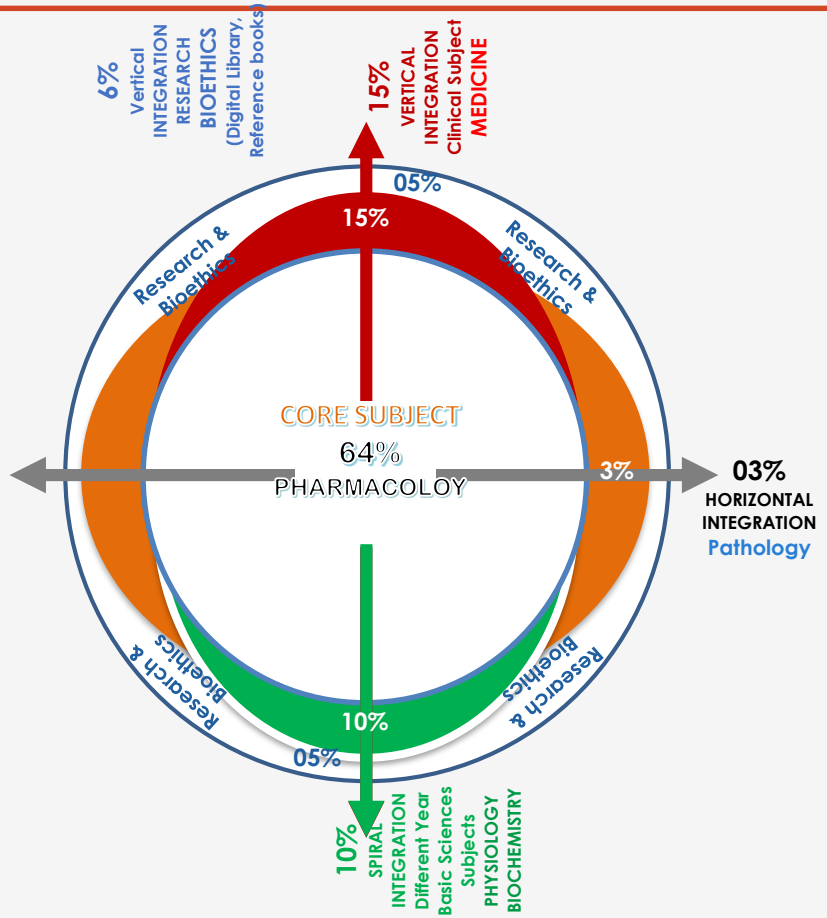
4/24/2025

MOTTO AND VISION VI

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof Umar's Clinically Oriented Integrated Model For Basic Sciences And Interactive Lectures



4th Year Pharmacology LGIS
Core Subject – 64%
Pharmacology
Horizontal Integration – 3%
Same Year Subjects • Pathology (2)
Vertical Integration – 6%
Clinical Subjects • Medicine (3)
Spiral Integration – 10%
Different Year Basic Sciences Subjects • Physiology • Biochemistry
Research & Bioethics,Digital library 9%

SEDATIVES AND HYPNOTICS

LEARNING OBJECTIVES

- Briefly discuss the excitatory and inhibitory target of CNS
- Different Components of Sleep Cycle
- Pharmacokinetic and Pharmacodynamic features of Different sedatives & Hypnotics
- Adverse effects and important drug interactions of sedatives and Hypnotic
- On going research on Melatonin receptor agonists and Z compounds

THERAPEUTIC USES OF BENZODIAZEPINES

1. **ANXIETY DISORDERS**

- **Primary / secondary / situational / GAD / panic disorders**
- Used for shorter period….Because of their addictive potential
- For treatment of panic disorders & agoraphobia(Alprazolam)
- For anxiety BDZs are preferred because:
    i. Rapid onset of action
    ii. Relatively high therapeutic index
    iii. Availability of antagonist in case of overdose
    iv. Low risk of drug interactions
    v. Minimal effects on cardiovascular or autonomic functions

