SEDATIVES AND HYPNOTICS

SEDATIVE:

Drug or dose of the drug that produce calmness of the mind without inducing sleep

→ Drowsiness/Sleepiness

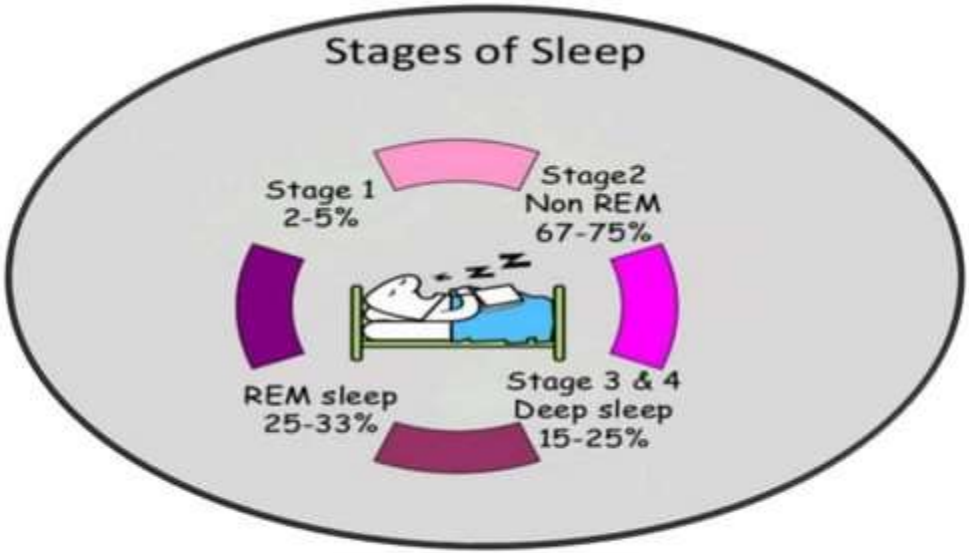
HYPNOTIC:

Drug that induce &/or maintains sleep from which a person can be aroused as during natural sleep

SLEEP

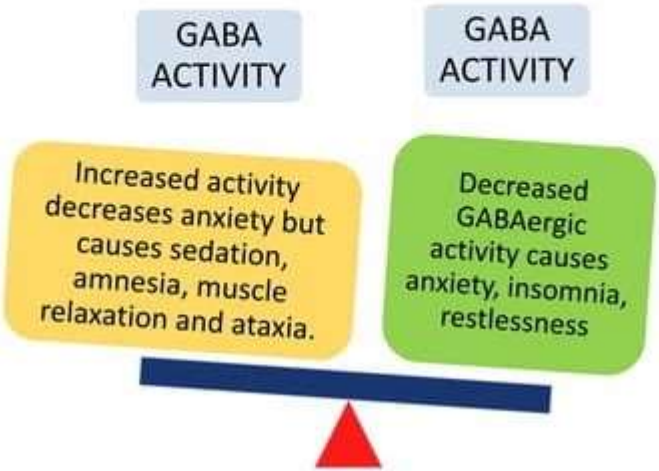
- Transient physiological depression.
- Characterised- cyclical eye movements, muscular relaxation, EEG changes
- 2 categories : NREM and REM sleep.
- NREM further divided into 5 stages : Phases 0, 1, 2, 3, 4.
- NREM → REM → NREM → REM

(1 hr) (20-25 min) (80-100 min) (20-25 min)


Stages of Sleep
Stage 1
2-5%
Stage2
Non REM
67-75%
REM sleep
25-33%
Stage 3 & 4
Deep sleep
15-25%

NEUROTRANSMISSION

- Balance should be maintained between excitatory (glutaminergic) and inhibitory (GABAergic) transmissions.



