Anxiolytic and Hypnotic Drugs

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DEPT. OF PHARMACOLOGY

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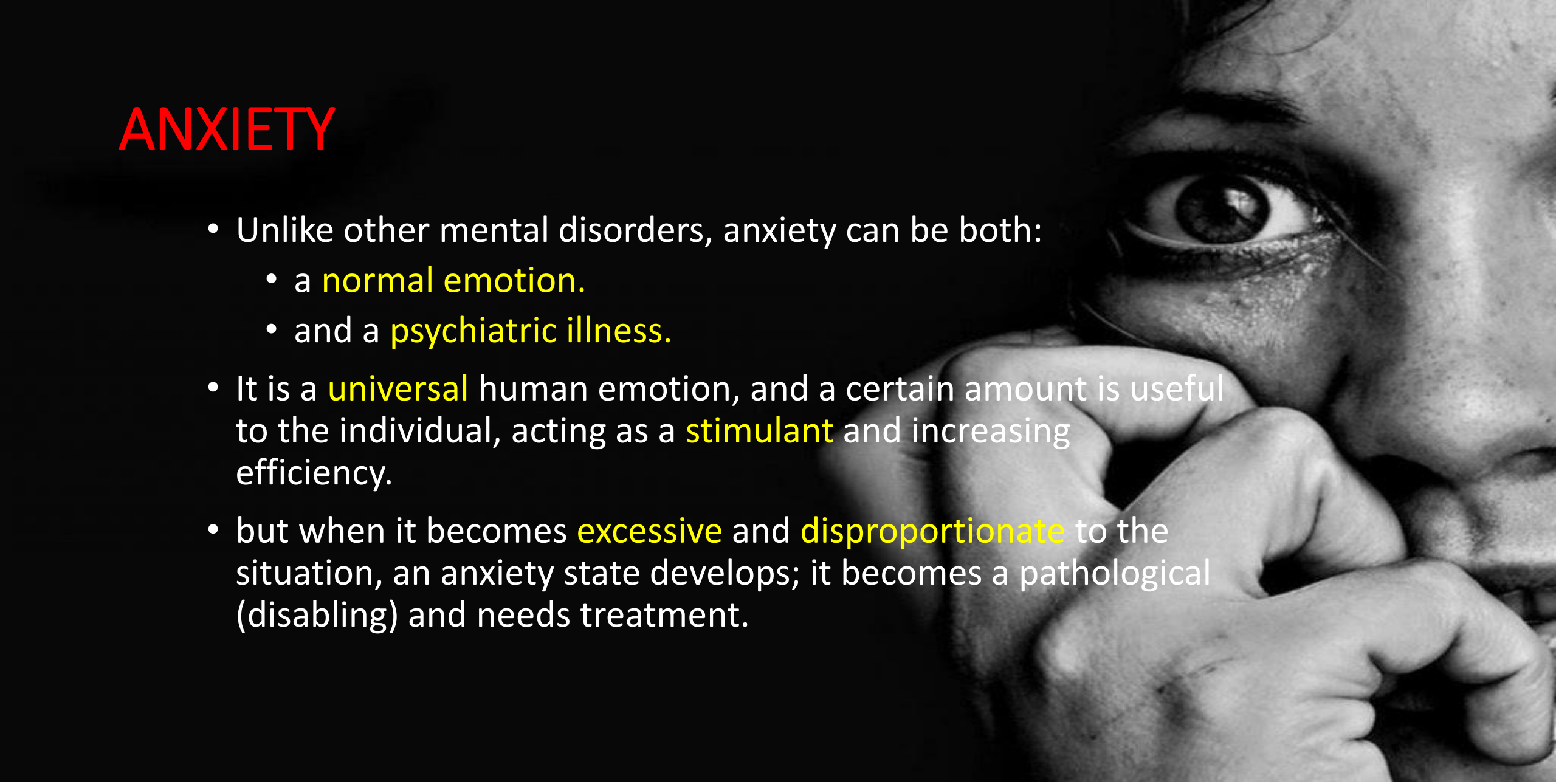
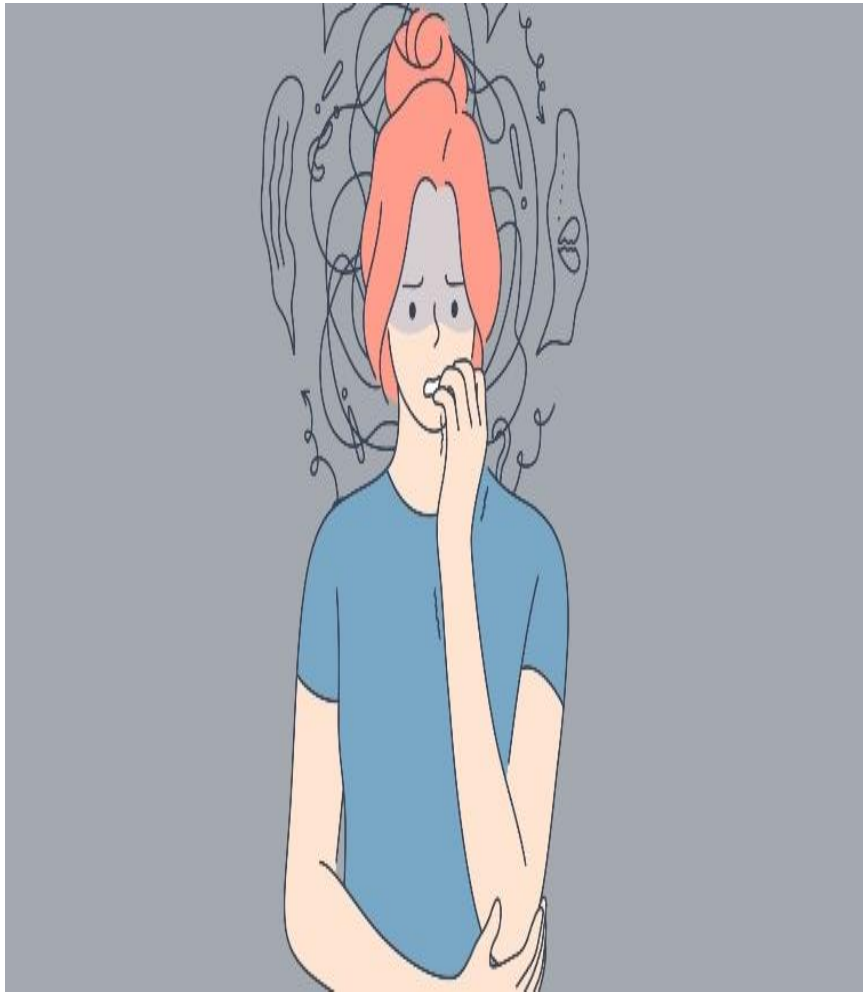
ANXIETY



- Unlike other mental disorders, anxiety can be both:
  - a normal emotion.
  - and a psychiatric illness.
- It is a universal human emotion, and a certain amount is useful to the individual, acting as a stimulant and increasing efficiency.
- but when it becomes excessive and disproportionate to the situation, an anxiety state develops; it becomes a pathological (disabling) and needs treatment.

Anxiolytic and Hypnotic Drugs

- anxiety are among the most common mental disorders.
- **Anxiety** is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source).
- The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.
- Episodes of mild anxiety are common life experiences and do not warrant treatment.
- severe, chronic, anxiety may be treated with antianxiety drugs (sometimes called anxiolytics).



