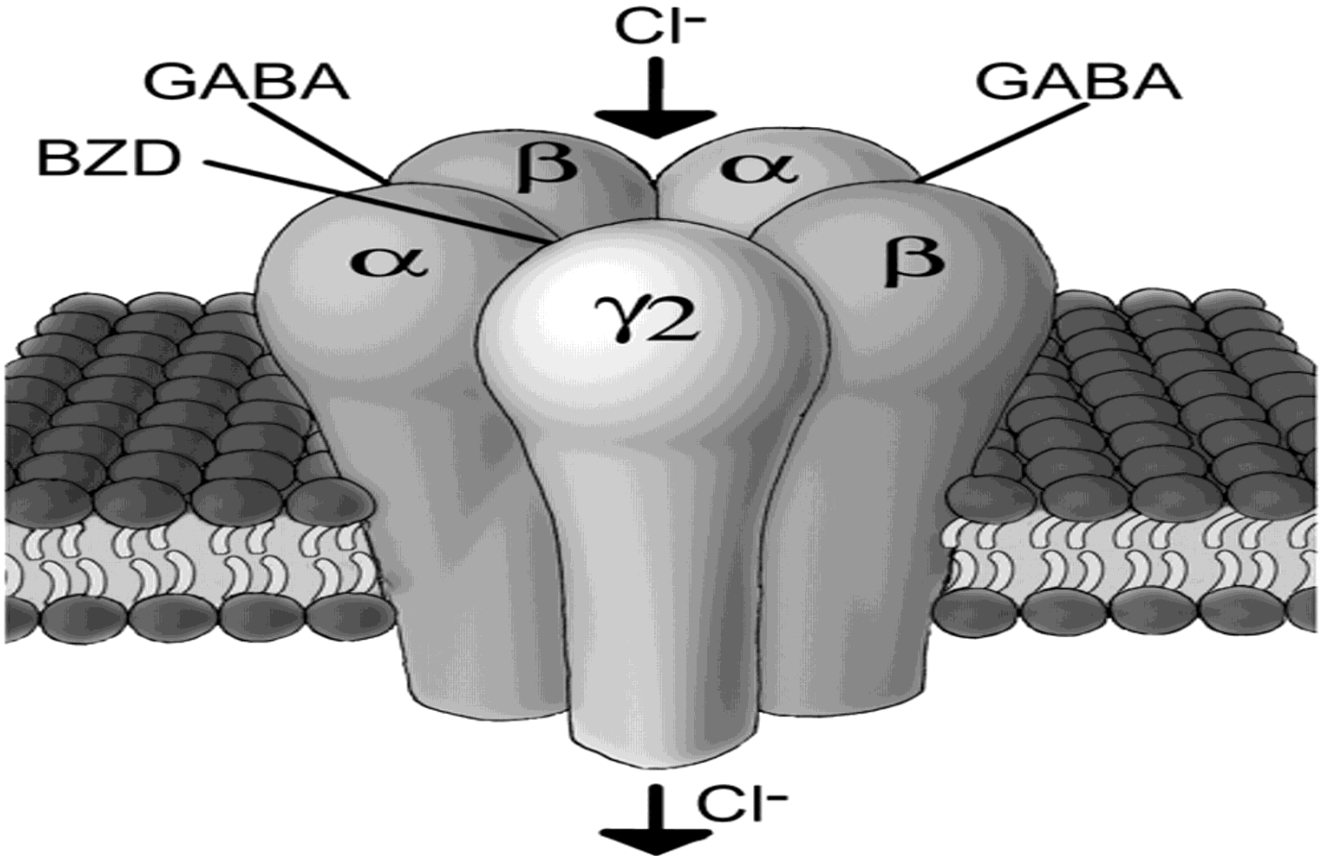
SEDATIVE-HYPNOTICS



DRUGs ACT ON CNS
(Pharmacology)
Unit-5(4)