SLEEP

NREM

80% of sleep
Slow wave sleep
BP,HR,RR decreased
Relaxed muscles
EEG : low frequency and high amplitude
For physical restoration

Somnabulism,Encuresis,
Somnoloqui,Bruxism,
Pavor Nocturnus

REM

20% of sleep
Fast wave sleep
BP,HR,RR fluctuating
Profoundly relaxed muscles
For consolidation of learning

Active dreaming, Night Mares,
Narcolepsy, Cataplexy,
Penile erection

SEDATIVE-HYPNOTICS

PHARMACOLOGICAL THERAPY

- **Ideal hypnotic :**

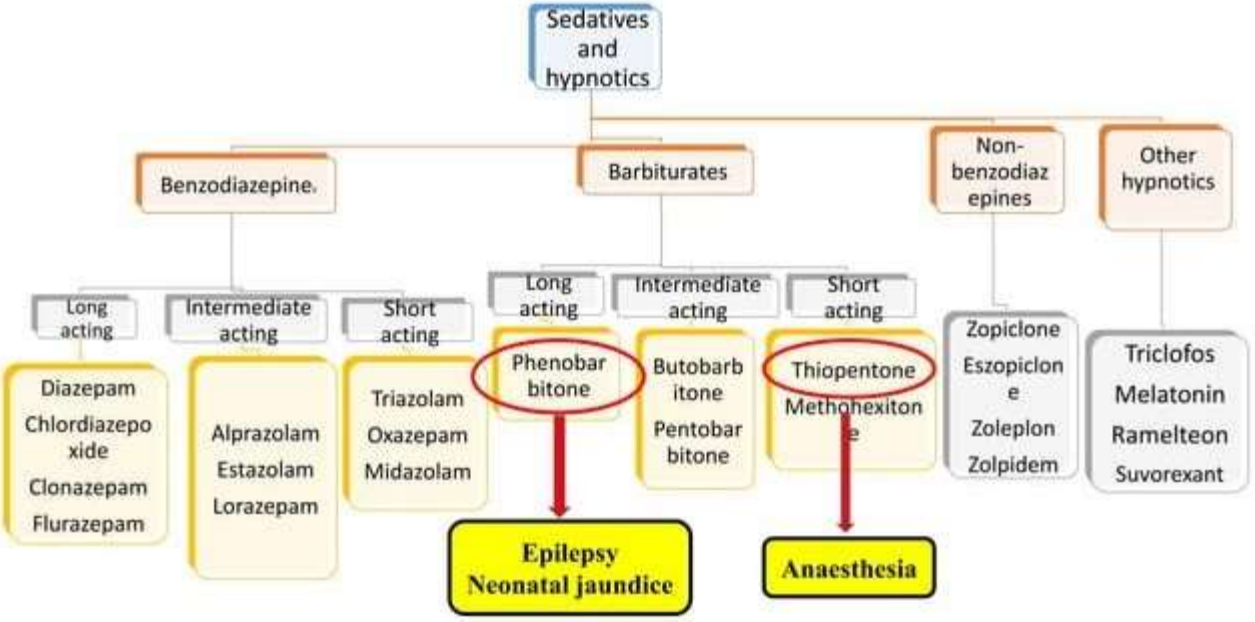
✓Induce and maintain sleep with normal architecture