ANXIETY CLASSIFICATION

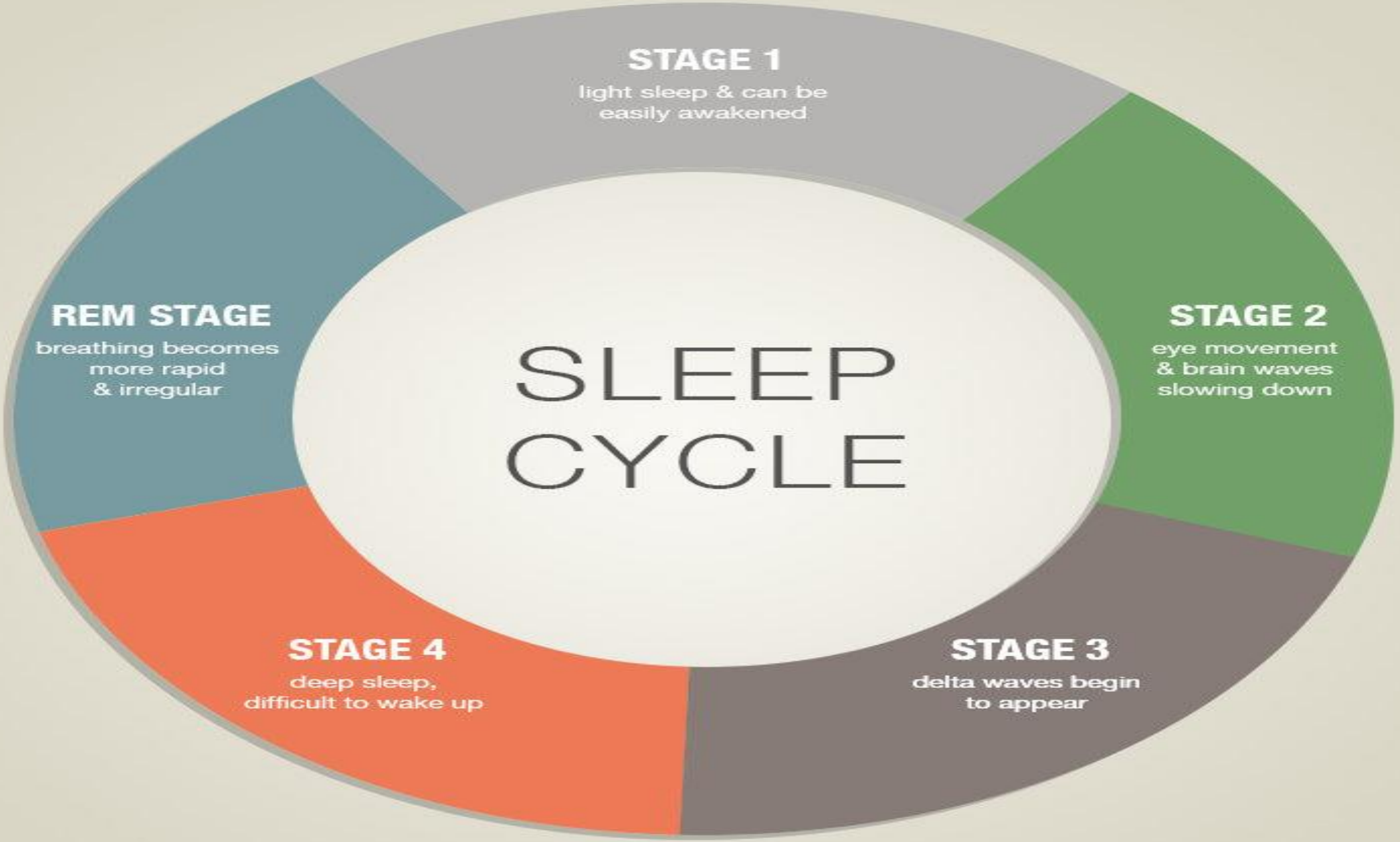
❖**Primary**

1. **Generalized anxiety disorder (GAD)**: apprehensive and tense for no particular reason.
2. **Panic disorder**: unexpected attacks of anxiety.
3. **Phobic disorders**: fears certain situation “agoraphobia”
4. **Obsessive compulsive disorder**: repetitive, anxiety driven behavior or obsessive thoughts and doubts (check things more than once)
5. **Post-traumatic stress disorder** (rape or warfare)

❖**Secondary** due to medical causes or substances

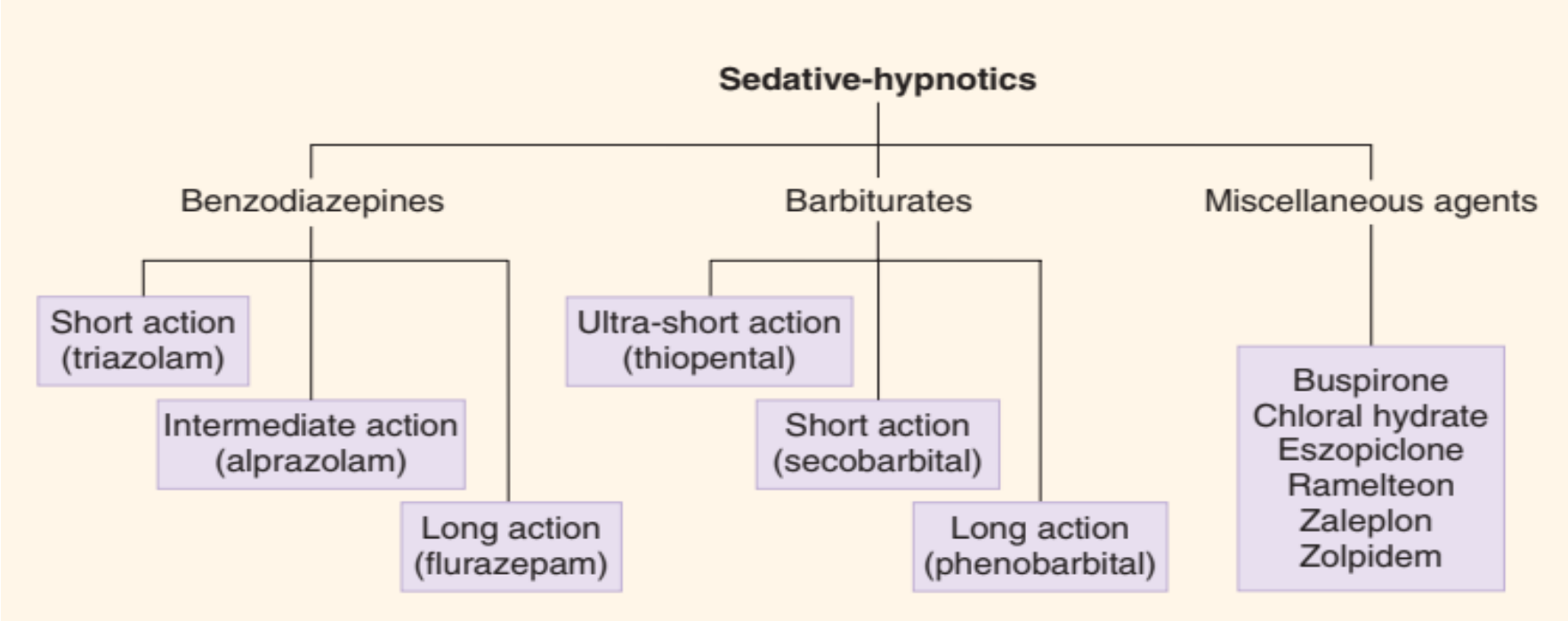
Anxiolytic and Hypnotic Drugs

- **Sedative** is a drug that reduces excitement and calms the person.
- **Hypnotic** is a drug that produces sleep-resembling normal sleep.
- Sedative-hypnotic drugs: in **small** dose (Sedative) & in **large** dose (Hypnotic).
- Both sedation and hypnosis are different grades of CNS depression.