DEFINITIONS

- **Sedative:** A drug that subdues excitement and calms the subject without inducing sleep, though drowsiness may be produced – refers to decreased responsiveness to any level of stimulation; is associated with some decrease in motor activity and ideation - depression of awareness to the environment and reduction of responsiveness to external stimulation
  - Newer - An effective sedative agent should reduce anxiety and exert a calming effect with little or no effect on motor or mental functions

- **Hypnotic:** A drug that induces and/or maintains sleep, similar to normal sleep which is can be aroused. Should not be confused with "Trans like state" - hypnosis, meditation, magic, flow, and prayer etc. – subjects are passive and highly suggestible
- **Older drugs:** alcohol, opium, bromides, chloral hydrate, paraldehyde – obsolete now

IN GENERAL …

- Sedative: Calm down, treat agitation

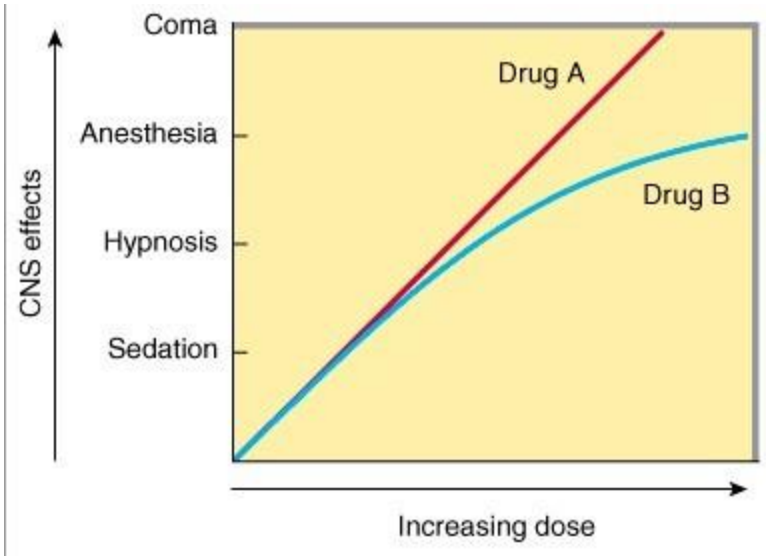

Sedative

- Hypnotic: Induce sleep
  - go to sleep fast, feel refreshed tomorrow !
  - Treatment of Insomnia
- Anxiolytic: Reduce anxiety
  - physical, emotional, cognitive


Hypnotic

IN GENERAL …

- All are CNS depressants – different time-action and dose –action relationship
- Quick action. But short duration of action and steeper DRC – hypnotic
- Slowly acting and flatter DRC – sedative
- But, overlaps – hypnotic at lower doses may act as sedative
- Anxiolysis > Sedation > Hypnosis >General Anaesthesia (grades of CNS depression)



The linear slope for drug A is typical of many of the older sedative-hypnotics, including the barbiturates and alcohols - an increase in dose higher than that needed for hypnosis may lead to a state of general anesthesia. At still higher doses, these sedative-hypnotics may depress respiratory and vasomotor centers in the medulla, leading to coma and death.

Deviations from a linear dose-response relationship for drug B - proportionately greater dosage increments to achieve central nervous system depression more profound than hypnosis. This appears to be the case for benzodiazepines and for certain newer hypnotics that have a similar mechanism of action.

Dose-response curves for two hypothetical sedative-hypnotics.

AVAILABLE DRUGS

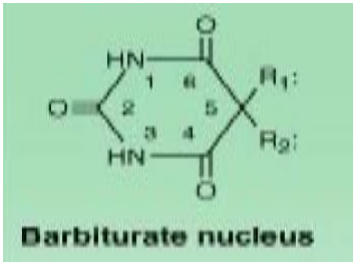
- Barbiturates:
  - Long acting: Phenobarbitone
  - Short acting (Intermediate): Pentobarbitone, Butobarbitone, Amylobarbitone
  - Ultra-short acting: Methohexitone, Thiopentone, Secobarbitone
- Benzodiazepines:

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

- Newer Non-benzodiazepines: Zopiclone, Zolpidem, Zaleplon etc.