BENZODIAZEPINES -- THERAPEUTIC USES

2. INSOMNIA

- **Non-pharmacologic therapies**
  - Proper diet & exercise
  - Avoiding stimulants before retiring
  - Ensuring a comfortable sleeping environment
  - Retiring at a regular time each night
- **BDZs used** for insomnia because:

i. Provides rapid onset of sleep (decreased sleep latency)

ii. Minimal “hangover” effects

3. AS MUSCLE RELAXANT:

Diazepam act as centrally acting muscle relaxant

Treatment of skeletal muscle spasms

BENZODIAZEPINES -- THERAPEUTIC USES

4. AS ANTI-CONVULSANTS

For status epilepticus → Diazepam, Lorazepam
For refractory seizures → Clonazepam Clobazam
For anxiety induced seizures → Alprazolam

5. AS PREANAESTHETIC MEDICATION:

Sedative effects
Amnestic effects
Anxiolytic effects

6. IV GENERAL ANAESTHESIA:

Midazolam for induction
Diazepam and Lorazepam for maintenance

BENZODIAZEPINES -- THERAPEUTIC USES

7. DURING ALCOHOL WITHDRAWAL

- Long-acting BDZs (diazepam, chlordiazepoxide) used to reduce withdrawal symptoms of physical dependence associated with alcohol or other sedative-hypnotics

8. DIAGNOSTIC (ENDOSCOPIES, BRONCHOSCOPY) & DENTAL PROCEDURES:

Sedative & amnesic properties

9. IN PSYCHIATRY: For initial control of mania, diazepam is used as an adjuvant

BENZODIAZEPINES -- ADVERSE EFFECTS

Adverse effects resulting from dose-related depression of CNS

- Light-headedness, increased reaction time, impairment of mental & motor functions, confusion, anterograde amnesia, residual daytime sleepiness, weakness, headache, blurred vision, vertigo, nausea, vomiting, epigastric distress, diarrhoea

Use of flurazepam, triazolam, & temazepam: serious allergic, hepatotoxic, & hematologic reactions

- Large doses taken just before or during labor may cause hypothermia, hypotonia, & mild respiratory depression in neonate (Floppy baby syndrome)
- Abuse by pregnant mother can result in a withdrawal syndrome in newborn

BENZODIAZEPINE ANTAGONIST

FLUMAZENIL

- Act as competitive antagonist on $GABA_A$ receptor
- Blocks action of BDZs, zolpidem, zaleplon, & eszopiclone
- Short half-life (0.7–1.3 hrs)
- D.O.A--- 30-60min….**Repeated doses for reversal of Toxicity**
- Only for IV administration
- Indicated for reversal of CNS depressant effects produced by BDZs overdosage during general anesthesia & diagnostic procedures
- REVERSAL OF RESPIRATORY DEPRESSION IS LESS PREDICTABLE

BENZODIAZEPINES -- DRUG INTERACTIONS

- CNS depressants like alcohol, opioid analgesics, antipsychotics, antiepileptics, antidepressants, antihistamines when given concurrently with BDZs can cause enhanced CNS depression

- Microsomal enzyme inhibitors like ketoconazole, omeprazole, erythromycin & others prolong $t_{1/2}$ of BZDs

BARBITURATES

- Are derivatives of barbituric acid
- Presence of alkyl or aryl groups at position 5 confers sedative-hypnotic
- Barbiturates in which oxygen at C2 is replaced by sulfur are called thiobarbiturates

