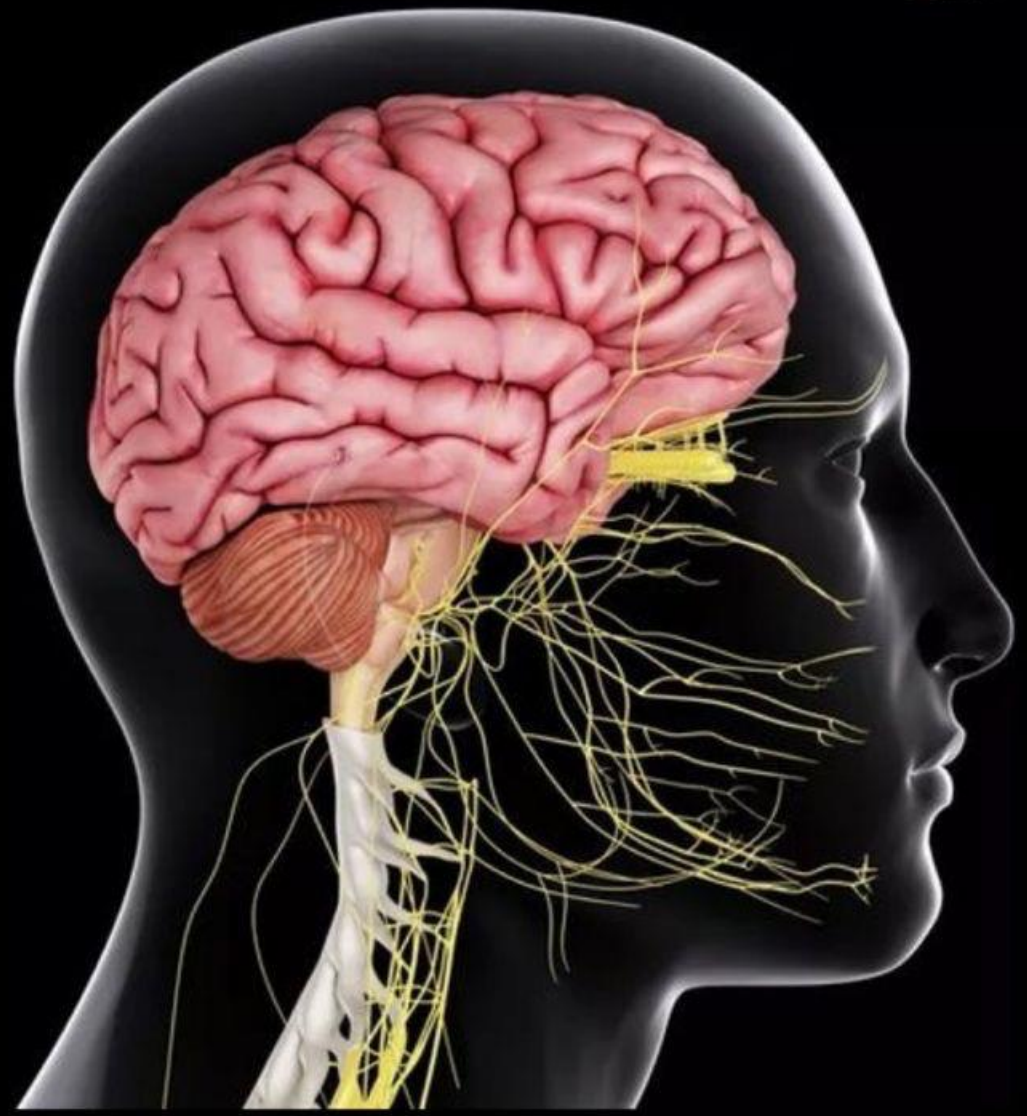
وَقُل رَّبِّ زِدْنِي عِلْمًا



النادي الطبي

CENTRAL NERVOUS SYSTEM

SUBJECT : Pharma

LEC NO. : Lec 6 anxiolytics

DONE BY : Enas wail hantash

- Anxiety is an unpleasant state of tension, apprehension or uneasiness (a fear that arises from either a known or an unknown source).
- Physical symptoms of anxiety are a result of sympathetic activation: tachycardia, sweating, trembling and palpitations).
- Anxiety disorders include: Generalized anxiety disorder, panic disorder, obsessive compulsive disorder, phobias, etc.

