Al-Mustaqbal University College
Department of Pharmacy
5th Stage
Applied therapeutics II
Lecture: 4

SLEEP DISORDERS

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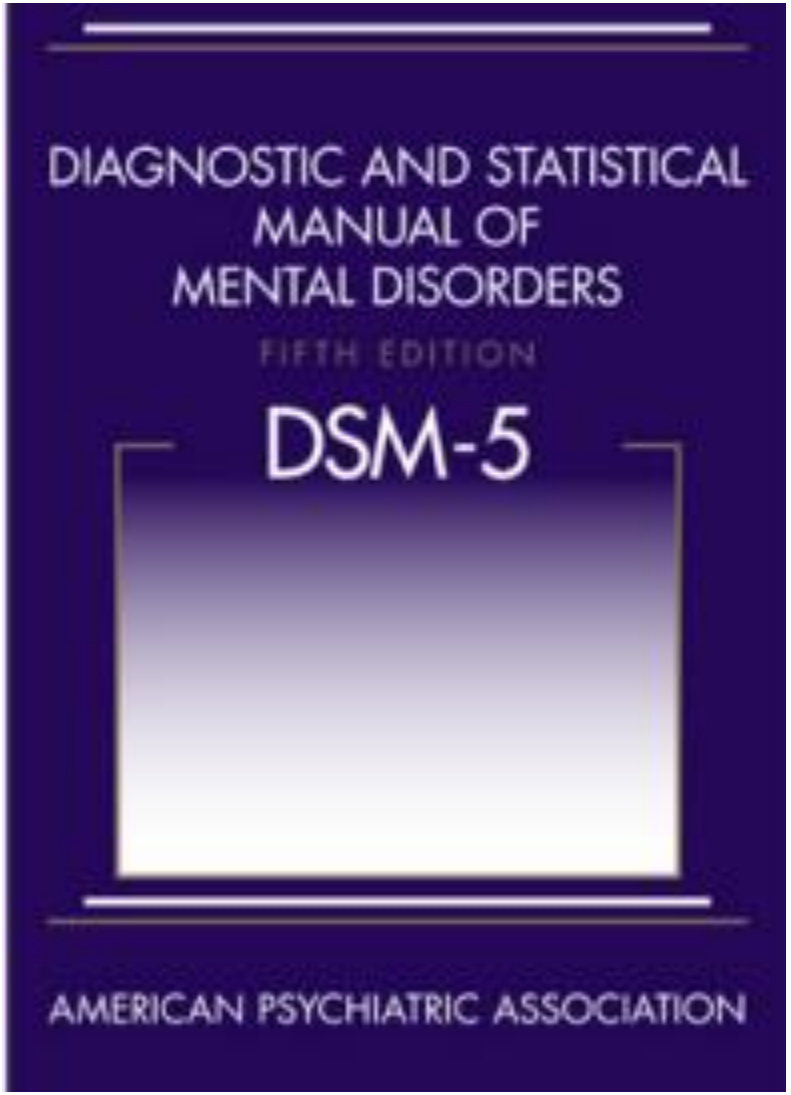
SLEEP–WAKE DISORDERS