BARBITURATES

CLASSIFICATION

Ultrashort-acting

- Thiopental, Methohexital

Short-acting

- Pentobarbital, Butabarbital

Intermediate acting

- Amobarbital

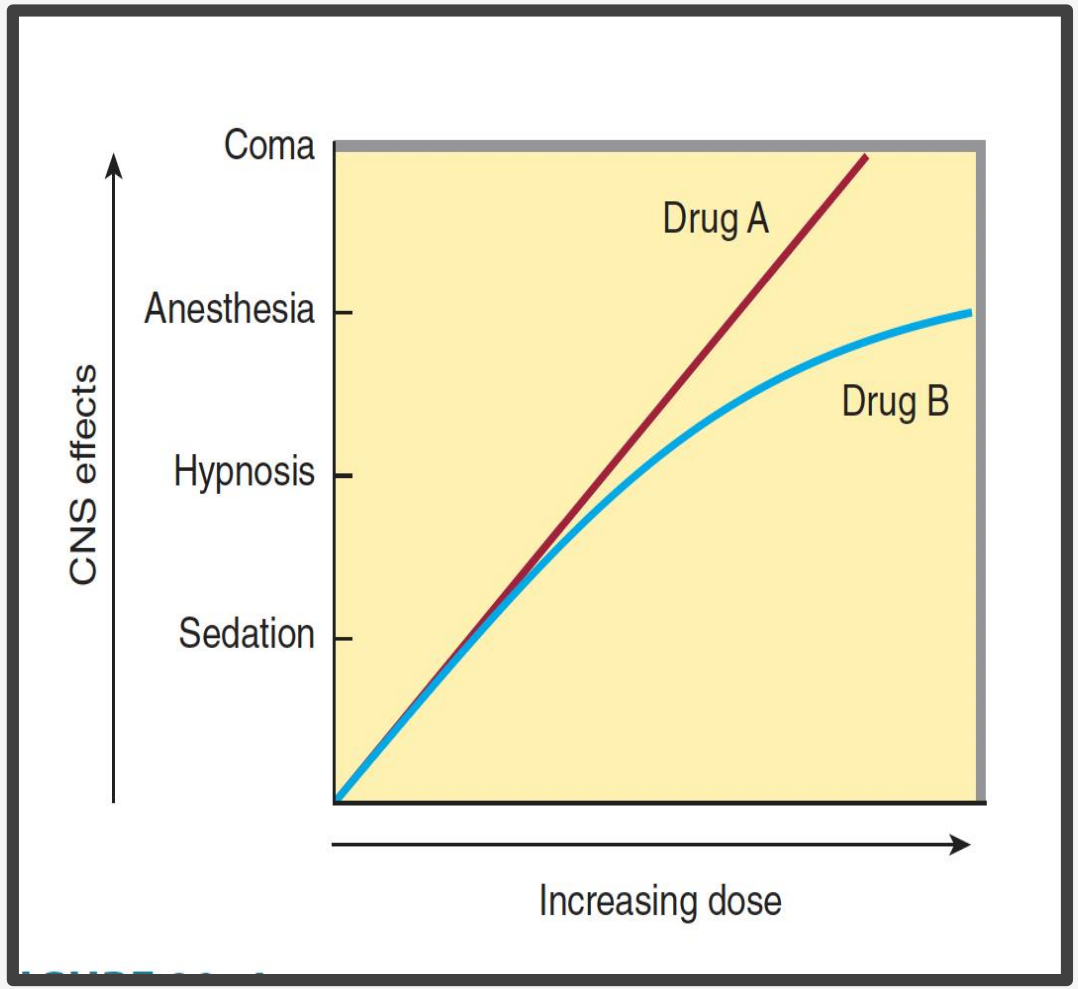
Long-acting

- Phenobarbital, Mephobarbitone

BARBITURATES—MECHANISM OF ACTION

- Bind to multiple isoforms of $GABA_A$ receptor but at different sites from BDZ binding sites — **increase duration of GABA-gated chloride channel openings**
- At high concentrations, barbiturates may also be GABA-mimetic, directly activating chloride channels
- Less selective in action — Depress actions of excitatory neurotransmitter glutamic acid via binding to AMPA receptor