STAGE 1
light sleep & can be easily awakened
STAGE 2
eye movement & brain waves slowing down
STAGE 3
delta waves begin to appear
STAGE 4
deep sleep, difficult to wake up
REM STAGE
breathing becomes more rapid & irregular
SLEEP CYCLE

CLASSIFICATION OF SEDATIVES AND HYPNOTICS

1. **Benzodiazepines** (BZDs):diazepame
2. **Barbiturates**: Phenobarbitone
3. **Nonbenzodiazepine** hypnotics: Zolpidem, zopiclone, zaleplon, eszopiclone.
4. **Others**: Melatonin, ramelteon suvorexant.

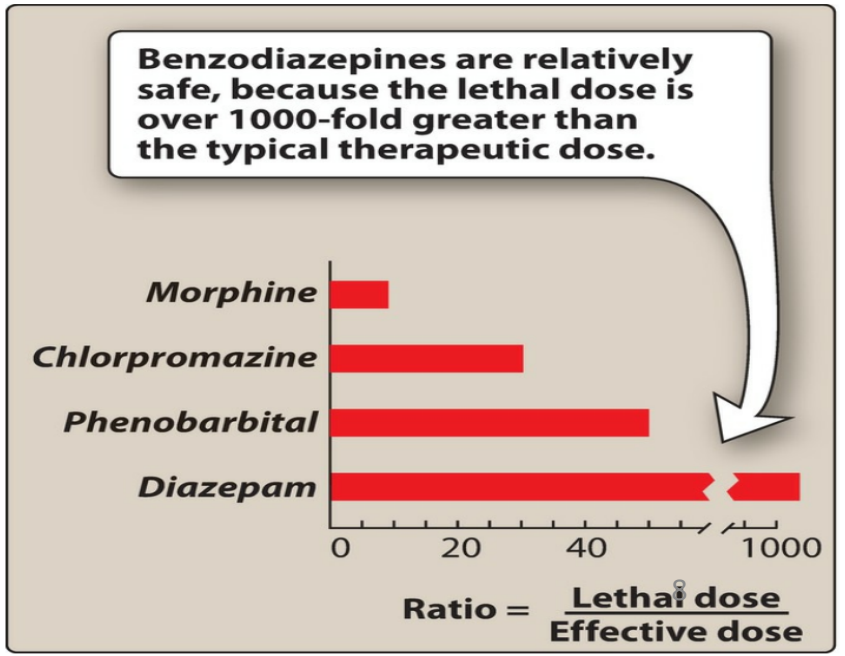


Benzodiazepines

- They are **widely** used anxiolytic drugs.
- They replaced barbiturates in the treatment of anxiety and insomnia, because BZD are generally considered to be **safer** and **more effective.**
- Though BZD are commonly used, they are **not** necessarily the **best choice** for anxiety or insomnia.
- Certain **antidepressants** with **anxiolytic** action, such as the selective serotonin reuptake inhibitors (SSRIs), are preferred in many cases, and **nonbenzodiazepine** hypnotics and antihistamines may be preferable for **insomnia**

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



Mechanism of action

- **GABA** is the principle **inhibitory** neurotransmitter in CNS.
- GABA acts via GABA receptors (**GABA A** and **GABA B**).
- BZDs bind to GABA A receptors→ this binding site is different from GABA-binding site.
- BZDs ↑ **affinity** of GABA for receptor.
- GABA ↑ **chloride** ion conduction through receptor.
- This action is **potentiated** by BZDs.
- BZDs enhance **frequency** of CL channel opening in response to GABA.
- ↑ CL entry in neurons leads to **hyperpolarization** → **CNS inhibition**.

Benzodiazepines

↓

Bind to specific site on $GABA_A$ receptor
(different from GABA-binding site)

↓

Increase in frequency of opening of Cl^- channels

↓

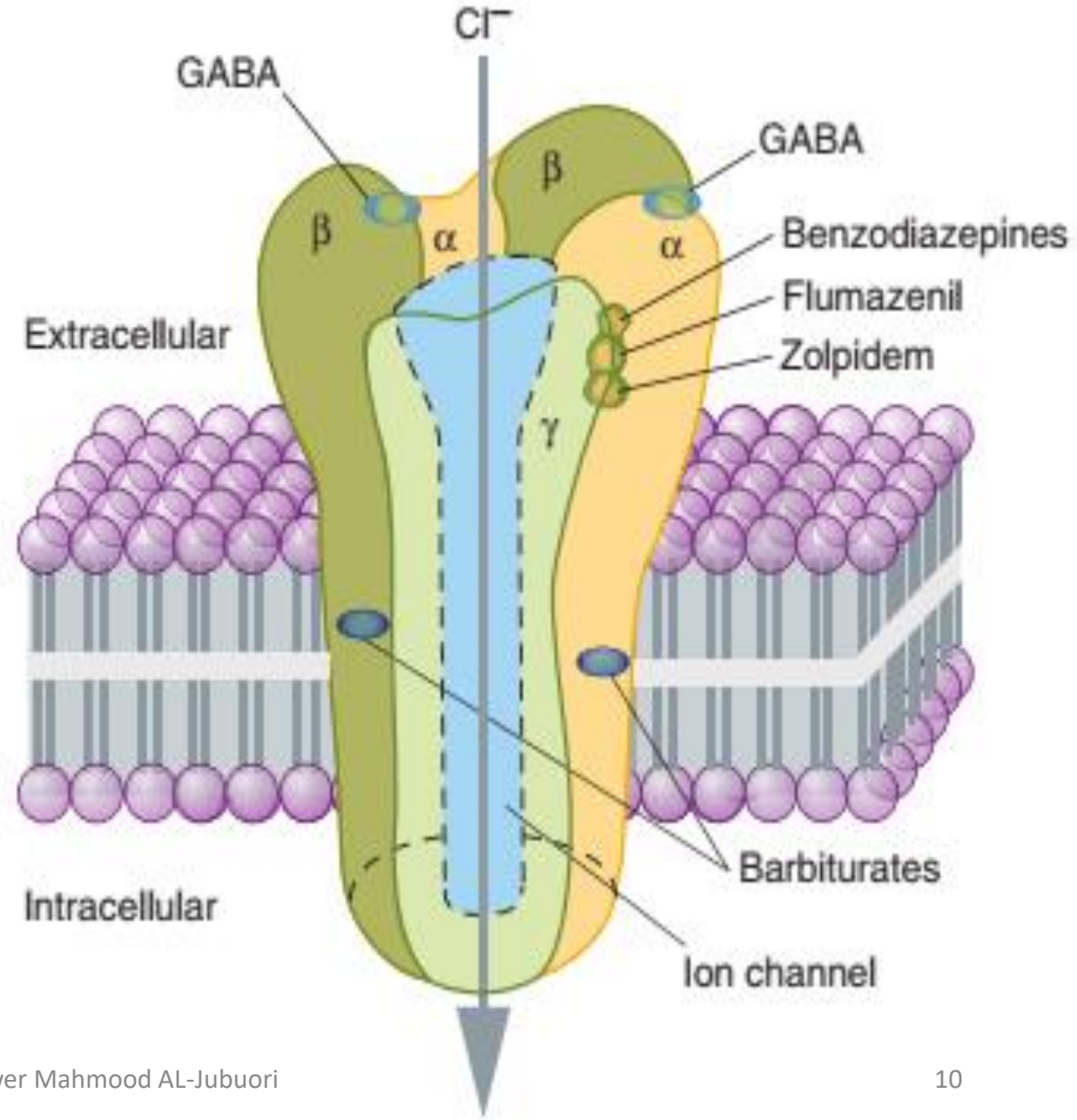
Increase in GABA-mediated chloride current