Classification According to Mechanism of Action

I. Drugs Facilitating GABA Action
- Barbiturates
- Benzodiazepines (BZDs)
- Zolpidem.
- Zaleplon

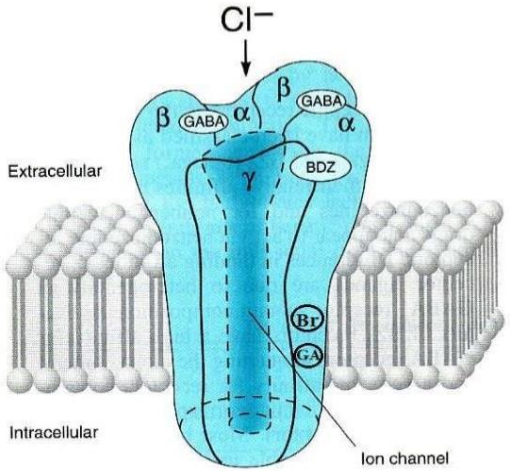
II. 5-HT_{1A} partial agonist
- Buspirone

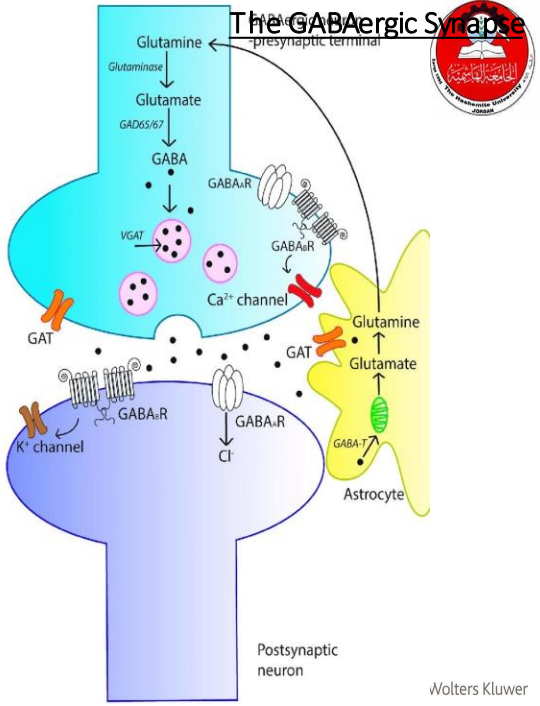
GABA Receptors

- Receptors for the inhibitory neurotransmitter γ-aminobutyric acid (GABA).
- Two main receptors types:

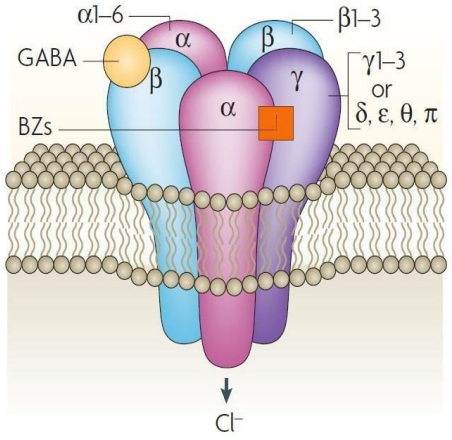
❑**$GABA_A$ receptors**: ligand-gated ion channels (*ionotropic*)

❑**$GABA_B$ receptors**: G-protein-coupled receptors (*metabotropic*)





- $GABA_A$ Receptor
- *pentamer* formed of 3 different types of subunits (two α, two β and one γ) surrounding a Cl^- ion channel.
- The GABA binding site is at the <u>interface between α and β subunits</u>.
- Binding of 2 GABA molecules triggers the opening Of the central ion channel allowing for chloride influx.
- The influx of chloride → hyperpolarization → decreases action potentials (neurotransmission).



BENZODIAZEPINES
Alprazolam XANAX
Chlordiazepoxide LIBRIUM
Clonazepam KLONOPIN
Clorazepate TRANXENE
Diazepam VALIUM, DIASTAT
Estazolam
Flurazepam DALMANE
Lorazepam ATIVAN
Midazolam VERSED
Oxazepam
Quazepam DORAL
Temazepam RESTORIL
Triazolam HALCION

BENZODIAZEPINE ANTAGONIST
Flumazenil ROMAZICON

OTHER ANXIOLYTIC DRUGS
Antidepressants VARIOUS (SEE CHAPTER 10)
Buspirone BUSPAR

BARBITURATES
Amobarbital AMYTAL
Pentobarbital NEMBUTAL
Phenobarbital LUMINAL SODIUM
Secobarbital SECONAL
Thiopental PENTOTHAL