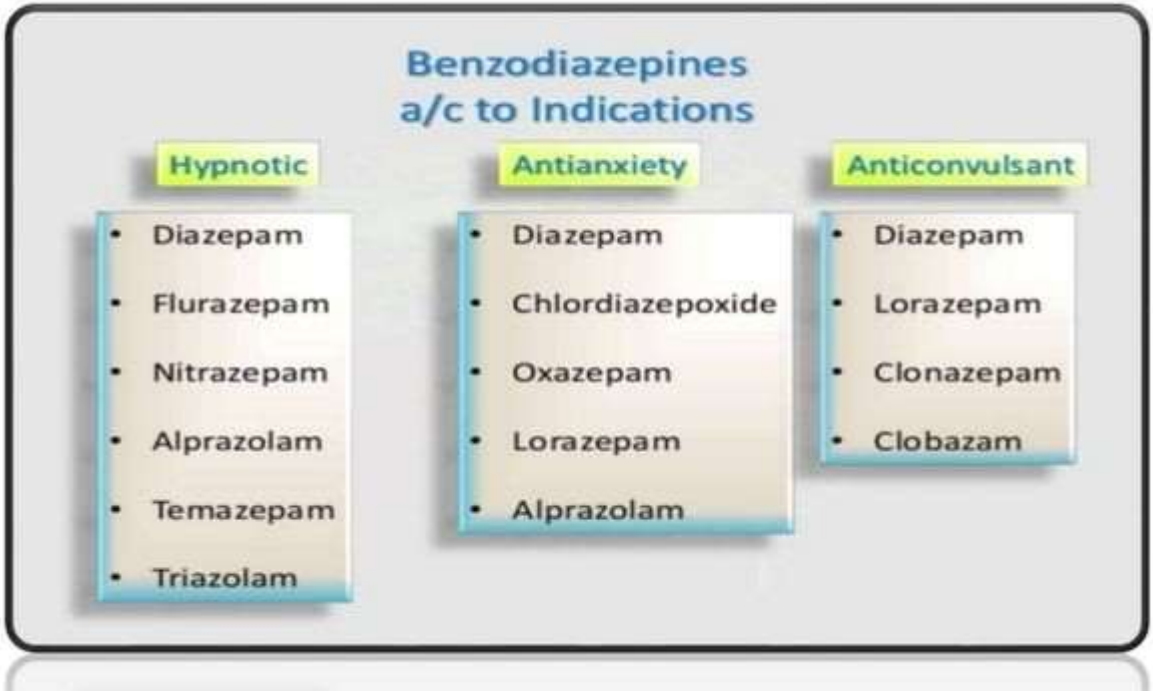
✓No rebound anxiety or sedation on next day

✓No rebound insomnia on discontinuation

✓No interaction with other drugs

✓No dependency on chronic usage


Sedatives and hypnotics
Benzodiazepine.
Barbiturates
Non-benzodiazepines
Other hypnotics
Long acting
Intermediate acting
Short acting
Long acting
Intermediate acting
Short acting
Diazepam
Chlordiazepoxide
Clonazepam
Flurazepam
Alprazolam
Estazolam
Lorazepam
Triazolam
Oxazepam
Midazolam
Phenobarbitone
Butobarbitone
Pentobarbitone
Thiopentone
Methohexitone
Zopiclone
Eszopiclone
Zoleplon
Zolpidem
Triclofos
Melatonin
Ramelteon
Suvorexant
Epilepsy
Neonatal jaundice
Anaesthesia


Benzodiazepines
a/c to Indications
Hypnotic
Diazepam
Flurazepam
Nitrazepam
Alprazolam
Temazepam
Triazolam
Antianxiety
Diazepam
Chlordiazepoxide
Oxazepam
Lorazepam
Alprazolam
Anticonvulsant
Diazepam
Lorazepam
Clonazepam
Clobazam