↓

Membrane hyperpolarization

↓

CNS depression



Pharmacological Actions

- **Reduction of anxiety**: At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission, thereby inhibiting neuronal circuits in the limbic system of the brain.
- **Sedative/hypnotic**: All benzodiazepines have sedative and calming properties, and some can produce hypnosis (artificially produced sleep) **at higher doses**.
- **Anterograde amnesia**: Temporary impairment of memory with the use of the benzodiazepines is also mediated by the α1-GABAA receptors. The ability to learn and form new memories is also impaired.
- **Anticonvulsant**: This effect is partially, although not completely, mediated by α1-GABAA receptors.
- **Muscle relaxant**: At high doses, the BZD relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the α2-GABA A receptors are largely located.

Uses of BZDs

❖**Insomnia**: BZDs ↓ time required to fall asleep (↓ sleep latency). The total sleep time is ↑ . BZDs reduce night awakenings and produce refreshing sleep.

1. **Short-acting triazolam** used with problems falling asleep. Higher risk of withdrawal and rebound insomnia is with **triazolam** than with other agents.
2. **Intermediate-acting temazepam** useful for frequent awakenings and have difficulty staying asleep.
3. **Long-acting flurazepam** is rarely used, due to its extended half-life, which may result in excessive daytime sedation and accumulation of the drug, especially in the elderly. In general, hypnotics should be used for only a limited time, usually **1 to 3** weeks.

❖**Muscular disorders**: **Diazepam** is useful in the treatment of skeletal muscle spasms and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

Uses of BZDs

- **Anxiolytic**: BZD used for anxiety disorder. They also used in anxiety related to depression and schizophrenia.
- They drugs should be reserved for severe anxiety and should not be used to manage the stress of everyday life.
- Because of their addictive potential, they should only be used for short periods of time.
- The **longer-acting** agents, such as clonazepam, lorazepam, and diazepam, are often **preferred** in patients with anxiety that **require prolonged** treatment.
- The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects.
- For panic disorders, alprazolam is effective for short- and long-term treatment

Uses of BZDs

❖ **Anticonvulsants**:

- Diazepam, lorazepam, clonazepam, clobazam, etc. have anticonvulsant effect.
- IV **diazepam/lorazepam** is used to control life-threatening seizures in status epilepticus, tetanus, drug-induced convulsions, febrile convulsions, etc.
- **Clonazepam** is used in the treatment of absence seizures.

Uses of BZDs

- **Diagnostic (endoscopies) and minor operative procedures(dental procedures)**: i.v. BZDs are used because of their sedative–amnesic–analgesic and muscle relaxant properties.
- **Preanaesthetic medication and general anaesthesia** (GA): These drugs are used as preanaesthetic medication because of their sedative–amnesic and anxiolytic effects. Hence, the patient cannot recall the perioperative events later. **i.v. diazepam, lorazepam, midazolam,** etc. are combined with other CNS depressants to produce GA.
- **To treat alcohol-withdrawal symptoms**: **Long-acting** BZDs, such as chlordiazepoxide and diazepam are used.

Pharmacokinetics

- BZDs are usually given **orally** or **IV** and occasionally by **rectal** route (**diazepam**) in children.
- The rate of absorption following oral administration is variable; absorption is erratic from **i.m**. route; hence rarely used.
- They have a **large volume** of distribution.
- They have a **short duration of action** on occasional use because of rapid **redistribution**, hence, are free of residual (hangover) effects, even though elimination half-life is long.
- BZDs are **metabolized in liver**. Some undergo **enterohepatic** recycling.
- Some of them **produce active metabolites** which have long half-life; hence, cumulative effects may be seen. **Oxazepam** is not significantly metabolized in liver.
- The metabolites are **excreted in urine**. BZDs cross placental barrier **not** recommended for use during pregnancy. Nursing infants may also be exposed to the drugs in breast milk.

DURATION OF ACTION OF BENZODIAZEPINES

Long-acting

Clorazepate
Chlordiazepoxide
Diazepam
Flurazepam
Quazepam

Intermediate-acting

10–20 Hours

Alprazolam
Estazolam
Lorazepam
Temazepam

Short-acting

3–8 Hours

Oxazepam
Triazolam

Adverse Effects

- BZDs have **a wide margin of safety**. They are **generally well tolerated**.
- The common side effects are drowsiness, confusion, amnesia, lethargy, weakness, blurred vision, ataxia, daytime sedation, impaired motor coordination hence avoid driving
- Paradoxical **irritability** and **anxiety** is seen in few patients
- Tolerance and dependence**: less potential** compared to barbiturates.
- Withdrawal symptoms are mild and slow in onset for long-acting BZDs. Withdrawal symptoms more intensive and abrupt in short-acting BZDs.
- Withdrawal after chronic use causes symptoms like tremor, insomnia, restlessness, nervousness and anorexia.
- When administered to **pregnant** women during labor **neonate** can develop hypotonia and respiratory depression.

Tolerance and Dependence

- **Tolerance—a** decrease in responsiveness occurs when sedative hypnotics are used chronically or in high dosage. It occures when used for more than 1-2 weeks. It is associated with a decrease in GABA receptor density.
- The antianxiety effects of the BDZs are less subject to tolerance than sedative and hypnotic effects.
- **Dependence** occurs within weeks to months of continued use.
- **Physiological dependence:** removal of the drug evokes unpleasant symptoms, usually the opposite of the drugs effects
- **Psychological dependence**: the drug taker feels compelled to use the drug & suffers anxiety when separated from drug.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LIBROXIDE 5
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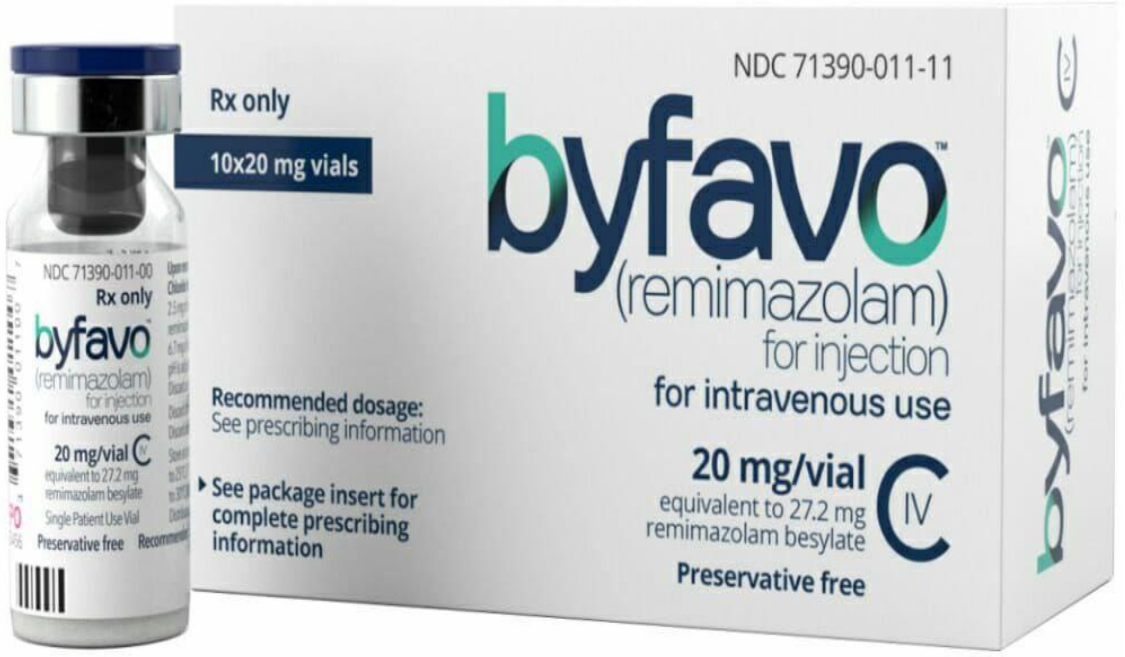
NDC 71390-011-11
Rx only
10x20 mg vials
byfavo
(remimazolam)
for injection
for intravenous use
Recommended dosage:
See prescribing information
See package insert for complete prescribing information
20 mg/vial
equivalent to 27.2 mg remimazolam besylate
Preservative free
IV
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for injection
for intravenous use
20 mg/vial
equivalent to 27.2 mg remimazolam besylate
Single Patient Use Vial
Preservative free