(Chloral hydrate, paraldehyde, meprobamate – not used anymore)

BARBITURATES



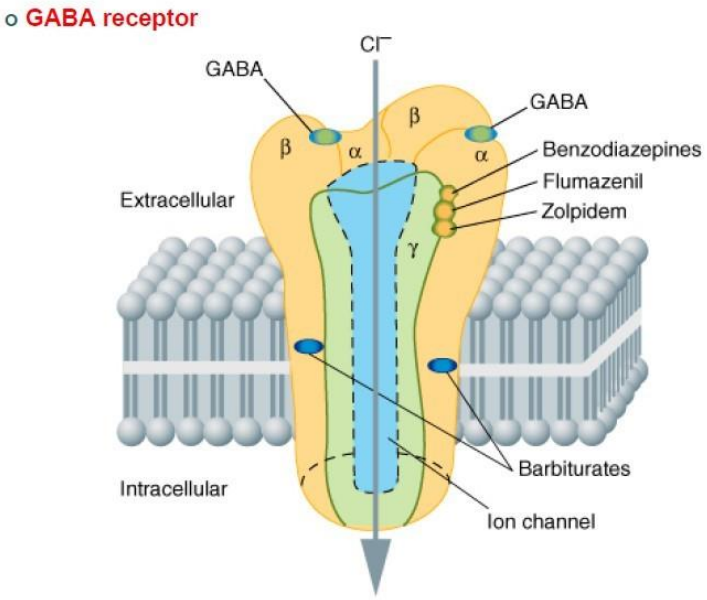
- Last century – upto 1960 – not used now – but prototype drug
- Chemically – condensation of malonic acid and urea – Barbituric acid
- Important drawbacks:
  - General depressants of all excitable cells (CNS)
  - Potentially Fatal Respiratory Depression
    - narrow therapeutic range
  - Potent liver inducers: interactions

BARBITURATE – CNS ACTION

- Dose dependant effect: sedation – sleep – anaesthesia – coma
- Short acting – hypnotic (100-200 mg)
  - Shortens time taken to fall asleep and increases sleep duration
  - Arousable – but confused and drowsy if aroused early
  - Night awakening – reduced
  - REM and stage 3 and 4 sleep reduced – disruption of sleep cycle
  - Progressively decreases effects on sleep – continuous use – rebound increase in REM sleep on discontinuation
  - Hang over in the morning – dizziness, distortions of mood, irritability and lethargy
  - Impair learning, short-term memory and judgment
  - No analgesic action – hyperalgesia instead
  - Phenobarbitone – higher anticonvulsant : sedative ratio

BARBITURATE - MOA

- Act primarily at GABA:BZD receptor-Cl^- channel
- Potentiates GABAergic inhibition by increasing the lifetime of Cl^- channel opening
- Bind to other site than GABA – located in α and ß subunit
- Also enhance BZD binding
- High doses – directly increases Cl^- conductance (GABA mimetic) and inhibit Ca^{++} dependent release of neurotransmitters
- Also depress Glutamate induced neuronal depolarization
- Very High doses – depress voltage sensitive Na^+ and K^+ channel



BARBITURATE – OTHER ACTIONS

- Respiration: Depressed – neurogenic, hypercapneic and hypoxic drives to respiratory centre depressed
- CVS: Slight decrease in BP and Heart Rate
  - Toxic doses: Marked fall in BP and HR – due to ganglion blockade, vasomotor centre depression and direct cardiac action – reflex tachycardia
- Skeletal Muscle: Little effect but anaesthetic doses reduce muscle contraction
- Smooth muscle: Tone and motility of bowel is decreased. Higher doses – more profound decrease
- Kidney: Reduce urine flow – due to decrease BP and ADH release