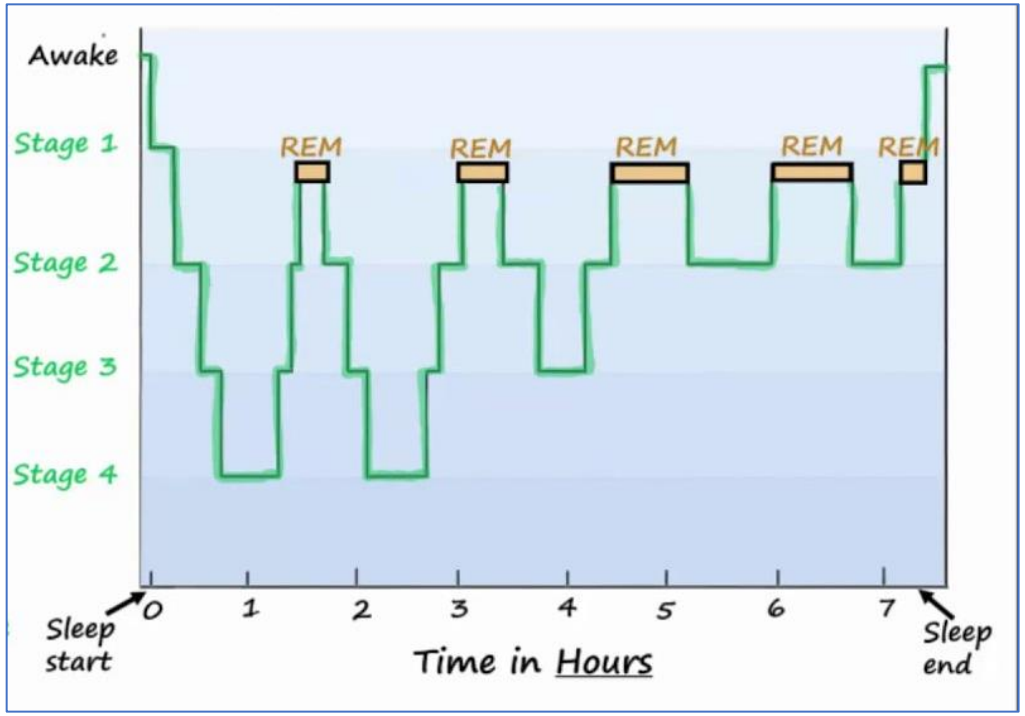
- According to DSM-5, the categories of sleep-wake disorders encompasses:

1. **Insomnia**
2. Hypersomnolence
3. **Narcolepsy**
4. **Breathing-related sleep disorders**
5. Circadian rhythm sleep-wake disorders
6. Nonrapid eye movement (NREM) sleep arousal disorders
7. Nightmare disorder
8. Rapid eye movement (REM) sleep behavior disorder
9. Restless legs syndrome
10. Substance/medication-induced sleep disorder