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XANAX
2 mg Alprazolamum
Tabletki
XANAX
2 mg Alprazolamum
Tabletki


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Midazolam
Injection, USP
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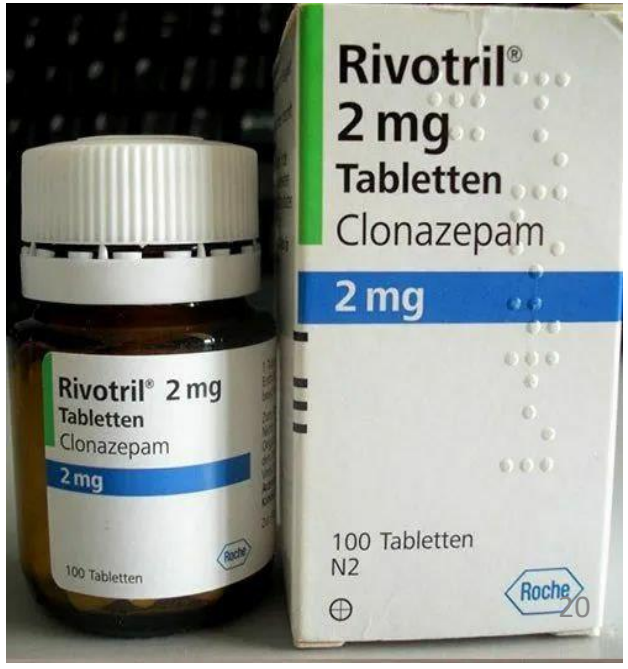
(5 mg/mL)
For I.M. or I.V. Use
CONTAINS BENZYL ALCOHOL
10 mL Multiple-Dose Vial
Almaject
Rx only
Sterile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Clonazepam
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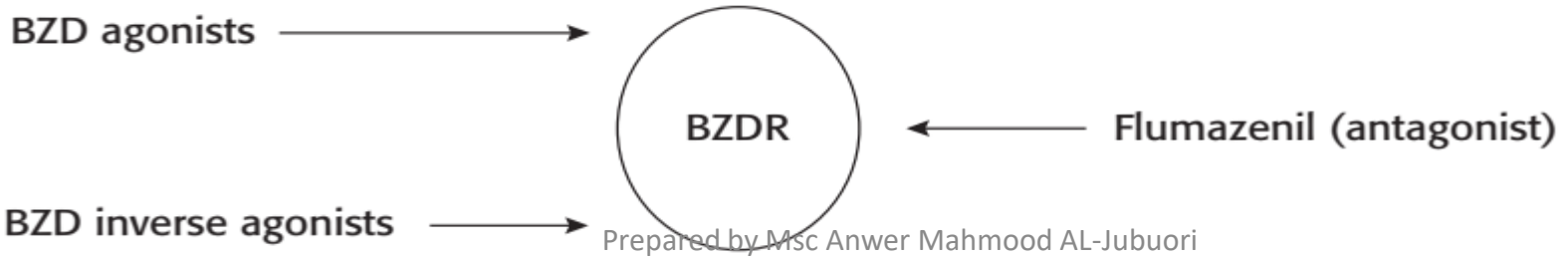
N2
Roche

Benzodiazepine Antagonist (Flumazenil)

- **Flumazenil competitively** reverses the effects of both **BZD agonists** (CNS depression) and BZD **inverse agonists(**β-Carboline).
- Flumazenil is not used orally because of its high first-pass metabolism. It is given by i.v. route and has a rapid onset of action.
- Flumazenil is **used** in the treatment of BZD overdosage and to reverse the sedative effect of BZDs during GA.
- It can also be used to reverse the hypnotic effect of zolpidem, zaleplon and eszopiclone.
- Adverse effects include confusion, dizziness and nausea. It may precipitate withdrawal symptoms (anxiety and convulsions) in dependent subjects.

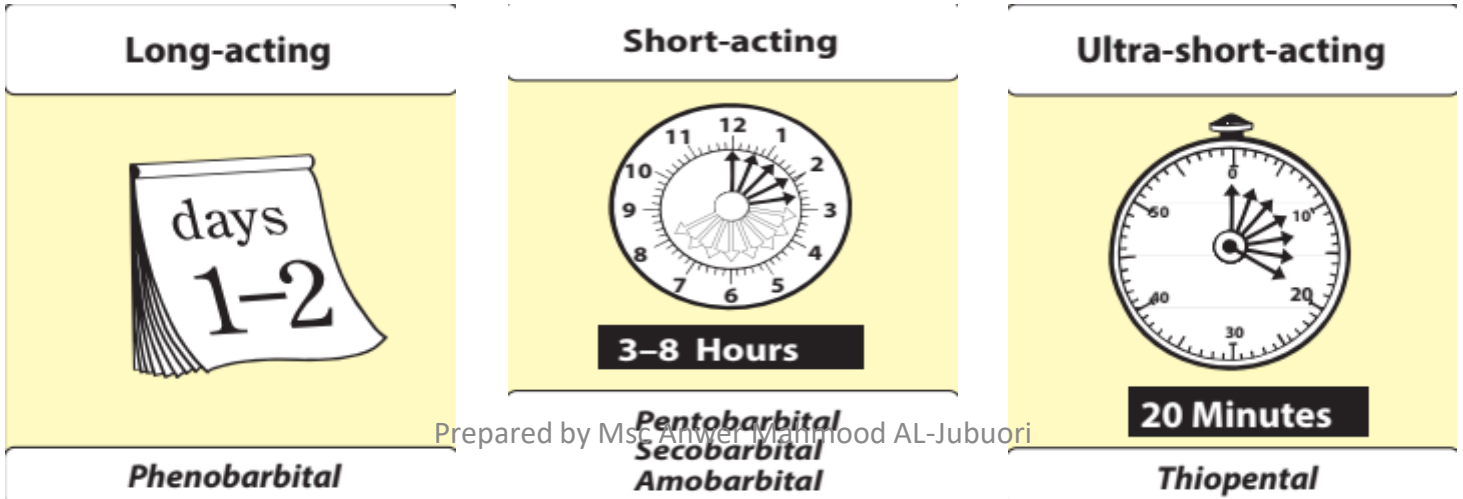


barbiturates

❖The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. They replaced by the BZD, because barbiturates induce tolerance and physical dependence, are lethal in overdose, and are associated with severe withdrawal symptoms.