BARBITURATE - KINETICS

- Well absorbed orally – widely distributed
- Entry into CNS depends on lipid solubility – Phenobarbitone Vs Thiopentone
- Plasma protein binding – Phenobarbitone – 20%, Thiopentone – 75%
- Crosses placenta and secreted in milk
- Redistribution: highly lipid soluble barbiturates (ultra short acting) – IV injection – consciousness after 6-10 minutes, but actual elimination by metabolism – half life 9 hours - Short acting ones – TE 6 – 10 hours and elimination half life is 12-40 hours
- Metabolism: metabolized in liver by oxidation, dealkylation and conjugation
- Excretion: Long acting – excreted significantly unchanged - Alkalinization – ↑ excretion
- Microsomal enzyme inducer – induce own metabolism and Others

BARBITURATES – CONTD.

- Adverse Effects: Hang over, tolerance and dependence, metal confusion, impaired performance – accidents
  - Idiosyncrasy: Occasional excitement – In elderly
  - Hypersensitivity: Rashes, swelling of eyelids, lips etc.
  - Tolerance and dependence: Cellular and pharmacokinetic – on repeated use
    - Physical and psychological dependence – abuse liability
- Drug Interactions:
  1. Induce metabolism of many drugs – warfarin, steroids, OCP, chloramphenicol, tolbutamide
  2. Alcohol, antihistamines, opioids – CNS depression
  3. Sodium valproate – increases plasma conc. Of phenobarbitone
  4. Phenobarbitone – competitively induces phenytoin metabolism

ACUTE BARBITURATE POISONING

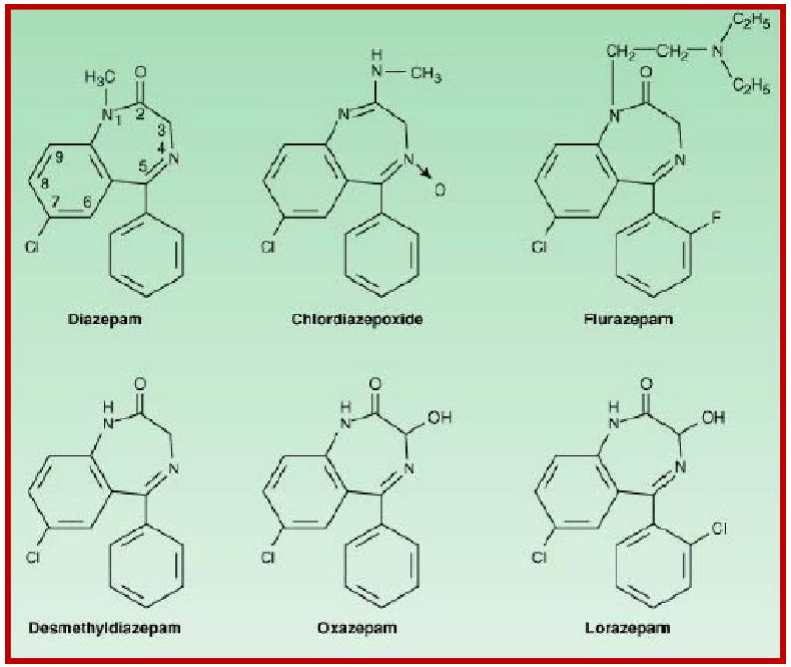
- Mostly suicidal – excessive CNS depression – flabby and comatose with shallow and failing respiration, CVS collapse, renal shut down, pulmonary complications
- Treatment:
  - Gastric lavage (activated charcoal)
  - Supportive – patent airway, assisted respiration, oxygen, IV fluid and vasopressors like Dopamine
  - Alkaline diuresis: Sodium bicarbonate 1 meq/kg IV with or without mannitol – for long acting ones
  - Haemodyalysis: highly effective in long as well as short acting ones
  - No specific antidote
- Contraindications: acute intermittent porphyria, Liver and kidney disease, severe pulmonary insufficiency