MOLECULAR PHARMACOLOGY OF GABA RECEPTOR

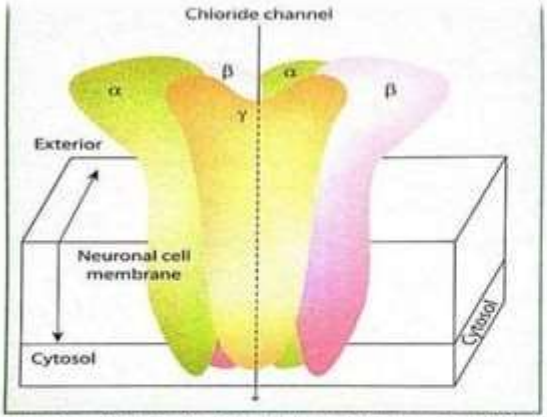


Fig. 36.4 Model of side view of structure of GABA-A receptor (ligand gated ion channel) chloride channel complex (ionophore). The GABA-A receptor is comprised of 5 units (two α, two β & γ) arranged like a rosette surrounding the chloride channel which is in the centre & it has binding site (see cross sectional view) for GABA (α & β subunits), benzodiazepines (α & γ subunits), barbiturates (β subunit) and alcohol (α subunit). These substances/ drugs after combining with their receptors/binding sites increase chloride conductance and thus facilitate GABAergic

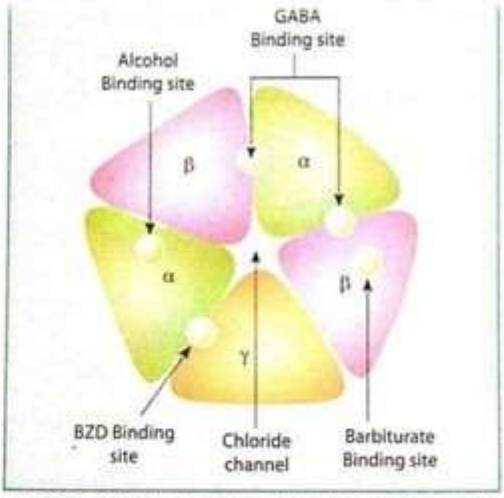
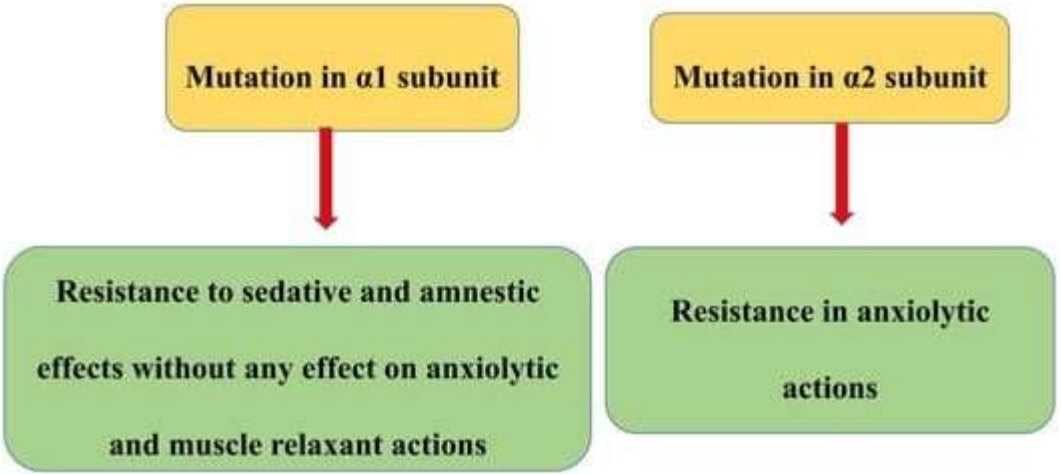


Fig. 36.5 Model of cross sectional view of structure of GABA-A receptor (ligand gated ion channel) chloride channel complex (ionophore) & binding site for GABA (α & β subunits), benzodiazepines (α & γ subunits), barbiturates (β subunit) and alcohol (α subunit)