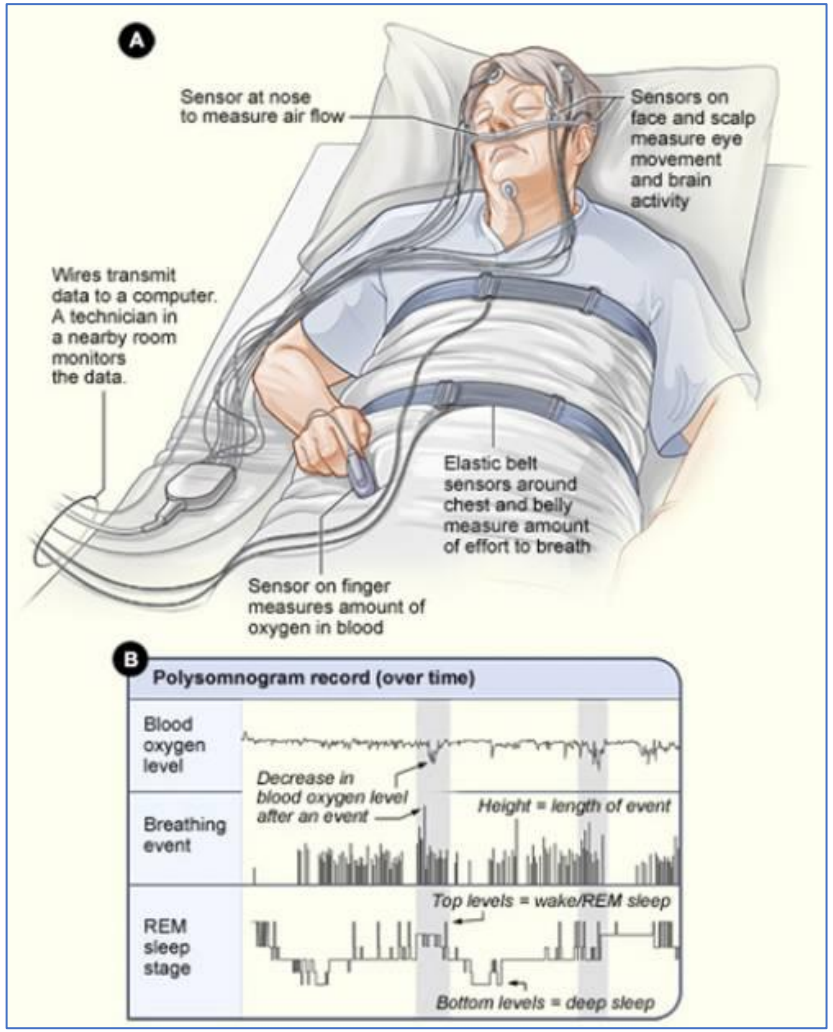
SLEEP PHYSIOLOGY

- Humans typically have **4-6 cycles** of NREM and REM sleep each night, each cycle lasting **70–120** minutes.
- Usually, there is a progression through the **4 stages** of **NREM** sleep before the first **REM** period.
- Stage **1** of NREM is the stage between wakefulness and sleep.
- Stages **3 and 4** sleep are called **delta** sleep (ie, slow-wave sleep).
- In **REM** sleep, there is a low-amplitude, mixed-frequency EEG, increased electrical and metabolic activity, increased cerebral blood flow, muscle atonia, poikilothermia, vivid dreaming, and fluctuations in respiratory and cardiac rate.
- **Older** individuals have **lighter more fragmented** sleep with **more arousals** and a gradual **reduction in SWS**.