Dose-response curves for two hypothetical sedative-hypnotics



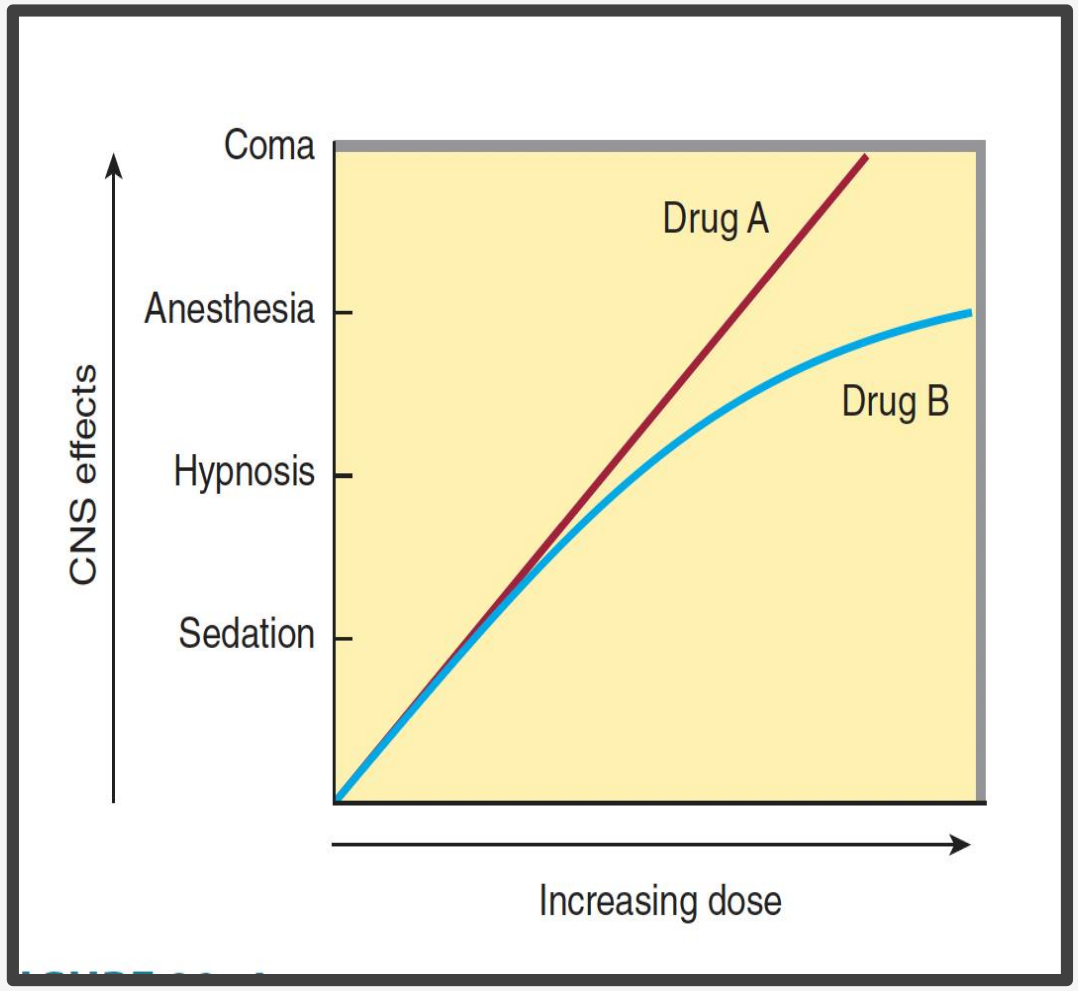
Drug A ---- linear dose-response relationship

- Higher than needed for hypnosis may lead to a state of general anesthesia
- Further higher doses, may depress respiratory & vasomotor centers in medulla → coma & death

Drug B

- Needs greater dose to achieve CNS depression
- Deviation from linear dose-response relationship