OTHER HYPNOTIC AGENTS
Antihistamines VARIOUS (SEE CHAPTER 30)
Doxepin SILENOR
Eszopiclone LUNESTA
Ramelteon ROZEREM
Zaleplon SONATA
Zolpidem AMBIEN, INTERMEZZO, ZOLPIMIST

Benzodiazepines

Mechanism of action:

- Benzodiazepines are allosteric modulators of $GABA_A$ receptors
- They bind to distinct, high-affinity site from the GABA-binding site located at the interface between the α and γ subunits.
- These binding sites are labeled as benzodiazepine (BZ) receptors.
- CNS BZ receptors:

❑ **BZ_1** includes α_1 subunits (mediate sedation, hypnosis, amnesia and antiepileptic effects)

❑ **BZ_2** includes α_2 subunits (anxiolytic and muscle relaxant effects)

❑ Binding of benzodiazepines to the BZ receptors on the $GABA_A$ receptor complex → **increases affinity** of GABA to bind to its receptors. This **increases the frequency of opening** of Cl^- channel → facilitating the inhibitory effects of GABA.

Actions:

- **Reduction of anxiety:** through α_2 subunit containing $GABA_A$ receptors.
- **Sedative/hypnotic:** through α_1 subunit containing $GABA_A$ receptors.
- **Anterograde amnesia:** through α_1 subunit containing $GABA_A$ receptors.
- **Anticonvulsant:** through α_1 subunit containing $GABA_A$ receptors.

Therapeutic uses:

- **Anxiety disorders:**
  - Panic disorder, GAD, OCD, social anxiety disorder, phobias.
  - Anxiety related to depression or schizophrenia.
  - **ONLY** for severe anxiety (NOT for the stress of everyday life).
  - Longer-acting drugs are preferred: **lora**-; **clona**-; and **diazepam**.
  - **Tolerance:** anxiolytic effects < sedative/hypnotic.
- Sleep disorders (insomnia)

❑ Decrease latency to sleep onset AND Increase stage II of non-rapid eye movement (REM) sleep.

❑ commonly used drugs:

1. Temazepam: intermediate-acting – given 1-2 hours before bedtime– Best for frequent awakening.
2. Triazolam: short-acting – best for inability to go/stay asleep – Rebound insomnia

(using long-acting like flurazepam may result in excessive daytime sedation)

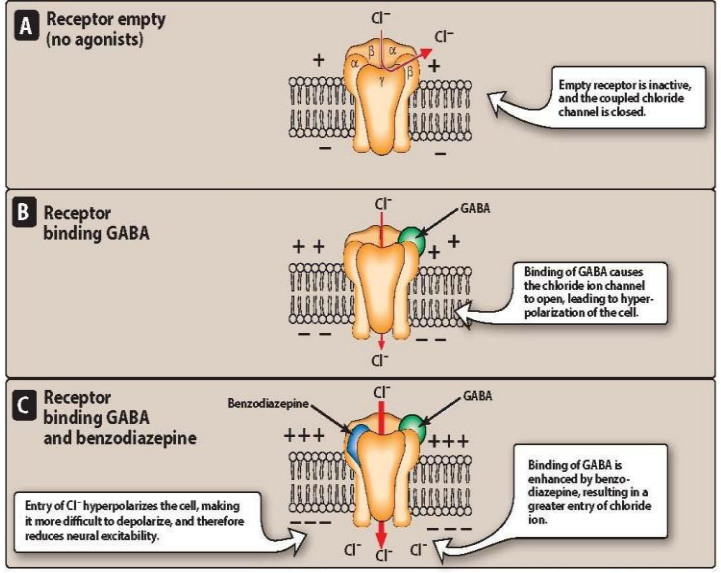
- **Amnesia** Used as an adjunct to anesthesia: to relief unpleasant, surgery- induced anxiety

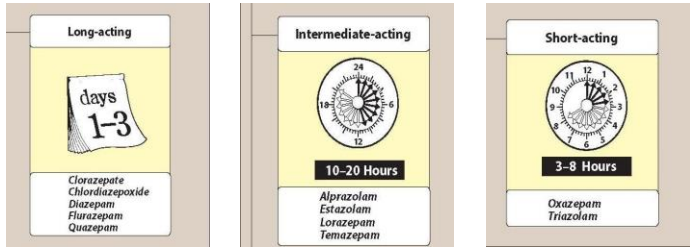
❑ **midazolam** is often used for this purpose

- Seizures Clonazepam used as adjunctive therapy for certain types of seizures.