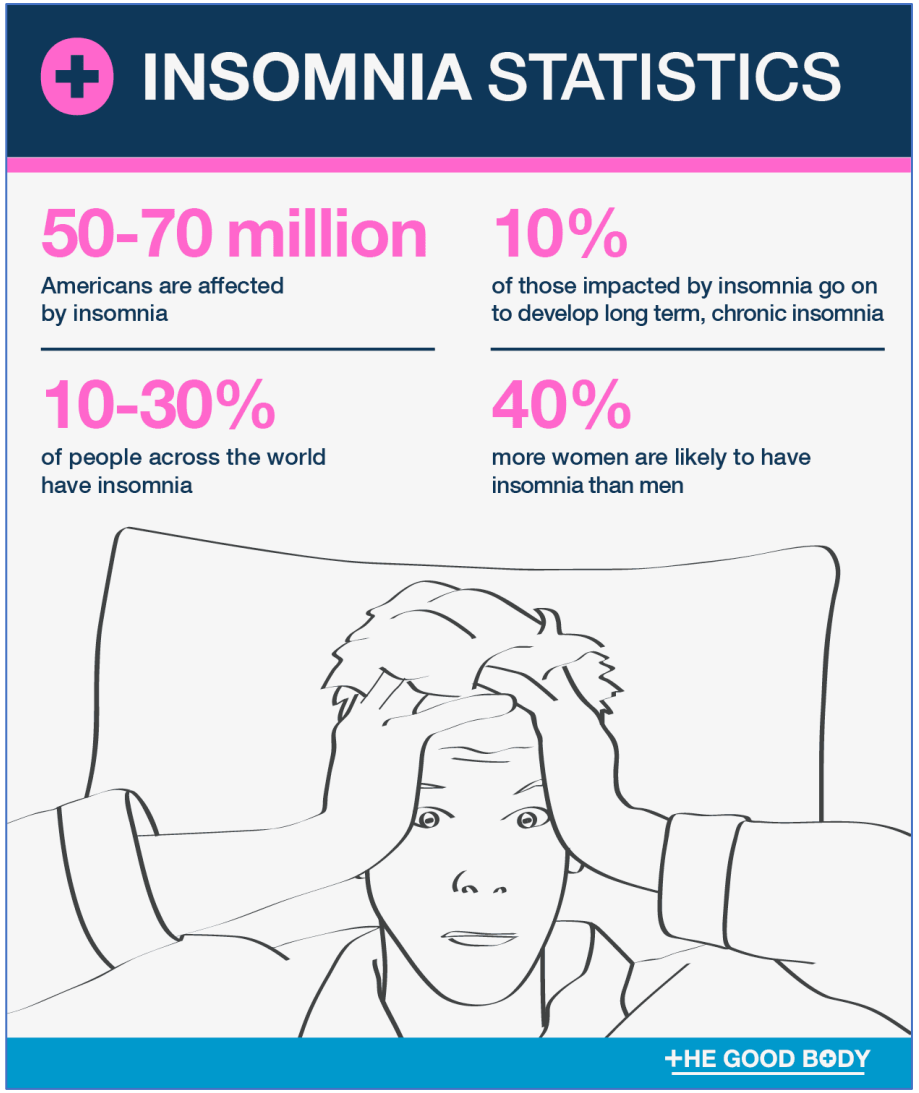


SLEEP PHYSIOLOGY

- **REM** sleep is turned on by **cholinergic** cells. Meanwhile, **dopamine** has an **alerting** effect.
- Neurochemicals involved in **wakefulness** include **NE** and **ach**. in the **cortex** and **histamine** and **neuropeptides** (eg, substance P and corticotropin-releasing factor) in the **hypothalamus**.
- **Polysomnography (PSG)** measures multiple **electrophysiologic parameters** simultaneously during sleep (eg, EEG, EOG of each eye, ECG, EMG, air thermistors, abdominal and thoracic strain belts, and oxygen saturation) to **characterize** sleep and **diagnose** sleep disorders.



INSOMNIA


INSOMNIA STATISTICS
50-70 million
Americans are affected by insomnia
10%
of those impacted by insomnia go on to develop long term, chronic insomnia
10-30%
of people across the world have insomnia
40%
more women are likely to have insomnia than men
+HE GOOD BODY

CLINICAL PRESENTATION

- Insomnia is subjectively characterized as **trouble initiating** or **maintaining** sleep associated with **daytime consequences**.

1. **Transient insomnia** (two or three nights)
2. **Short-term insomnia** (less than 3 months) is common
3. **Chronic insomnia** (more than 3 months duration) occurs in 9%–12% of adults and in up to 20% of older individuals.

DIAGNOSIS

- A **complete** diagnostic **examination** should include routine laboratory tests, physical and mental status examinations, as well as **ruling out** any medication- or substance-related causes.
- **Causes** of insomnia include stress; jet lag or shift work; pain or other medical problems; mood or anxiety disorders; substance withdrawal; stimulants, steroids, or other medications.

TREATMENT

- Goals of Treatment: **Correct** the underlying sleep complaint, **improve** daytime functioning, and **avoid** adverse drug effects.
- It includes **nonpharmacological** and **pharmacological** approaches.

NONPHARMACOLOGIC THERAPY

- **Behavioral** and **educational** interventions that may help **include** short-term cognitive behavioral therapy, relaxation therapy, stimulus control therapy, cognitive therapy, sleep restriction, paradoxical intention, and sleep hygiene education.
- **Management** includes **identifying the cause** of insomnia, **educating** about sleep hygiene, **managing** stress, **monitoring** mood symptoms, and **eliminating** unnecessary pharmacotherapy.
- In patients aged **55 years and older**, cognitive behavioral therapy may be **more effective** than pharmacologic therapy at improving certain measures of insomnia.
- **Transient** and **short-term** insomnia should be **treated** with **good sleep hygiene** and **careful** use of sedative-hypnotics if necessary.
- **Chronic** insomnia calls for **careful assessment** for a medical cause, **nonpharmacologic** treatment, & **careful** use of sedative-hypnotics if necessary.