GABA RECEPTOR



DOSE RESPONSE CURVE

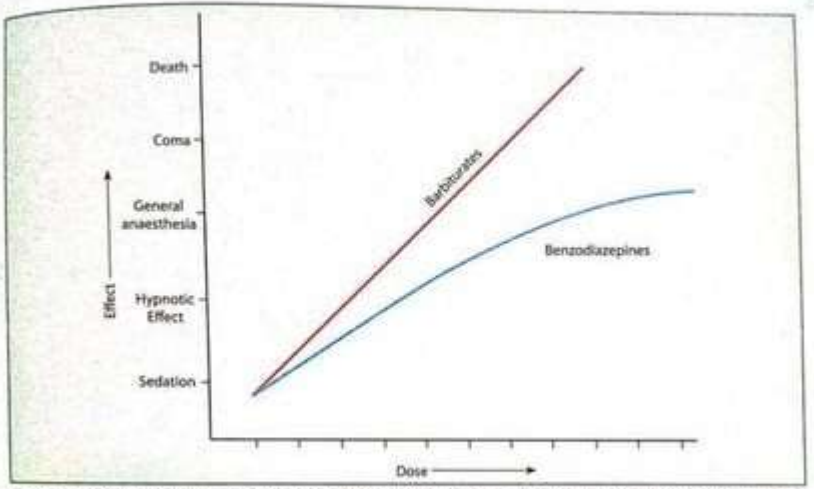


Fig. 36.1 Dose response curve (DRC) of barbiturates & benzodiazepines on oral administration of these drugs. DRC of barbiturates is linear exhibiting all degree of CNS depresion ranging from sedation to coma & death while DRC of benzodiazepines (BZD) show a ceiling effect and do not produce respiratory depression. Very high dose orally which is seldom used or i.v. administration of BZD may produce general anaesthesia.

MECHANISM OF ACTION

BENZODIAZEPINES

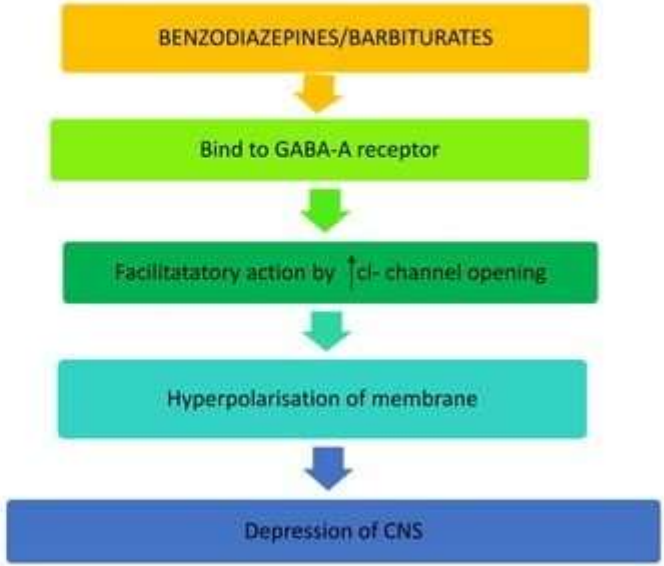
- Facilitatory action

Increase frequency of chloride channel opening

BARBITURATES

- Facilitatory action by increasing the duration of the chloride channel

At higher doses, show GABA mimetic action, directly increase ion conductance



BARBITURATES

CLASSIFICATION

ULTRA SHORT ACTING

- THIOPENTAL , METHOHEXITAL

SHORT ACTING (3-8HRS)

- PENTOBARBITAL
- SECOBARBITAL
- AMOBARBITAL

INTERMEDIATE ACTING (8-24H)

- AMYLOBARBITONE

LONG ACTING (>24H)

- PHENOBARBITONE

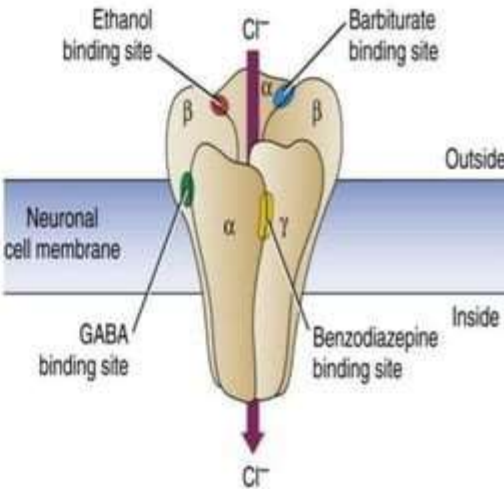
MECHANISM OF ACTION

1. GABA facilitatory action : by prolonging the duration of chloride channel opening and at higher doses directly activate and increase influx of chloride.

