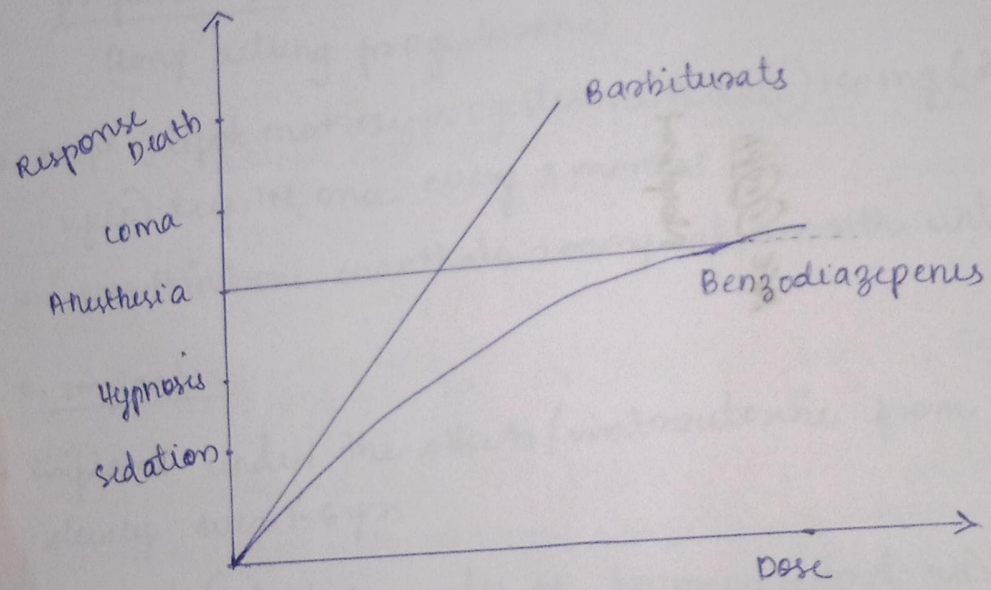
SEDATIVE HYPNOTICS & ANTI-ANXIETY DRUGS

A sedative drug decreases activity, moderate excitement and calms the recipient

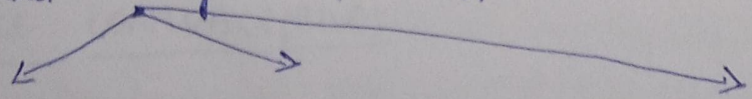
A hypnotic drug produces drowsiness and facilitates onset and maintenance of a state of sleep that resembles natural sleep in its electroencephelographic characteristics and from which the recipient can be aroused easily.





1. BARBITURATES

- once used extensively as sedative hypnotic
- Replaced by much safer benzodiazepenes.
- described as they are prototype of CNS depressants



long acting	short	ultrashort
• phenobarbitone	• Butobarbitone • pentobarbitone	• Thiopentone • methohexitone

MOA

- GABA mimetic
- Acts on GABA : BZD receptor - chloride channel complex
- Prolongs the duration of opening of chloride channels.
- Thus potentiate GABAergic inhibition

→ pharmacological properties

- Reversibly depress activity of excitable tissue
- CNS : most sensitive
  - dose dependend depression
  - sedation → sleep → Anasthesia → coma.
  - GABA facilitatory & GABA mimetic
  - ↑ binding of GABA & benzodiazepines
  - inhibit excitatory AMPA receptors
  - Very high concentration : depress Na^+ & K^+ channels
- sleep
  - ↑ total sleep time
  - Alter stages of sleep
  - ↓ sleep latency ; awakenings, REM & stages 3, 4
  - Tolerance on repeated dose
  - discontinuation → rebound insomnia
- CVS
  - ↓ BP, HR
  - Toxicity = marked BP fall
- Anticonvulsant action
  - 5 phenyl substituent (phenobarbital, mephobarbital)
  - High anticonvulsant : sedative hypnotic ratio
  - No tolerance to this
- pain
  - No analgesia, Hyperalgesia
  - ↓ pain threshold
- Respiration
  - depress respiratory drive & rhythm
- liver
  - microsomal enzyme inducer

- Tolerance
  - on mood, sedation, hypnosis > anticonvulsant
- Abuse & dependance :- euphoric effects.

- PK
  - well absorbed from GIT
  - wide distribution
  - cross placenta, secreted in milk

3 processes,
1. redistribution - Thiopintone
2. metabolism - short acting - by liver
3. excretion - long acting - unchanged in urine

- uses
  - induction of anesthesia & short surgical procedures
    - Thiopentone, methohexitone (IV)
  - Epilepsy
    - > phenobarbitone - grand mal, cortical focal, status epilepticus
    - > Thiopintone - status epilepticus
  - Hyperbilirubinemia, kernicterus
    - > phenobarbitone
  - Narco analysis | Brain mapping
    - > Thiopentone

- AE
  - > Hangover, Tolerance, dependence, confusion
  - > idiosyncrasy - paradoxical excitement (elderly)
    - porphyria precipitation
  - > HS rn - Asthma, urticaria, swelling of eyelids & lips, fatal exfoliative dermatitis

- C/I
  - Avoid long acting - renal dysfunction
  - Avoid short acting - hepatic dysfunction
  - Absolute C/I : porphyrias