BENZODIAZEPINES (BZDS)

Chlordiazepoxide and Diazepam - Since 1960

BENZODIAZEPINES (BZDS)

- Chemically – all are 1,4-benzodiazepines, and most contain a carboxamide group in the 7-membered heterocyclic ring structure
- A substituent in the 7 position, such as a halogen or a nitro group, is required for sedative- hypnotic activity



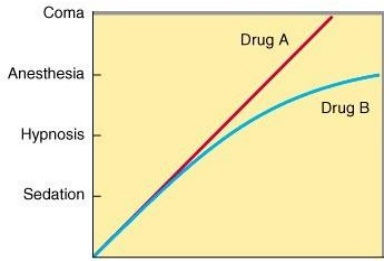
BENZODIAZEPINES VS OLDER ONES

- Most widely used sedative-hypnotics now since 1960 and replaced Barbiturates
  1. High therapeutic index – 20 hypnotic doses – no loss of consciousness or respiratory depression – patient can be aroused
  2. Hypnotic doses – do not depress CVS or respiratory function. Higher doses may be
  3. BZDs have no action on other body system – only IV injection BP may fall – Barbiturates ?
  4. BZDs cause less distortion of sleep architecture
  5. No microsomal induction – less drug interaction
  6. Low abuse liability, mild tolerance, psychological and physical dependence and less withdrawal symptoms
  7. Specific antagonist - flumazenil

BZDS – CNS ACTIONS

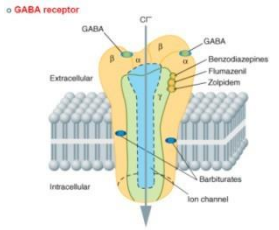
- All agents - Qualitatively similar, but different members are used for different purposes – selectivity and time course of action different
  - Midbrain (RAS), limbic system, medulla and cerebellum
- Not general CNS depressants – exert selective - anxiolytic, hypnotic, muscle relaxant and anticonvulsant effects
- Even anaesthetic doses of Diazepam – some degree of awareness maintained (although, events of recovery may not be remembered by patient anteretrograde amnesia)

BZDS –EFFECTS



- On sleep: Basic actions (Note the comparisons)
  - Hastens onset of sleep, reduce intermittent awakening and increased total sleep time – Like Barbiturates
  - Time spent in stage 2 (unequivocal sleep) is increased (Unlike Barbiturates) and stage 3 & 4 decreased (Like Barbiturates)
  - Regulates a Key on sleep - Shorten REM (Unlike Barbiturates), but more REM cycles (Unlike Barbiturates) – such that overall effects on REM less marked (Nitrazepam) – more sleep cycles
  - Night terror (at stage 4) and body movements are reduced
  - Stage shift to stage 1 and 0 are reduced (awake and dozing) and wake up fresh (no Hang over) – some degree of tolerance
- Centrally mediated muscle relaxant – Clonazepam and Diazepam
- Anticonvulsant: Clonazepam, diazepam and flurazepam
- Diazepam – on IV use - analgesia (no hyperalgesia) and decreases nocturnal gastric secretion – stress ulcer prevention

MOA – BZD



- Midbrain ascending reticular activating system (RAS) and limbic system (thought and mental function); also medullary sites and cerebellum
- Acts via (inhibitory) ligand gated BZD: $GABA_A$ receptor- Cl^- channel complex
- α/γ subunits carries the BZD binding site - BZD receptors are integral to $GABA_A$ receptor
- BZDs modulate action on GABA receptor - increases frequency of channel opening (unlike Barbiturate - Potentiation)
- Also enhances binding of GABA to $GABA_A$ receptor
- Bicuculine ($GABA_A$ antagonist) antagonizes BZD action as non-competitive
- BZDs are GABA facilitator but not Mimetic (unlike Barbiturates)
- Constitutive action – fine tunes GABA action – bidirectional
- BZD agonists enhance GABA action (hyperpolarization) – but antagonists like dimethoxyethyl-carbomethoxy-β-carboline (DMCM) inhibits GABA