Dose-response curves for two hypothetical sedative-hypnotics



Drug A --- Barbiturates

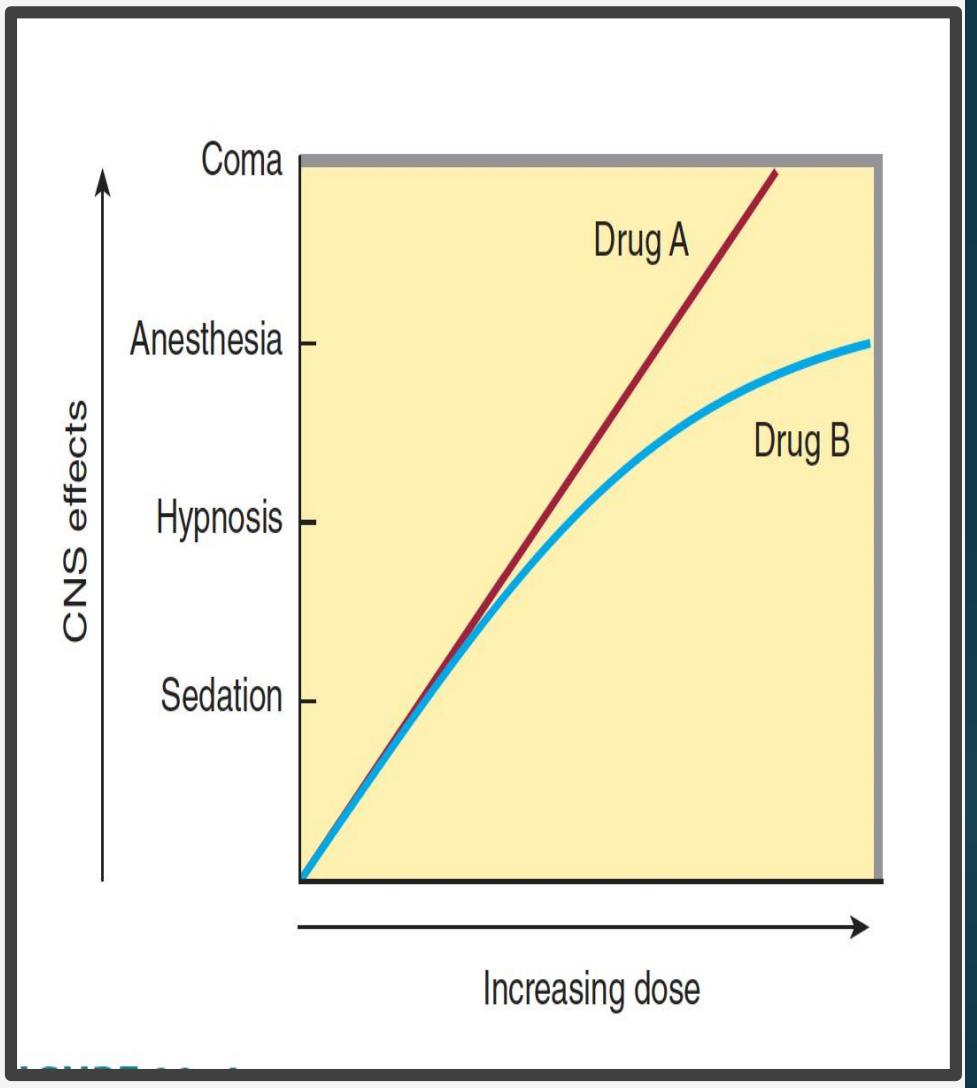
- Steeper DRC
- Narrow margin of safety
- Slight increase in dose → severe CNS depression leading to coma

Drug B --- BDZs

- Flatter DRC
- Greater margin of safety

BARBITURATES

- Replaced by BDZs, because barbiturates induce tolerance & physical dependence, lethal in overdose, & associated with severe withdrawal symptoms



BARBITURATES -- THERAPEUTIC USES

- **Antiepileptic**
- **Anaesthesia**
- **Hyperbilirubinemia & Kernicterus**
  - Being enzyme inducer, enhances production of glucuronyl transferase, required for metabolism of bilirubin, so reduce serum bilirubin level, helps in clearance of jaundice in neonates
  - Increase binding of bilirubin to albumin thus decreasing levels of unconjugated bilirubin
- **Insomnia**
- **As sedative** have been replaced by BZDs

