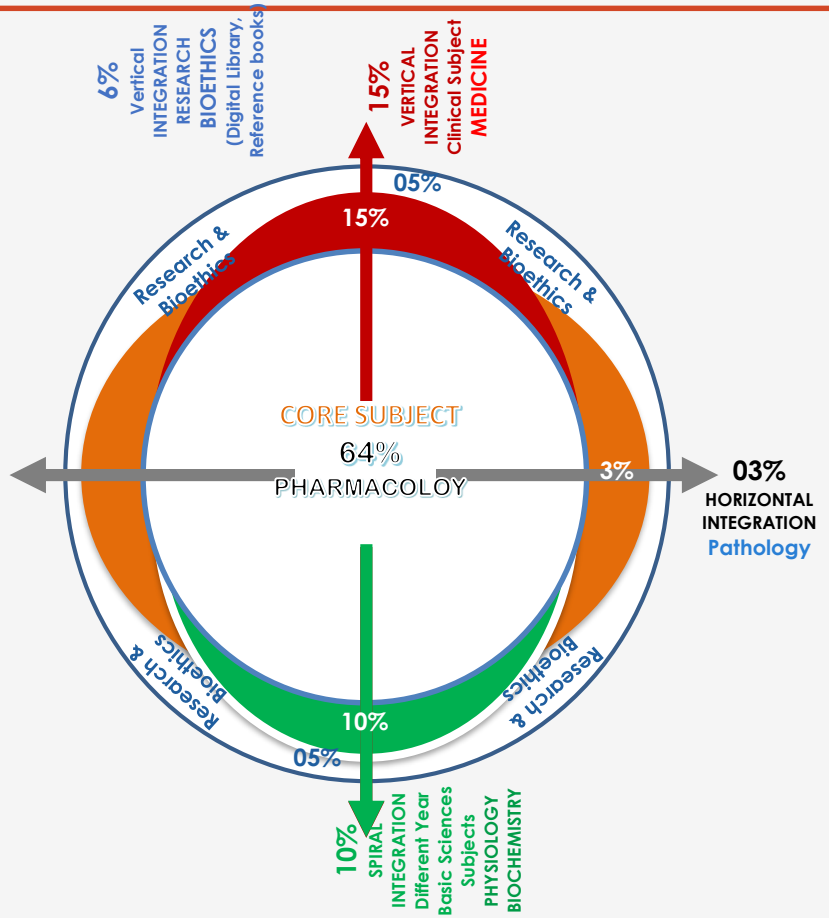

بسم الله الرحمن الرحيم

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

NEUROTRANSMITTERS--FUNCTIONAL CLASSIFICATION

1.Excitatory

- Glutamate
- Aspartate
- Orexin

2.Inhibitory

- GABA (Gamma-amino butyric acid)
- Glycine
- Endocannabinoids

3.Mixed

- Acetylcholine
- Norepinephrine
- Dopamine
- 5-Hydroxytryptamine (Serotonin)
- Histamine
- Peptides