❖Classification

1. Ultra short-acting→ Thiopentone
2. Short-acting → Pentobarbitone
3. Long-acting → Phenobarbitone



Mechanism of action

- The sedative–hypnotic action of the barbiturates is due to their interaction with **GABA A** receptors, which **enhances** GABAergic transmission.
- The binding site of barbiturates on the GAB A receptor is **distinct** from that of the BZD.
- Barbiturates **potentiate** GABA action on chloride entry into the neuron by **prolonging** the **duration** of the chloride channel openings.
- In addition, barbiturates can **block excitatory glutamate** receptors. These molecular actions lead to decreased neuronal activity.
- At **high concentrations**, barbiturates have GABA-mimetic effect (i.e. barbiturates can directly increase Cl conductance into the neuron).

Barbiturates

↓

Bind to $GABA_A$ receptor
(different from BZD-binding site)

↓

The duration of Cl^- channel kept open is increased

↓

Increase in GABA-mediated chloride current

↓

Membrane hyperpolarization

↓

CNS depression

Pharmacological action

❖Depress **all excitable tissues(except liver)**→ CNS is most sensitive.

❖CNS: **Sedation and hypnosis**

1. they induces **sleep**. Prolongs duration of sleep Alters NREM–REM sleep cycle. Residual sedation and hangover on awakening.
2. They reduces **anxiety**, impairs short-term memory and judgment.
3. Produces **euphoria** → so has addiction potential.
4. **Paradoxical dysphoria**, hyperalgesia in some patients.
5. **Anesthesia**: In high doses. Seen with conventional doses of ultra short-acting barbiturates IV thiopentone
6. **Anticonvulsant:** All barbiturates are anticonvulsants in conventional doses. This effect Seen with sub-hypnotic doses of phenobarbitone

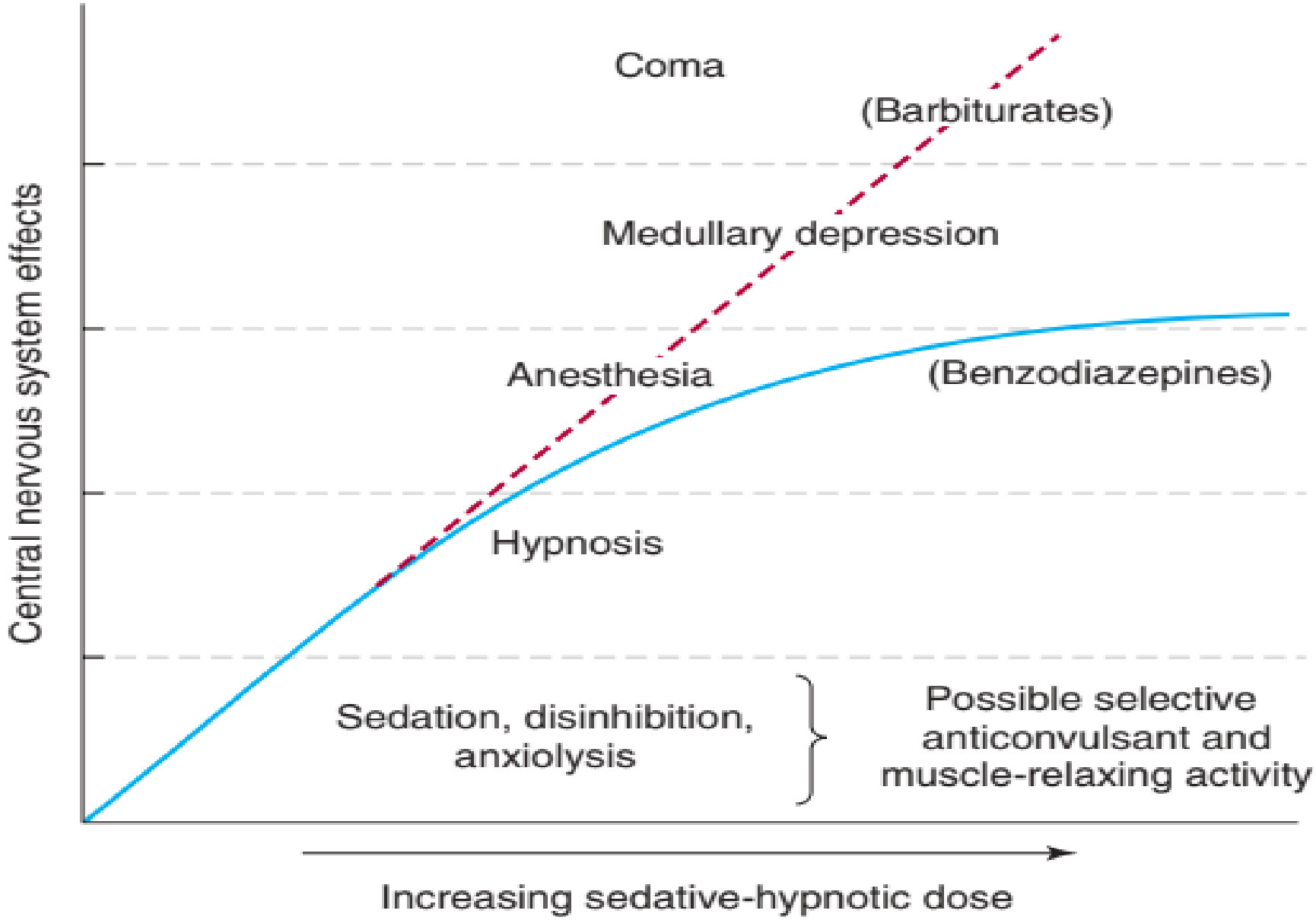


FIGURE 22–2 Relationships between dose of benzodiazepines and barbiturates and their CNS effects.

Pharmacological action

- **Respiratory system**: Significant respiratory depression. Additional direct paralysis of medullary center. Barbiturates suppress the hypoxic and chemoreceptor response to CO2, and overdose is followed by respiratory depression and death.
- **CVS**: Hypnotic doses, causes slight ↓ in BP and HR. Toxic doses, causes significant ↓ in BP due to direct depression of myocardium and vasomotor center.
- **Skeletal muscles:** ↓ Excitability
- **Liver** :induction of liver enzyme

Therapeutic uses

- Not preferred nowadays because of respiratory depression and abuse potential
- **Sedation and hypnosis:** However, BZD are preferred
- **Anesthesia:** The **ultra–short-acting** barbiturates have been historically used intravenously to induce anesthesia but have been replaced by other agents.
- **Anticonvulsant**: **Phenobarbitone** has anticonvulsant effect and is used in the treatment of status epilepticus and generalized tonic–clonic seizures. phenobarbital can depress cognitive development in children and decrease cognitive performance in adults, and it should be used for seizures only if other therapies have failed.
- **Neonatal jaundice** ∴ Phenobarbitone is a microsonal enzyme inducer. It increase production of glucoronyl transferase. This enzyme metabolizes and excretes excess bilirubin so helps in clearance of jaundice.