❑ Lora-; and diazepam used for the treatment of *status epilepticus (given IV)* and alcohol-withdrawal associated seizures.

- **Muscular disorders** used for skeletal muscle spasms ,,, used for spasticity associated with multiple sclerosis and cerebral palsy





Duration of action

- determine therapeutic uses **(half-life is very important)**
- **with some benzodiazepines, the clinical duration of action does NOT correlate with the actual half-life**

Pharmacokinetics Benzodiazepines

- **Absorption**

  - highly lipophilic

CNS distribution? Fat? Pregnancy?

- **Metabolism**

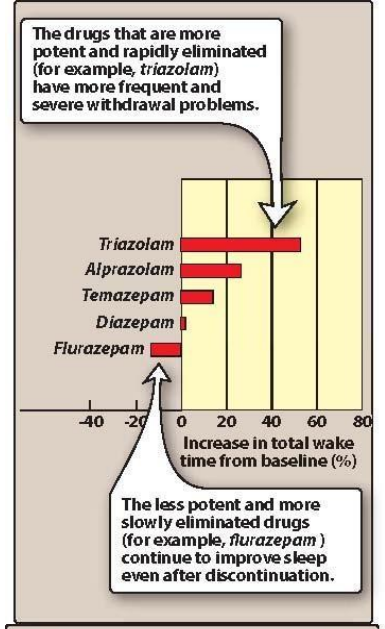
❑ metabolized by hepatic microsomal system

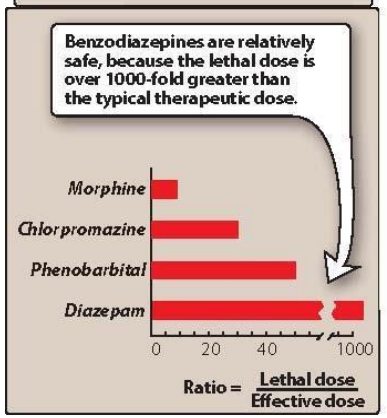
❑ mostly the metabolites are also active

❑ excreted in the urine

Adverse effects

- Drowsiness and sedation
  - ➢ Driving
  - ➢ Cognitive impairment
- Combination with other sedatives can be dangerous:
  - ➢ Alcohol, barbiturates, anesthetics, …
- Anterograde amnesia
  - ➢ Impaired ability to learn new information.





Dependence

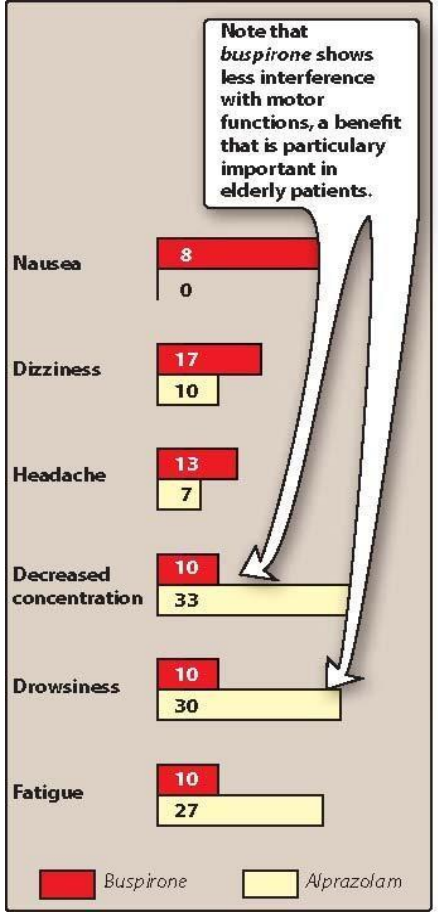
- Psychological and physical dependence can develop rapidly
- Used for short periods of time
- Abrupt discontinuation → WITHDRAWAL:

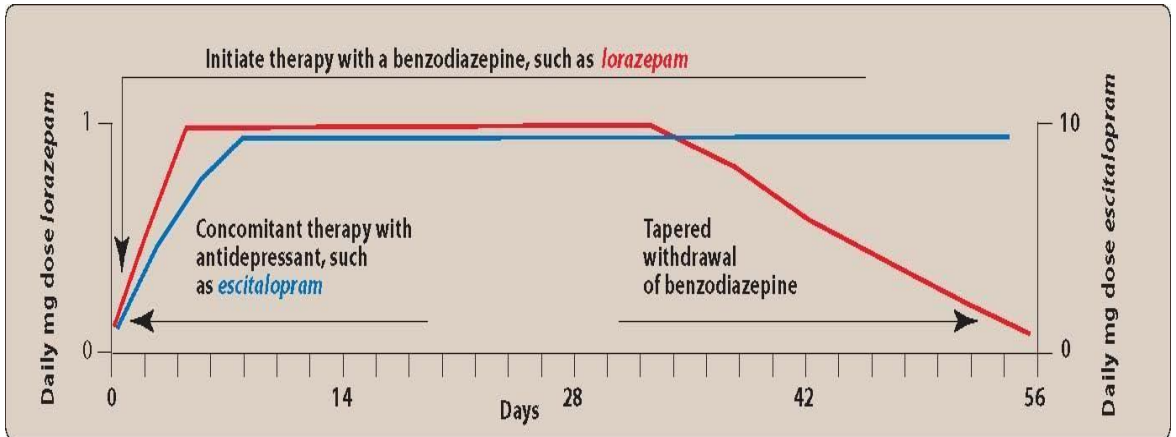
-confusion, anxiety, agitation, rebound insomnia, tension and seizures.

-withdrawal happens more with short-acting

- Benzodiazepine Antagonist: antidote
- Flumazenil
  - GABA receptor antagonist
  - used for benzodiazepine toxicity/overdose
  - IV only
  - rapid onset, short duration of action
  - may precipitate withdrawal in dependent patients

- Other anxiolytics: antidepressants
- Remember: many antidepressants are used to treat anxiety.
- **SSRIs** (escitalopram, paroxetine) and **SNRIs** (duloxetine, venlafaxine) are FIRST LINE to treat anxiety.
- Often used with a benzodiazepine initially (first 4-6 weeks)
- Other anxiolytics: Buspirone
- Useful for the chronic treatment of generalized anxiety disorder.
- Ineffective for short-term "on demand" "as needed" treatment of acute anxiety: slow onset of action.
- Effect mediated by 5-HT1A receptors.
- No anti-seizure or muscle relaxant properties
- No dependence





Barbiturates

Overview:

- Old
- Largely replaced by benzodiazepines as sedative/hypnotics

❑ Induce tolerance/dependence/withdrawal/lethal overdose >>>> benzodiazepines

- Some still in use but the majority are not

- example: thiopental is a short-acting barbiturate have been used to induce anesthesia.

Mechanism of action: Site of action: $GABA_A$ receptors.

- **Binding site**: different from benzodiazepines

❑ Barbiturates potentiate GABA action on chloride entry by **prolonging the duration** of Cl channel opening.

Actions:

- **CNS depression:**

❑ low doses→ sedation

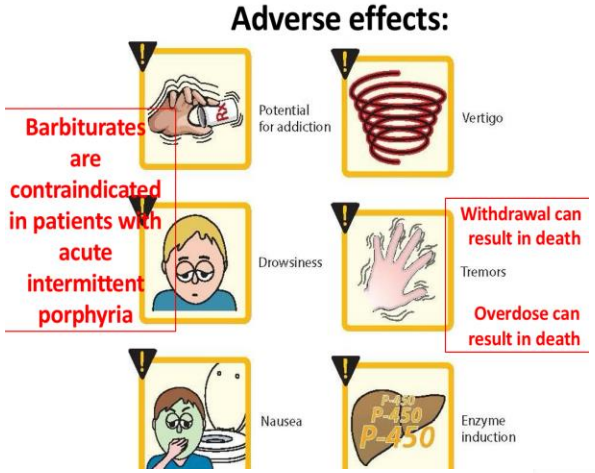
❑ High doses→ hypnosis >>> anesthesia

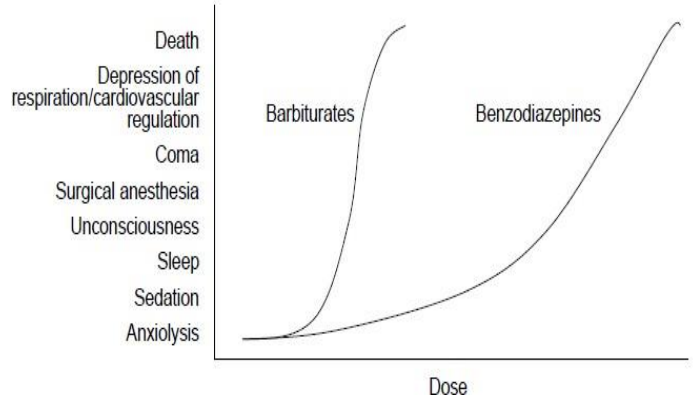
❑ Higher doses → coma and DEATH!