2. Decrease glutamate-induced depolarization (by inhibiting AMPA receptors).

3. Inhibit voltage dependent Na^+ and K^+ conductances.

- Multiplicity of actions – surgical anaesthesia
  profound CNS depression and
  low margin of safety



PHARMACOKINETICS

- Absorption : - rapid oral absorption
  - IM Injection : Necrosis

- Distribution : - wide distribution (high lipid solubility)
  - redistribution into muscle and fat occurs- terminates the action
  - readily crosses placenta

PHARMACOKINETICS

- Metabolism : - by liver microsomal enzymes
  - oxidation ⟶ conjugation ⟶ excreted in urine
  - oxidation at 5th carbon – terminates the action
  - 25% of phenobarbital and aprobarbital are excreted unchanged in urine

- Excretion : - ↑t1/2 in elderly and cirrhotic patients
  - drug accumulation occurs on repeated administration
  - weak acids – ALKALINIZATION increases their excretion

PHARMACOLOGICAL ACTIONS

- Dose dependent action :

- Presence of even moderate pain – decreases sedative activity → HYPERALGESIC action.

- Higher doses : - suppress hypoxic and chemoreceptor drives → Respiratory depression.
  - cardiodepressant
  - circulatory collapse due to medullary vasomotor depression

PHARMACOLOGICAL ACTIONS

- Hypnotic : ↑ total sleep time
  ↓ sleep latency
  ↓ REM sleep and Slow-wave sleep
  number of awakenings
  > 2 wks – tolerance
  discontinuation : rebound increase of all parameters

- Enzyme induction : - potent enzyme inducer of CYP'S – drug interctions and tolerance.
  - induces ALA synthetase, exacerbations in Acute Intermittent Porphyria.

THERAPEUTIC USES

- INSOMNIA : amobarbital, butabarbital, pentobarbital, secobarbital.
- PREOP-SEDATION : amobarbital, butabarbital, pentobarbital, secobarital, thiopental
- INDUCTION OF ANAESTHESIA : thiopental, methohexital
- ANTICONVULSANT : phenobarbital in status epilepticus
  mephobarbital as second line anticonvulsant
- HYPERBILIRUBINEMIA OF NEONATES : due to increased activity of glucornyl transferase.

ADVERSE EFFECTS

- TOLERANCE : - mood, sedation, hypnosis >> anticonvulsant
- DEPENDENCE AND ABUSE
- WITHDRAWAL SYMPTOMS
- HANGOVER
- DRUG AUTOMATISM

ADVERSE EFFECTS :

- HYPERSENSITIVITY

- VITAMIN K AND D METABOLISM : increased by phenobarbital
  – impairs bone mineralization and coagulation defects in newborns.

- UNWANTED PREGNANCY : due to increased metabolism of OCP'S.

CONTRAINDICATIONS : - Acute Intermittent Porphyria
- respiratory insufficieny
- liver diseases
- elderly
- pregnancy

BARBITURATE POISONING

- Suicidal >> Accidental - >> 10 times the hypnotic dose.
- With Alcohol or CNS depressants – occurs at low doses.
- Severe intoxication : - patient – comatose
  - respiration : shallow and rapid
  - cardiac depression and circulatory collapse
  - renal failure
- Treatment : - supportive measures
  - artificial respiration
  - gastric lavage
  - forced alkaline diuresis
  - hemodialysis if necessary

BENZODIAZEPINES

BENZODIAZEPINES - PHARMACOKINETICS

- Lipophilic
- Complete oral absorption except for CLORAZEPATE which is rapidly decarboxylated to N-desmethyldiazepam (Nordazepam) by gastric juice.
- Rapid distribution into brain followed by redistribution into muscle and fat.
- Metabolism : by CYP'S 3A4 and 2C19.
- Cross placenta and excreted in milk - fetal and neonatal depression.