Pharmacokinetics

- Good oral absorption.
- Wide tissue distribution
- High lipid solubility so have a rapid onset e.g., Thiopentone
- Redistributed to adipose tissue so have a short duration of action e.g Thiopentone
- Potent microsomal enzyme inducers
- These agents are metabolized in the liver, and
- Inactive metabolites are excreted in urine.
- Barbiturates readily cross the placenta and can depress the fetus.

Adverse reactions

- Hangover due to residual CNS depression
- Mood distortion
- Impaired judgment and fine motor skills
- Excitement and irritability In children
- Respiratory depression. It is severe in patients with respiratory disorders even in therapeutic dose
- Contraindicated in porphyrias ∴ They ↑ porphyrin synthesis
- Tolerance on prolonged use
- Physical and psychological dependence Hence there is high abuse potential
- Withdrawal symptoms: Anxiety, restlessness, hallucinations, delirium and convulsions.

Drug Interactions

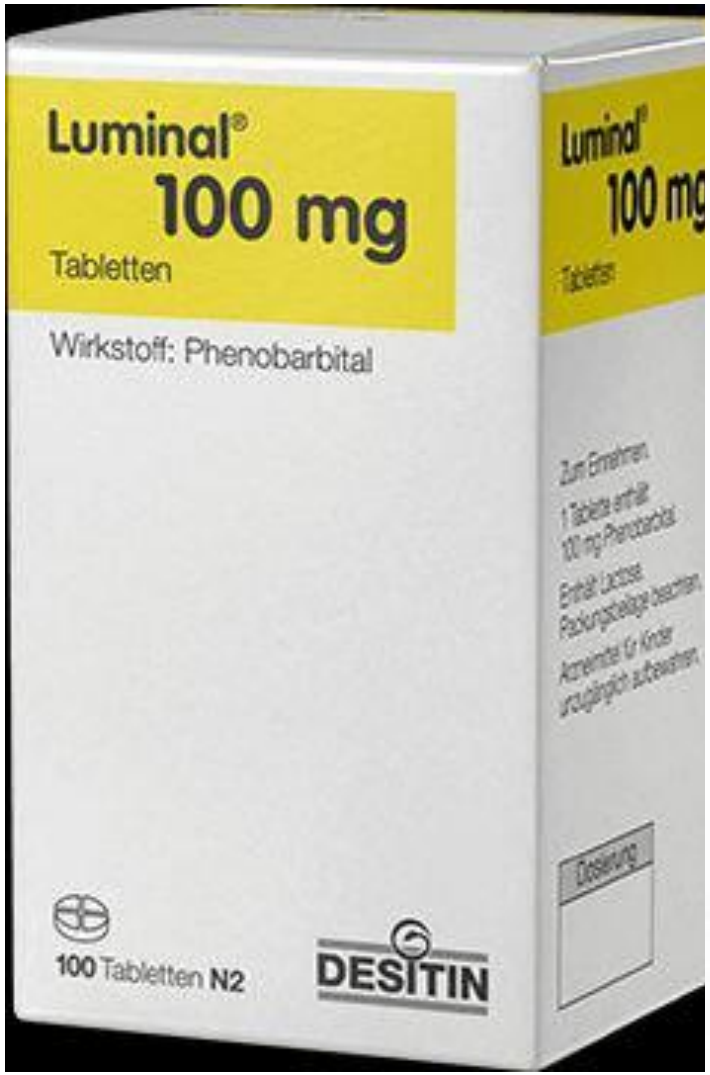
- ❖ Hepatic Microsomal Enzyme Induction → increase metabolism of other drugs e.g. increase metabolism of oral anticoagulants, hypoglycemic & contraceptives.
- ❖Barbiturates + Ethyl alcohol → Synergism → Severe ↓↓C.N.S.
- ❖Barbiturates + Aspirin → Potentiation.
- ❖Barbiturates + Caffeine → Physiological antagonism

WHY BENZODIZEPINES HAS REPLACED BARBITURATES?

BZS	BARBITURATES
➢ They do not produce anesthesia in high doses & patient can be aroused.	➢ Produce loss of consciousness and have low margin of safety
➢ These are not enzyme inducers,	➢ enzyme inducers.
➢ Very low abuse liability.	➢ High abuse liability.
➢ Lesser distortion of normal hypnogram.	➢ Marked suppression of REM sleep.
➢ BZS have no hyperalgesia.	➢ Hyperalgesic action.
➢ BZS can be used as day time anxiolytic.	➢ Unacceptable drowsiness is seen.
➢ Do not effect respiratory or cvs function.	➢ Causes respiratory depression & hypotension.
➢ There is a specific antagonist-Flumazenil.	➢ No specific antagonist.

Other Anxiolytic Agents (Z drug)

- **Newer** agents e.g., Zolpidem, zopiclone, eszopiclone zaleplone
- They are **oral non-BZDs** But produce their effects by **bind to GABA A** receptor **Facilitate** inhibitory transmission
- **Lesser** incidence of dependence and tolerance compared to BZDs
- **Insignificant** alteration of sleep pattern
- Used for **short duration** in insomnia
- **Rapid** onset and **short** duration of action so there is less hangover
- Flumazenil blocks/ reverses actions
- **Zolpidem**: Good **hypnotic**. Weak anticonvulsant, anxiolytic, and muscle relaxant Short-acting (t½ of 2 h). Sleep duration – 8 h. ADR Dizziness, diarrhea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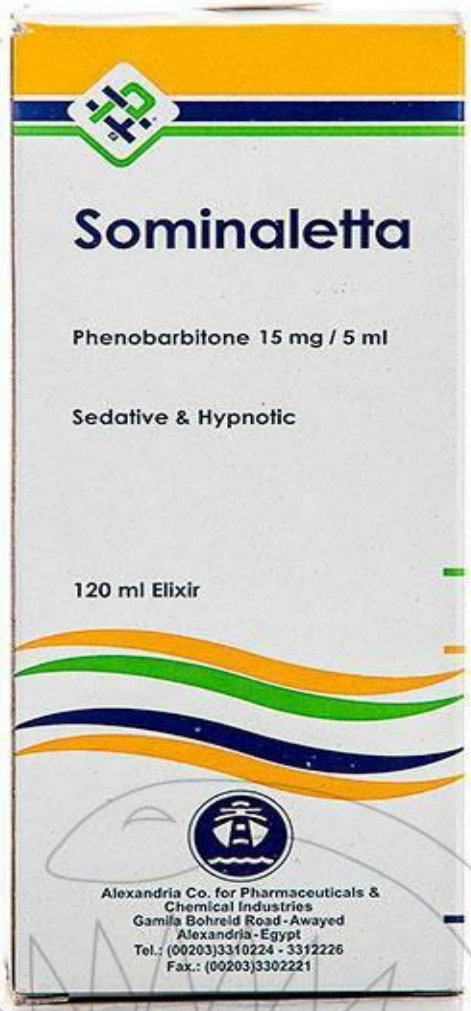
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ZOPICLONE