BZD - KINETICS

- Marked pharmacokinetic differences – differ in lipid solubility
- Oral absorption – some rapid, some slow; on IM injection– irregular absorption except lorazepam
- Plasma protein binding also varies (Flurazepam –10%; Diazepam 99%)
- Usually short duration of action – with a single dose – REDISTRIBUTION – prediction of duration of action is difficult
- Metabolism: In Liver by dealkylation and hydroxylation to metabolites (some are active) – Biological half-life longer than plasma half life
- Enterohepatic circulation – Diazepam and excreted in urine as glucoronide conjugate
- BZDs are secreted in milk and crosses placenta

BZD - COMPARISON

Drugs	Half life (hour)
Diazepam	30 - 60
Nitrazepam	30
Flurazepam	50-100
Alprazolam	12
Chlordiazepoxide	15 - 40
Lorazepam	10 - 20
Temazepam	8 - 12

INDIVIDUAL DRUGS

- Slow elimination but rapid redistribution
  - Diazepam: Generates active metabolite (desmethyl-diazepam, oxazepam) – single dose no residual effects – regular use accumulation and prolonged anxiolytic effect – Difference with others
  - Nitrazepam: Accumulates - Residual effects – day time sedation (not on single dose) – for frequent nocturnal awakening patients (if day time sedation acceptable)
  - Flurazepam: Slow elimination of parent drug or metabolite - Produces active metabolite which have long half life – residual effects frequently (morning) – cumulation – day time sedation (if day time sedation acceptable)
- Rapid elimination and marked redistribution
  - Alprazolam: Basically used as anxiolytic – but also night time hypnotic – withdrawal phenimenon after regular use - sedation
  - Temazepam: No residual effect, no metabolite – used in sleep onset difficulty
- Ultrarapid elimination: Triazolam – potent, quick acting – for induction of sleep

BZDS – ADVERSE EFFECTS

- Older individuals are more susceptible – Be careful
- Hypnotic doses: Dizziness, vertigo, ataxia, disorientation, amnesia, prolongation of reaction time – impairment of psychomotor skill
  - Hang over with larger doses – long acting ones
  - Weakness, blurring of vision, dry mouth and urinary incontinence
  - Paradoxical stimulation, irritability and sweating – Flurazepam
  - Nightmares and behaviuoral alteration – Nitrazepam
  - Tolerance to sedative effect very slowly – little tendency to increase dose – cross tolerance to alcohol and other CNS depressants
  - Dependence liability and drug seeking behaviour – low (bland) - Midazolam
  - Low withdrawal syndrome – more with ultrarapid ones – anxiety, insomnia, restlessness, malaise, loss of appetite, bad dreams
  - Pregnancy – flaccidity and respiratory depression in neonate

NONBENZODIAZEPINES - ZOPICLONE

- Cyclopyrrolone derivative - active metabolite – N-desmethylzopiclone
- MOA: Binds to α subunit of BZD receptor (Unlike BZD) – hypnotic action
- Vs BZD: Sleep resembles but – does not alter REM and tends to prolong stage 3 and stage 4 (Unlike BZD)
- No sleep architecture distortion or withdrawal phenomena
- Uses: to wean off insomniacs on BZD and short term therapy for insomnia
- ADRs: Metallic taste, impairment of judgment and alertness, psychological disturbance – addictive property (rarely)
- Half life: 5 – 6 hours