PHARMACOLOGICAL ACTIONS

1. SEDATIVE AND HYPNOTIC :

↓ latency of sleep
↓ number of awakenings
↓ REM sleep duration
↓ stages 1, 3 , 4 of NREM sleep
↑ total sleep duration by increasing stage 2

> 2 WEEK USE : tolerance occurs.

Discontinuation : rebound increase in REM sleep.

2. ANXIOLYTIC : Mainly used for Acute Anxiety States.

3. PREANAESTHETIC MEDICATION : Eg: chlordiazepoxide, diazepam, lorazepam, midazolam.

PHARMACOLOGICAL ACTIONS

4. ANTICONVULSANT : diazepam , lorazepam – used in status epilepticus.

5. ANTEROGRADE AMNESIA : mediated by α1 subunit of GABA-A receptor.

6. MUSCLE-RELAXANT : at higher doses, mediated by α2 subunit of GABA-A receptor.

7. RESPIRATORY : higher doses- decreases hypoxic drive and depress alveolar ventilation, hence not used in COPD patients.

Even hypnotic doses decrease muscle tone of upper airway in Obs.Sleep Apnea patients.

THERPEUTIC USES

- Longer t1/2 BZD'S : anticonvulsants and anti-anxiety agents
- Shorter t1/2 BZD'S : sedative-hypnotics.
- ANXIOLYTICS : Acute Anxiety States

  Alprazolam – panic disorders, and agoraphobia.

  Diazepam, Lorazepam, Oxazepam.
- INSOMNIA : short acting agents more preffered.

  eg : estazolam, triazolam, temazepam.
- ALCOHOL WITHDRAWAL : Chlordiazepoxide, Clorazepate, Diazepam, Oxazepam.

THERAPEUTIC USES

- ANAESTHESIA : Preanaesthetic medication to produce amnesia – diazepam, lorazepam
  Both introperative and preanaesthetic medication – midazolam

- STATUS EPILETICUS : Diazepam, Lorazepam.

- OTHER EPILEPSIES : Clonazepam – Myoclonic Seizures.
  Clorazepate – Complex Partial Seizures.

- SKELETAL MUSCLE RELAXANT : Diazepam in Spastic disorders.

ADVERSE EFFECTS

- Common side effects : headache, blurred vision, nausea ,vomiting.
- Impaired cognition
- Residual day time sleepiness
- Tolerance
- Dependency and Abuse liability : eg : Flunitrazepam (ROHYPNOL)
- Withdrawal syndromes : rebound insomnia, anxiety, tremors, unpleasant dreams, anorexia, dizziness.

BENZODIAZEPINES

- Drug interactions : seen with enzyme inhibitors (erythromycin, ketoconazole)

- CIMITIDINE and OCP'S : inhibit dealyklation and hydroxylation of BZD'S.

- ETHANOL – synergistic effect on CNS depression, hence should not be used along ethanol and other CNS depressants.

- Neonatal depression and HYPOTONIA (FLOPPY BABY SYNDROME) when given in pregnant female.

- Dose reduction : Elderly

  Liver disease

ADVANTAGES OF BENZODIAZEPINES

BARBITURATES	BENZODIAZEPINES
• Narrow therapeutic index	• High therapeutic index
• More suppression of REM sleep	• Less suppression of REM sleep
• Enzyme inducer	• Not an enzyme inducer
• High abuse liability	• Lesser abuse liability
• Produces non-specific CNS depression	• Do not produce
• No antidote available	• Antidote – **Flumazenil** available