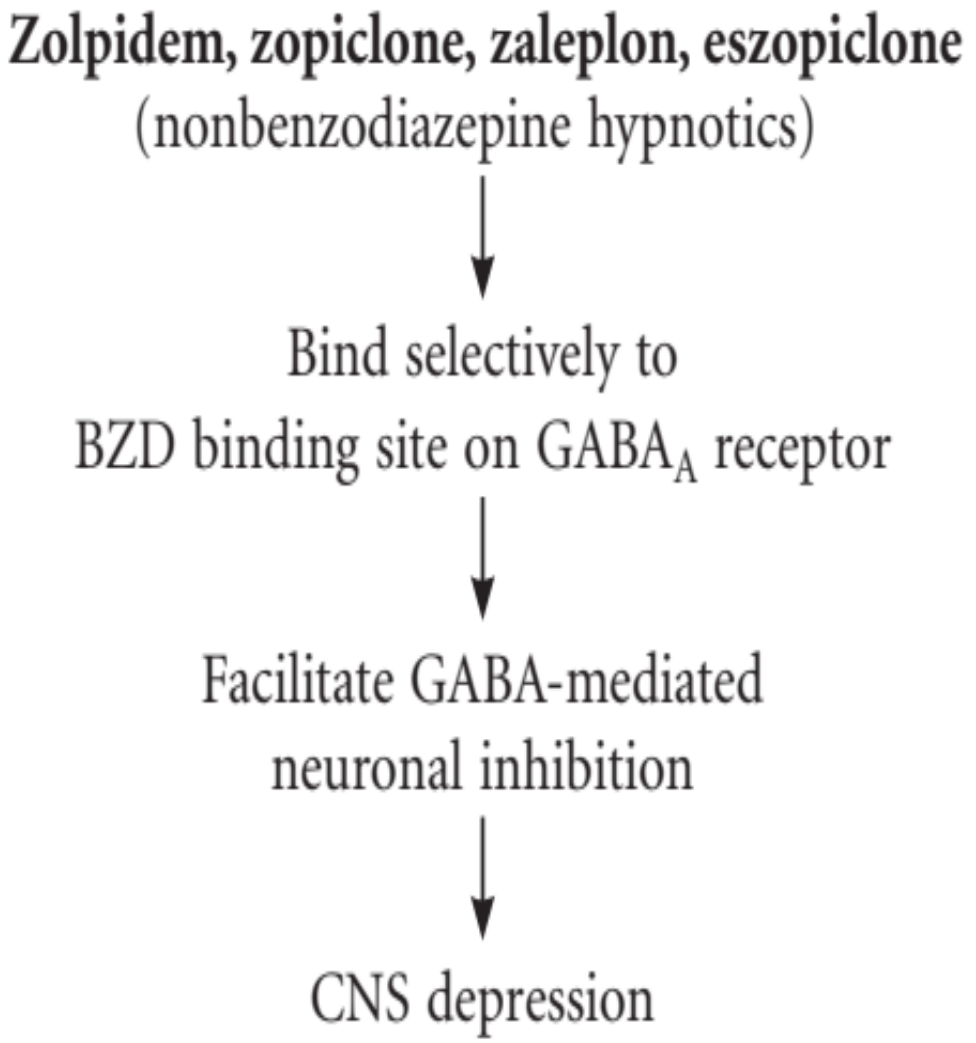
used for short-term treatment of **insomnia**. The side effects are headache, drowsiness, GI disturbances and metallic taste.

ZALEPLON

Useful for patients with long **sleep latency**. Long time to fall sleep. It is the **shortest** acting non-BZD hypnotic.

ESZOPICLONE

used for short- and long-term treatment of **insomnia**.

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pharma science

Other

- **MELATONIN:** It is the hormone secreted by the **pineal gland**; involved in the maintenance of **sleep– wake** cycle and circadian rhythm.
- **RAMELTEON:** It is a melatonin-receptor (MT1 and MT2) agonist, can be used **orally** for the treatment of **sleep onset** insomnia. It reduces sleep latency and prolongs total duration of sleep. There is **no rebound** insomnia on withdrawal; does **not cause tolerance** on chronic use. The important adverse effects are fatigue and dizziness. It **↑ prolactin** levels.
- **TASIMELTEON:** It is another melatonin-receptor agonist used for the treatment of **circadian rhythm disorder** in blind patients.
- **SUVOREXANT:** It prevents orexin from maintaining wakefulness by **blocking orexin** receptors. Orexin is a neuropeptide that promotes wakefulness. It is useful in **chronic** insomnia.


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Melatonin
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Healthy Sleep Cycle*
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100 Tablets
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Rev.: 07/19
Each film-coated tablet contains 8 mg of ramelteon.
Usual Dosage: See package insert for dosage and complete prescribing information.
Store at 25°C (77°F); excursions 15°C to 30°C (59°F to 86°F).
Dispense in a tightly closed, light-resistant container. Protect from moisture and humidity.
Keep this and all drugs out of the reach of children.
Do not accept if seal over bottle opening is broken or missing.
Manufactured by: Cadila Healthcare Ltd., Ahmedabad, India
NDC 70771-1495-3
Ramelteon Tablets
8 mg
1344
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
This package is child resistant.
30 Tablets
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zydus pharmaceuticals
N 3 70771 14953 7


NDC 43068-220-01
Hetlioz™
(tasimelteon) capsules
20 mg
Dispense in original container.
Do not cover Braille.
30 Capsules


MSD
Belsomra®
SUVOREXANT
Comprimidos Recubiertos
VÍA ORAL
30 comprimidos recubiertos
20 mg

Buspirone

- **Buspirone** useful for **chronic** treatment of **GAD**.
- It has a **slow onset** of action and is **not** effective for **short-term** or "as-needed" treatment of acute anxiety.
- its mode of action **differs** from that BZD. It has **5-HT1A** receptors as a **partial** agonist.
- buspirone **lacks** the anticonvulsant and muscle-relaxant properties of the benzodiazepines.
- adverse effects: the most common effects being headache, dizziness, nervousness, nausea, and light-headedness.
- Sedation and cognitive dysfunction are **minimal**, and **dependence** is **unlikely**.
- Buspirone does **not** potentiate the CNS depression of alcohol.
- **The drug appears to be safe in pregnancy.**

Antidepressants

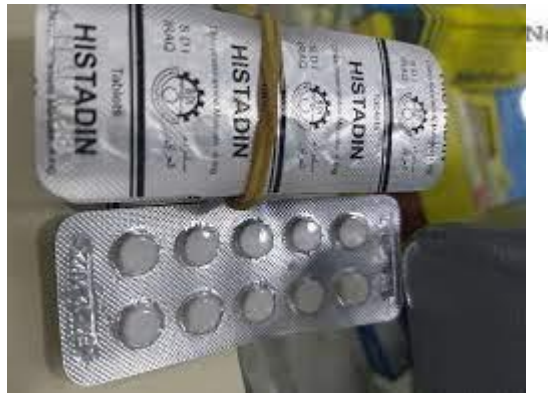
- Many of this drug used for **chronic** anxiety disorders.
- **first line** agents → in patients with addiction or dependence
- **SSRIs** such as escitalopram or paroxetine or **SNRIs**, such as venlafaxine or duloxetine may be used **alone** or in **combination** with a BZD during the first week of treatment.
- After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the BZD dose can be tapered.
- **Long-term** use of antidepressants and BZD for anxiety disorders is often required to **maintain** ongoing benefit and **prevent** relapse.

Antihistamines

- **Antihistamines** with sedating properties, such as diphenhydramine, hydroxyzine, and doxylamine, are effective in treating **mild** situational insomnia.

- they have undesirable adverse effects (such as anticholinergic effects) that make them less useful than the BZD and the non-BZD.

- Sedative antihistamines are marketed in numerous over-the-counter products.




THANK
YOU