SEDATIVES & HYPNOTICS

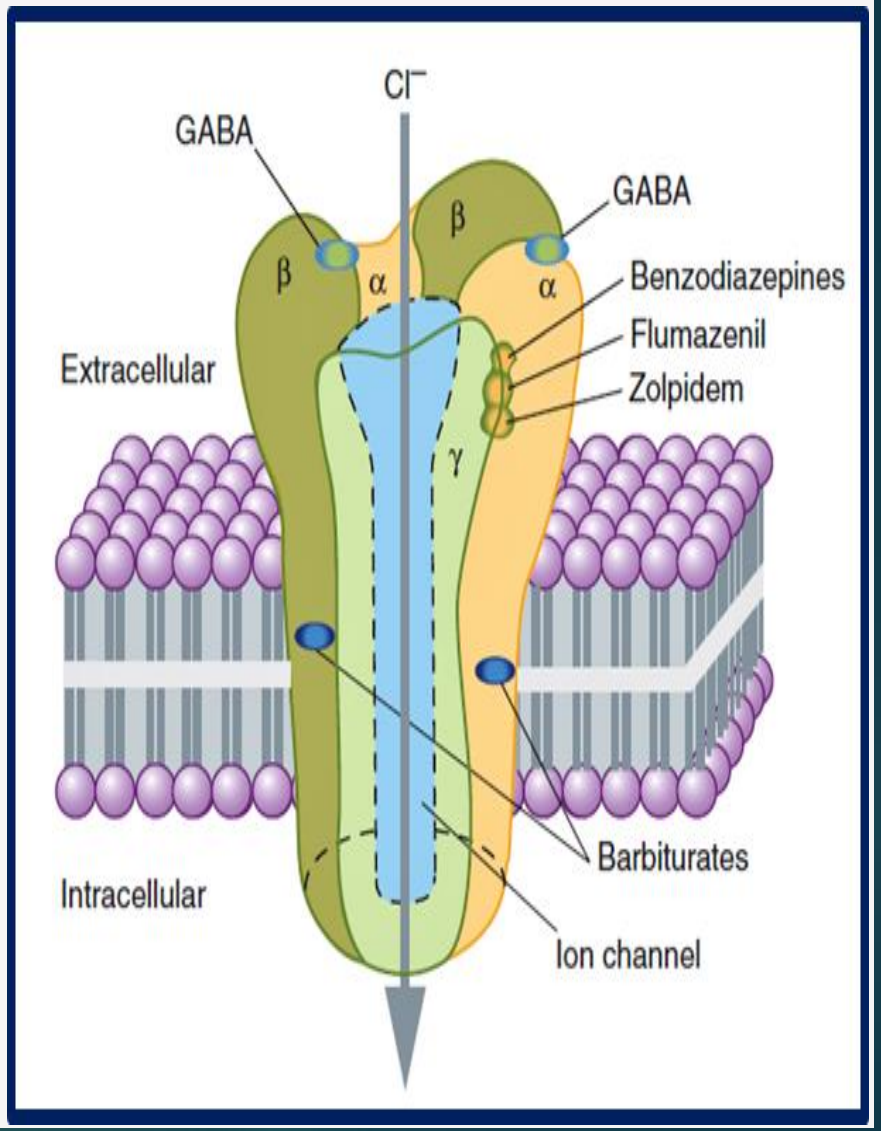
- **Sedatives/**anxiolytics, reduce anxiety & exert a calming effect with minimum CNS depression
- **Hypnotics,** produce drowsiness & encourage onset & maintenance of sleep, from which recipient can be aroused easily
- Hypnotic have more pronounced depression of CNS than sedation

CLASSIFICATION-SEDATIVES & HYPNOTICS

1. **BENZODIAZEPINES(BZDs)**
   Diazepam, Clonazepam,
   Flurazepam
   Lorazepam, Nitrazepam,
   Oxazepam
   Quazepam, Temazepam
   Alprazolam, Triazolam, Midazolam
   Clobazam,Clorazepate,
   Chlordiazepoxide
2. **NON-BENZODIAZEPINE HYPNOTICS (Z-drugs)**
   Zolpidem, Zaleplon, Zopiclone
   Eszopiclone
3. **BARBITURATES**
   Phenobarbital, Pentobarbital
   Secobarbital, Mephobarbital
   Methohexital
4. **MELATONIN RECEPTOR AGONIST**
   Ramelteon, Tasimelteon
5. **5-HT RECEPTOR AGONIST**
   Buspirone
6. **OREXIN RECEPTOR ANTAGONIST**
   Almorexant, Suvorexant
7. **ANTI-DEPRESSANTS**
   Amitryptyline

GABA RECEPTORS

- Two types of GABA receptors
  - $GABA_A$
  - $GABA_B$
- BZDs, barbiturates and non BZs hypnotics bind to $GABA_A$
- A pentameric structure, 5 subunits (α, β, γ, δ, ε, π, ρ)
- Binding site for BZD, between an α & γ subunits
- Barbiturates bind to multiple isoforms (non specific)
- Non BZs hypnotics Interact only with α_1 subunits