BARBITURATES – ADVERSE EFFECTS

- Drowsiness, hangover, vertigo & distortions of mood, impaired judgement & fine motor skills
- Excitement & irritability
- Respiratory depression in presence pulmonary insufficiency
- Rapid IV injection cause cardiovascular collapse, apnea, laryngospasm, coughing
- Hypersensitivity reactions like skin rashes, swelling of eyelids, cheeks & lips & rarely exfoliative dermatitis
- Tolerance & dependence
- Barbiturates enhance porphyrin synthesis, **absolutely contraindicated in patients with acute intermittent porphyria**

BARBITURATES – DRUG INTERACTIONS

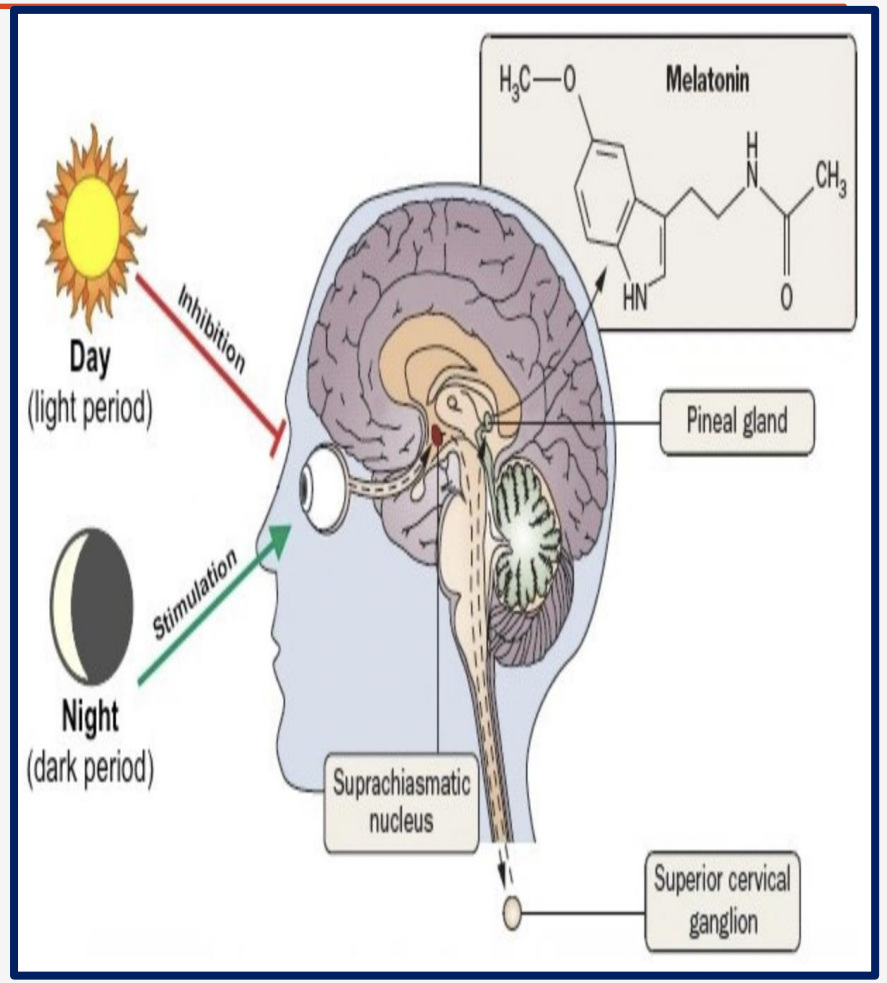
- Barbiturates combine with other CNS depressants, cause severe depression; interactions with ethanol & first-generation antihistamines are common
- Induce hepatic CYP450 microsomal enzymes, chronic administration enhances metabolism of endogenous steroid hormones, oral contraceptives that are metabolized by CYP450 system

NON-BENZODIAZEPINE HYPNOTICS

- Commonly referred as “Z compounds.” include zolpidem, zaleplon, zopiclone, & eszopiclone
- Bind selectively only with $GABA_A$ containing α_1 subunits
- **Lack antianxiety, anticonvulsant & muscle relaxant properties**
- **Are widely used for <u>short-term management of insomnia</u>**
- Little incidence of REM rebound
- Risks of abuse, tolerance & dependence lower than with BZDs & withdrawal symptoms are milder
- All are rapid & short-acting agent & produce minimum hangover
- Actions are blocked by flumazenil