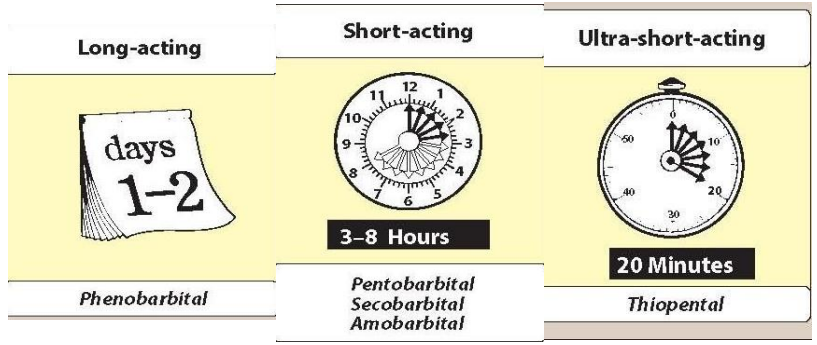
- **Respiratory depression**

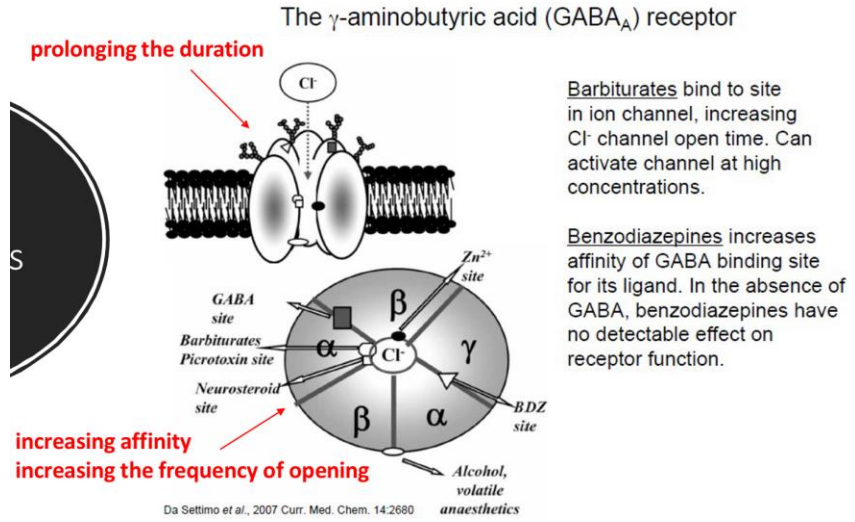
Therapeutic uses:

1. **Anesthesia:** e.g., <u>thiopental</u> for induction of anesthesia (not anymore).
2. **Anticonvulsant:** e.g., <u>phenobarbital</u> for refractory seizures.
3. **Sedative/hypnotic:** for insomnia (no longer accepted)









- Other Hypnotics: Zolpidem
- Not a benzodiazepine, but the same mechanism of action (on BZ1)
- short half-life (2-3 hrs), rabid onset of action.
- Most commonly prescribed drug for insomnia in the US.
- Decrease sleep latency, no effect on sleep.
- Adverse effect: impaired performance in the morning, driving, and dependence.
- Other Hypnotics: Ramelteon
- Selective agonist: melatonin receptors 1 and 2
- Indicated for the treatment of insomnia (decreases sleep latency)
- No abuse potential/dependence/withdrawal
- Other Hypnotics: Over-The-Counter
- **Antihistamines:**
  - Insomnia (mild).
  - Diphenhydramine.
  - Chlorphenamine (Allerfin).

Summary of Clinical Uses

- Benzodiazepines are indicated only in severe anxiety or insomnia.
- Drug therapy should be started with a small oral dose for a limited Period (less than 3 weeks forinsomnia) to avoid drug abuse and dependence
- Gradual termination of therapy should be done to avoid withdrawal.
- *Longer-acting* drugs are preferred as *anxiolytics* …*shorter-acting* as *hypnotics*.
- Most benzodiazepines are metabolized in liver → dose adjustment is Required in liver cirrhosis to avoid accumulation to toxic levels

  Specially of long acting agents and those metabolized to active metabolites such as diazepam**.**