BENZODIAZEPINES CLASSIFICATION

According to Duration of Action

Ultra Short acting($t_{1/2}$ < 3 h)

Triazolam, Midazolam

Short acting($t_{1/2}$ < 6 h)

Lorazepam, Temazepam

Intermediate acting ($t_{1/2}$, 6–24 h)

Alprazolam, Nitrazepam

Oxazepam, Quazepam

Long acting ($t_{1/2}$ > 24 h)

Flurazepam, Diazepam

Clorazepate, Chlordiazepoxide

According to Therapeutic Use

1. **Anxiolytic**

Alprazolam, Diazepam, Lorazepam Clorazepate, Chlordiazepoxide, Oxazepam

2. **Hypnotic**

Triazolam, Estazolam Temazepam, Flurazepam Quazepam

3. **Anticonvulsant**

Diazepam, Lorazepam, Clonazepam Nitrazepam, Clobazam

4. **Anesthetic**

Diazepam, Lorazepam, Midazolam

5. **Muscle relaxant** Diazepam

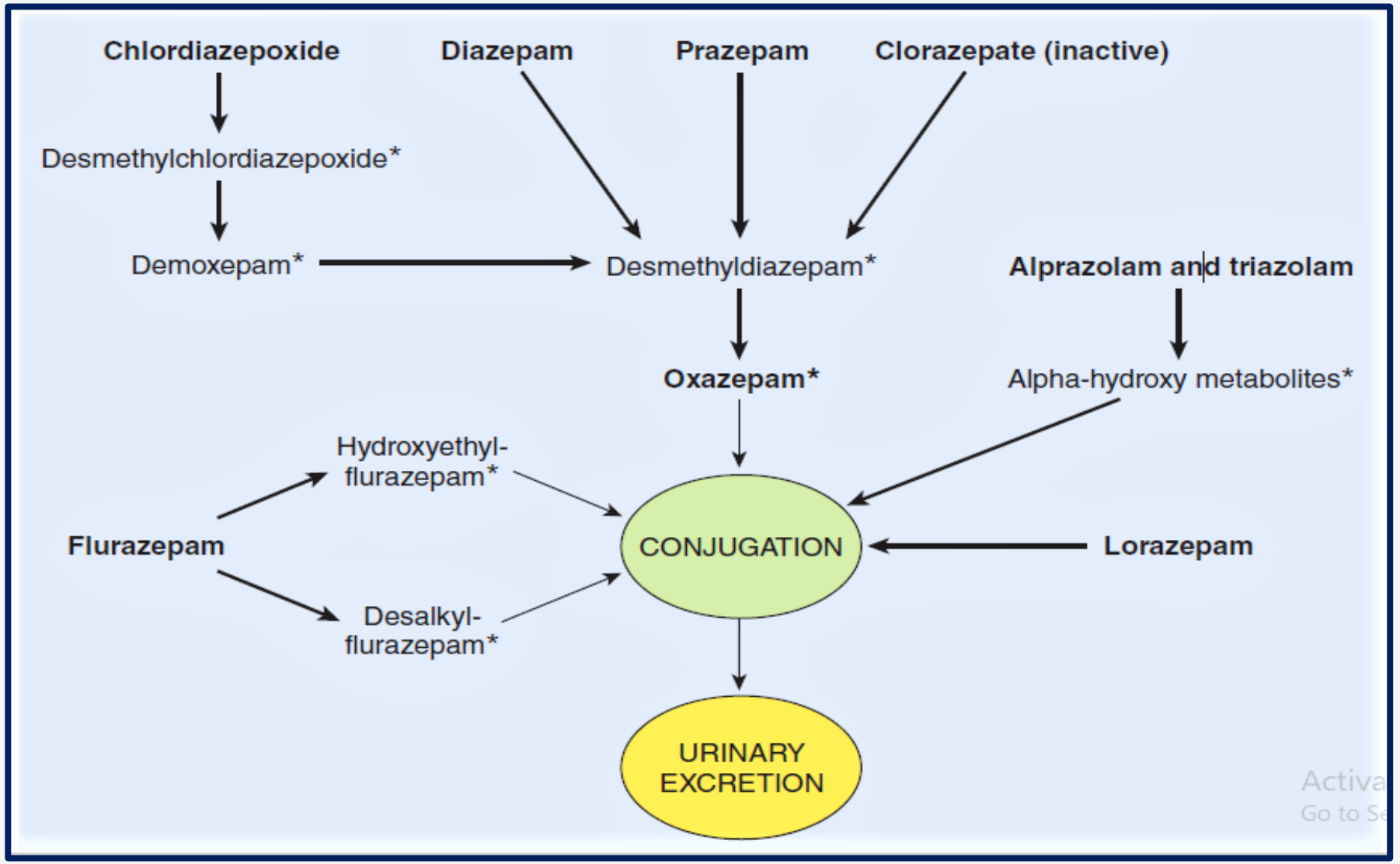
BENZODIAZEPINES-- PHARMACOKINETICS

- Rapid Oral Absorption
- After I/V administration
  - Rapid uptake into brain & highly perfused organs……. Redistribution phase into less well perfused tissues especially muscle & fat
- **Metabolism:**
- Hepatic, undergo microsomal oxidation reactions catalyzed by CYPP450 isozymes
- Metabolites conjugated to form glucuronides that excreted in urine

BENZODIAZEPINES--PHARMACOKINETICS

- Half-lives of these drugs ↑ed in older patients, & patients with severe liver disease.
- BZDs cross placenta & secreted in milk.
- Activity of CYP450 enzymes ↑ed with older sedative hypnotics like barbiturates

Biotransformation of benzodiazepines



BENZODIAZEPINES—MECHANISM OF ACTION

- BDZ are allosteric modulators of $GABA_A$, enhance GABA's effects without directly activating $GABA_A$ thus **increase frequency of opening of Cl^- channel in response to GABA**
- Inverse agonists (β-carbolines) act as negative allosteric modulator of GABA-receptor function, produce anxiety & seizures.

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

1. Sedation:

- Produce calming effects with reduction of anxiety
- Depressant effects on psychomotor & cognitive functions

2. Anterograde amnesia:

- Produce dose-dependent anterograde amnesia

3.Anesthesia:

- Long acting BZDs can produce stage III of general anesthesia

4. Anticonvulsant effect:

- Inhibit development & spread of epileptiform electrical activity in CNS

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

5. Hypnosis:

General effects of BZDs on normal sleep pattern are as follows:

i. Latency of sleep onset is decreased (time to fall asleep)
ii. Duration of NREM sleep ↑
iii. Duration of REM sleep ↓
iv. Duration of stage 4 NREM slow-wave sleep ↓

- **REM rebound"**
- Abrupt cessation of older short acting agents (triazolam) →↑ amount of REM sleep, anxiety & irritability
- Little incidence with newer hypnotics

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

6. Cardiovascular System:

- In pts with impair CV function & in hypovolemic states, normal doses may cause CV depression
- Diazepam increases coronary flow by increasing interstitial concentrations of cardio depressant adenosine → Negative inotropic effects
- **At toxic doses**, myocardial contractility & vascular tone both depressed by central & peripheral effects, via accumulation of adenosine

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

7. Respiration:

- Significant respiratory depression in patients with pulmonary disease

8. GI Tract:

- Diazepam markedly decreases nocturnal gastric secretion

9. Muscle relaxation:

- At high doses BZDs depress transmission at skeletal neuromuscular junction

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

9. Tolerance:

Decreased responsiveness to a drug following repeated exposure

- **Metabolic tolerance**

  Increase in the rate of drug metabolism

- **Pharmacodynamics tolerance**

  Changes in responsiveness

PHARMACOLOGICAL ACTIONS OF BENZODIAZEPINES

10. Dependence:

- BDZs cause physiologic dependence when used on a long term basis.
  Abrupt withdrawal leads to more serious withdrawal signs.
- Drugs with longer half lives are eliminated slowly leading to gradual with-drawl.
- Drugs with very shorter halflives may lead to signs of with drawal even between doses.

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.

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SPIRAL INTEGRATION


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