MELATONIN RECEPTOR AGONISTS

- **Melatonin** synthesised in pineal gland in response to darkness
- Two GPCRs for melatonin, MT_1& MT_2, in suprachiasmatic nucleus
- MT_1 & MT_2 mediate sleep & involved in circadian rhythm
- Melatonin, Ramelteon & Tasimelteon, agonists at MT_1 & MT_2



MELATONIN RECEPTOR AGONISTS

RAMELTEON

- Reduces latency of sleep onset
- effective in treating insomnia

Advantages

- ✓ No effects on sleep pattern
- ✓ Does not impair next-day cognitive function
- ✓ No evidence of rebound insomnia or withdrawal effects
- ✓ Well tolerated & also useful in both transient & chronic insomnia with no tolerance & abuse liability
- ✓ **Useful in jet lag**
- Extensive first-pass metabolism by CYP1A2 & CYP2C9, duration of action is prolonged in combination with microsomal enzyme inhibitors & hepatic failure

TASIMELTEON

- Approved for non- 24-hour sleep-wake disorder in totally blind patients

OREXIN RECEPTOR ANTAGONISTS

- Orexin A & B, wake-promoting neuropeptides found in hypothalamus
- Orexin levels are high in day & low at night
- Orexins act on receptors OX_1 & OX_2
- Loss of orexin neurons is associated with **NARCOLEPSY**
- Orexin antagonists **SUVOREXANT & ALMOREXANT,**
- **Suvorexant:** decreases sleep onset latency & increases total sleep time
- Also a substrate of CYP3A4, half-life prolonged by enzyme inhibitors
- Most common adverse reaction: daytime somnolence

5-HT RECEPTOR AGONIST-- BUSPIRONE

- Anxiolytic effects **by acting as a partial agonist at brain 5-HT_{1A} receptors**, & also has affinity for dopamine D_2 receptors
- Do not interact with GABAergic systems
- Relieves anxiety without causing marked sedative, hypnotic, or euphoric effects
- Has no anticonvulsant or muscle relaxant properties
- Causes less psychomotor impairment than BDZs
- Has minimal abuse liability
- Anxiolytic effects take 3–4 weeks to become established
- Used in generalized anxiety states but is less effective in panic disorders

BIO ETHICAL ISSUE- DATE RAPE

Certain benzodiazepines, particularly flunitrazepam (Rohypnol) have been misused for this purpose

1. Sedative Effects

Impair a person's ability to resist unwanted advances.

2. Amnesia

Individuals may not remember events that occurred while under the influence of the drug, including the assault.

3. Detection Challenges

These drugs can be difficult to detect in standard drug tests, especially if the victim does not report the assault immediately.

ROLE OF AI

Monitoring Benzodiazepine Use

- Wearable devices integrated with AI can track physiological parameters (like heart rate and sleep patterns) to detect adverse effects or overdose in real time.
- By predictive analytics, AI can improve patient safety and outcomes in the context of benzodiazepine therapy.

FURTHER READING

- Lewandowska, K., Małkiewicz, M.A., Siemiński, M., Cubała, W.J., Winklewski, P.J. and Mędrzycka-Dąbrowska, W.A., 2020. The role of melatonin and melatonin receptor agonist in the prevention of sleep disturbances and delirium in intensive care unit–a clinical review. *Sleep Medicine*, *69*, pp.127-134.
- De Crescenzo, F., D'Alò, G.L., Ostinelli, E.G., Ciabattini, M., Di Franco, V., Watanabe, N., Kurtulmus, A., Tomlinson, A., Mitrova, Z., Foti, F. and Del Giovane, C., 2022. Comparative effects of pharmacological interventions for the acute and long-term management of insomnia disorder in adults: a systematic review and network meta-analysis. *The Lancet*, *400*(10347), pp.170-184.