→ Acute barbiturate poisoning

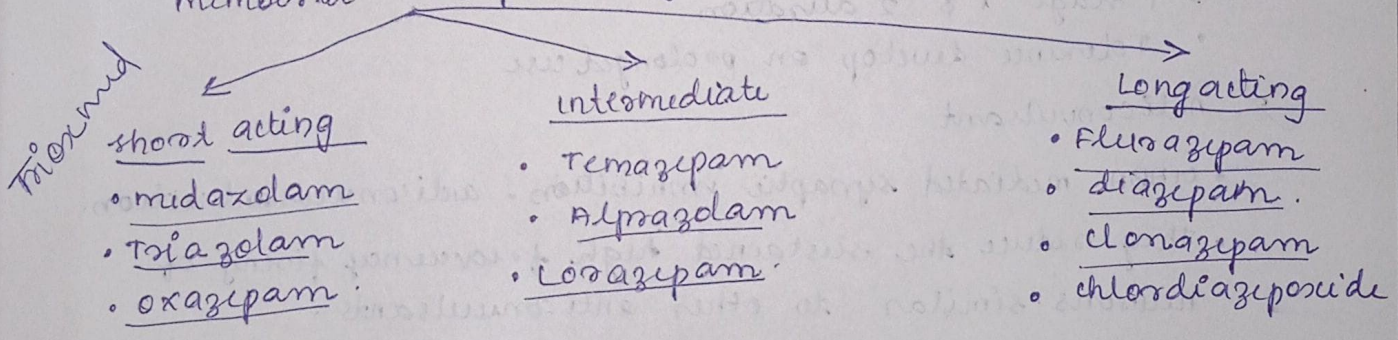
- suicidal / accidental (drug automatism)
- excess CNS depression
- flabby, comatose, shallow & failing respiration, BP fall, CVS collapse, renal failure, pulmonary complication, bullous eruptions.
- lethal dose : 2-3g (short acting)
  5-10g (long acting)

Treatment

- Gastric lavage with activated alcohol
- supportive measures
- Forced alkaline diuresis with $NaHCO_3$
- Hemodialysis, Hemoperfusion
- NO specific antidote.

→ BENZODIAZEPINES

- compound having the benzene ring fused to a seven membered diazepine ring



MOA

- GABA facilitatory action
- They increase the frequency of opening of $GABA_A$ receptor Cl^- channel
- increase the affinity of $GABA_A$ receptor for GABA
  - empty receptor is inactive and coupled chloride channel is closed
  - Binding of GABA causes the chloride ion channel to open leading to hyperpolarisation of the cell
  - Binding of GABA is enhanced by benzodiazepine, resulting in greater entry of chloride ion
  - entry of Cl^- hyperpolarisation of cell, making it more difficult to depolarize, & therefore reduces neural excitability

BZD receptor ligands

- Agonist : diazepam, z compounds
- Antagonist : flumazenil
- inverse agonist : β carboline

→ pharmacological actions

I CNS actions

1. sedation - anxiolysis
   - dose dependent sedation
   - useful in acute anxiety
   - NO tolerance to anti anxiety effects
2. Hypnosis
   - promote the onset of sleep
   - ↑ total sleep time
   - ↓ duration of stage 3 & 4 REM sleep
   - ↑ stage 1 & 2 duration
   - Tolerance develop on prolonged use
3. Anticonvulsant
   - GABA mediated synaptic inhibition - anticonvulsant action
   - they reduce the sustained high frequency firing of neurons similar to other anticonvulsants.
   - clonazepam, diazepam, lorazepam, nitrazepam.
   - Tolerance develops on repeated use
4. muscle relaxant
   - centrally acting skeletal muscle relaxant
   - sedation limits the dose which can be used for reducing muscle tone
   - Tolerance occurs to the muscle relaxant effect

II Respiration

- dose dependent respiratory depression
- significant only in
  - extremes of age, Alcoholics, COPD, with another AP

- contraindicated in OSA

III CVS

- minimal effect except in case of intoxication
- ✓ At pre-anesthetic doses: ↓BP & ↑HR.

IV GIT

- ✓ decreases nocturnal gastric acid secretion; prevent stress ulcers.
- improves anxiety related GI disorders

P/K

- ✓ extensive hepatic metabolism by CYPs
- those with no cyp metabolism: OXAZEPAM/TEMAZEPAM/LORAZEPA
- Not significantly induce CYPs
- ✓ crosses placenta & secreted into milk.

ADR

- withdrawal syndrome
- ✓ Higher doses taken before labor: hypotonia, respiratory depression in neonates
- predominantly CNS effects: psychomotor impairment, ↑reaction time, confusion, anterograde amnesia, headache, blurred vision
- ✓ epigastric distress, nausea, vomiting
- long acting agents cause residual daytime sleepiness

CI

- pregnancy, liver diseases
- Resp depression

uses

① ✓ Anxiety disorders

- Alprazolam, Lorazepam, oxazepam, Diazepam, chlordiazepoxid
- oxazepam prefered in elderly as well as those with liver dysfunction
- diazepam/Lorazepam prefered in acute panic anxiety states

✓ insomnia

✓ epilepsy

✓ As a skeletal muscle relaxant

✓ Alcohol withdrawal

✓ Anesthesia

D/D

- BZD potentiate other CNS depressants
- CYP3A4 inhibitors prolong action of benzodiazepines
  - BZD + propofol / opioid / alcohol → additive resp depression

* FLUMAZENIL

- competitive antagonist at BZD receptor
- Antagonize the binding and allosteric effects of BZD
- oppose the electrophysiological and behavioral effect of agonist & inverse agonists
- Available only for IV administration
- Hepatic metabolism
- short half life

use

- antidote for BZD overdose
- To reverse BZD induced sedative effects following anesthesia