ZOLPIDEM - IMIDAZOPYRIDINE

- MOA: Acts on α_1 subunit of BZD receptor (hypnotic)
- Actions: Sleep latency shortened, prolongs sleep time –but no anticonvulsant, antianxiety or muscle relaxant effects
  - Lack of effect on sleep stages (REM)
  - Minimal residual day time sedation or fading of effects on repeated use
  - Little rebound insomnia on discontinuation
  - Absence of tolerance, physical dependence and low abuse potential
- Kinetics: Completely metabolized in liver – half life – 2 hrs
- Uses: short term therapy of sleep onset insomnia – day time sedation less (short half life) – late night (!)
- Most popular – even large doses no respiratory depression

ZALEPLON

- Shortest acting - acts on α_1 subunit of BZD receptor (hypnotic)
- Rapidly absorbed (30% bioavailability – high first pass) – rapidly cleared by hepatic metabolism – Half life (1 hr) – no active metabolite
- Does not prolong total sleep time or reduce the number of awakenings
- Can be taken late night – no morning sedation, anxiety or insomnia
- No tolerance or dependence
- Uses: Sleep-onset insomnia (1-2 weeks therapy)

USES OF BZDS

- As Hypnotic: Not all are useful as hypnotic agents, although all have sedative or calming effects
- As anxiolytic and for day time sedation
- As anticonvulsant – status epilepticus, febrile convulsion, tetanus
- As Muscle relaxant (centrally acting)
- Preananesthetic medication, IV anaesthesia and conscious sedation
- Before procedures: ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies and other minor procedures
- Alcohol and other sedative-hypnotic withdrawal
- Along with analgesics, NSAIDs, spasmolytics, antiulcer and many other drugs

AS HYPNOTIC

- A hypnotic should not be casually prescribed for every case of insomnia – BZDs and Non-BZDs are most frequently used
- The choice of a particular BZD to treat a sleep disturbance is generally based on Pharmacokinetic criteria:
  - Long-acting compounds (e.g. flurazepam) may ensure that a patient will sleep through the night, they also may cause cumulative effects resulting in daytime sluggishness or drug hangover
  - Short-acting compounds (e.g. triazolam) avoid the hangover problem, but their use may be associated with early awakening and an increase in daytime anxiety

BZD AS HYPNOTIC – GENERAL POINTS

- A hypnotic should be used – (1) shorten sleep latency, (2) to reduce nocturnal awakening and (3) to provide anxiolytic effect the next day
- Should consider onset of action and duration of action of the drug
- Should consider next day effects – prolonged sedation or rebound anxiety
- All become useless after regular use – except `z` drugs
- Should consider the subjects perception and assessment

INSOMNIA

- Chronic Insomnia (> 3 weeks) – Be cautious prescribing hypnotics
  - May be Personality disorder; chronic hypnotic user; alcoholic; somatic diseases – GERD, pain, COPD
  - Other measures - Exercise, yoga, counseling – advice avoiding anxiety, attempting sleep when maximum sleepiness, avoid napping day time, coffee/alcohol restriction treatment of concurrent diseases
  - Intermittent use of hypnotics
- Short term insomnia (3 – 21 days): Emotional problem – stress, bereavement and physical illness etc. – either induction difficulty or waking up early – Hypnotic free of residual effects (sometimes may be needed) - short acting drugs in elderly
- Transient insomnia (1 – 3 days): Alterations in the circumstances – new place, journey, work related, night shift, travel jetlag etc. – a short acting without residual effects

FLUMAZENIL

- BZD analogue, but specific BZD receptor antagonist – no IA – no effect on normal person
- Competes with BZD agonists and inverse agonists – reverses their action
- Absorbed orally (20% bioavailability), but used IV and intranasal - half life- 1 hr
- Uses:
  - To reverse BZD anesthesia – quick action within 1 minute – Resedation
  - BZD overdose

SUMMARY

- Name of different Barbiturates – Details of Phenobarbitone and Thiopentone
- Benzodiazepine Classification (long and short acting)
- Mechanism of action of BZD
- Uses of BZD
- Non-benzodiazepines
- Pharmacotherapy of Insomnia
- Remember Flumazenil

THANK YOU