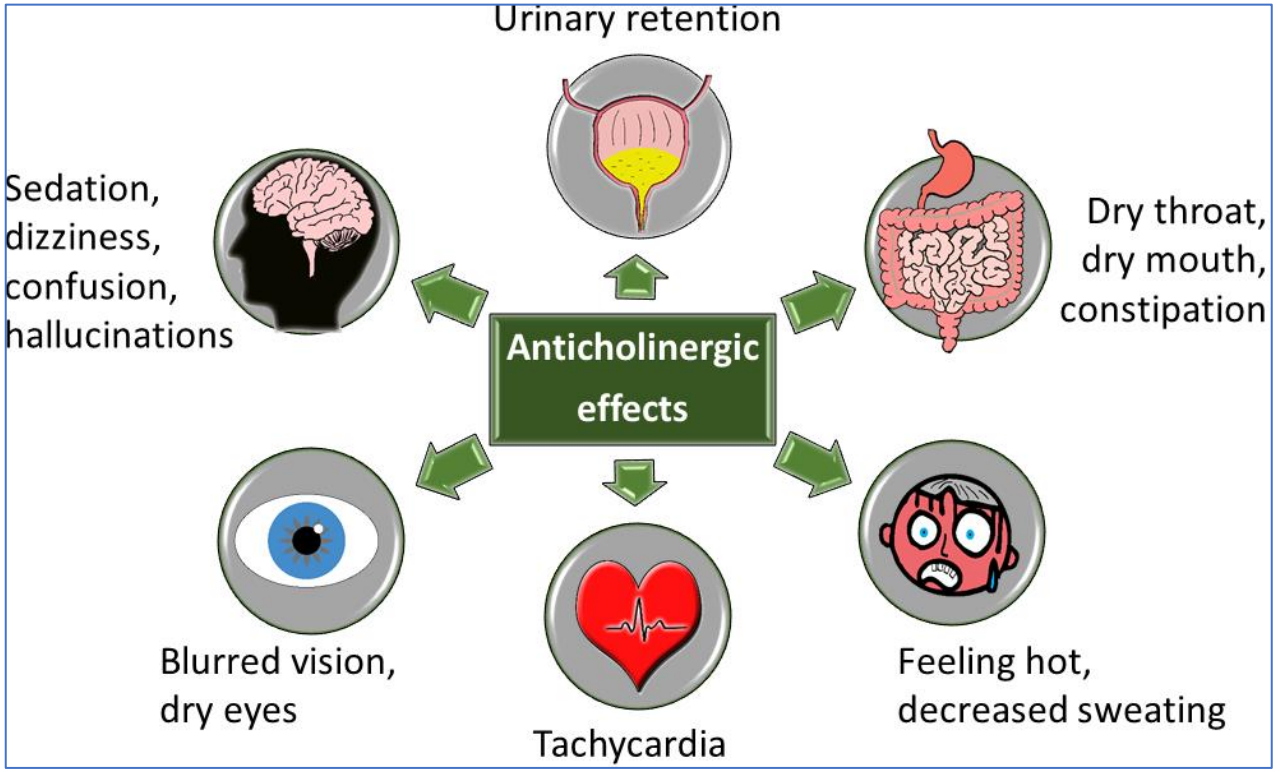
PHARMACOLOGIC THERAPY

Pharmacological treatments may include but are not limited to:

1. Antihistamines
2. Antidepressants
3. Suvorexant
4. Ramelteon
5. Valerian
6. BZDRAs
7. Non-BZDRAs

1. Antihistamines

- Such as **diphenhydramine**, **doxylamine**, and **pyrilamine** are **less effective** than **benzodiazepines**, but **side effects** are usually **minimal**.
- Their **anticholinergic** side effects may be problematic, especially in **older** individuals.



2. Antidepressants

- They are good **alternatives** for patients who should **not** receive **benzodiazepines**, especially those with depression, pain, or a history of substance abuse.

✓**Amitriptyline, doxepin, and nortriptyline** are effective, but side effects include sedation, anticholinergic effects, adrenergic blockade effects, and cardiac conduction prolongation.

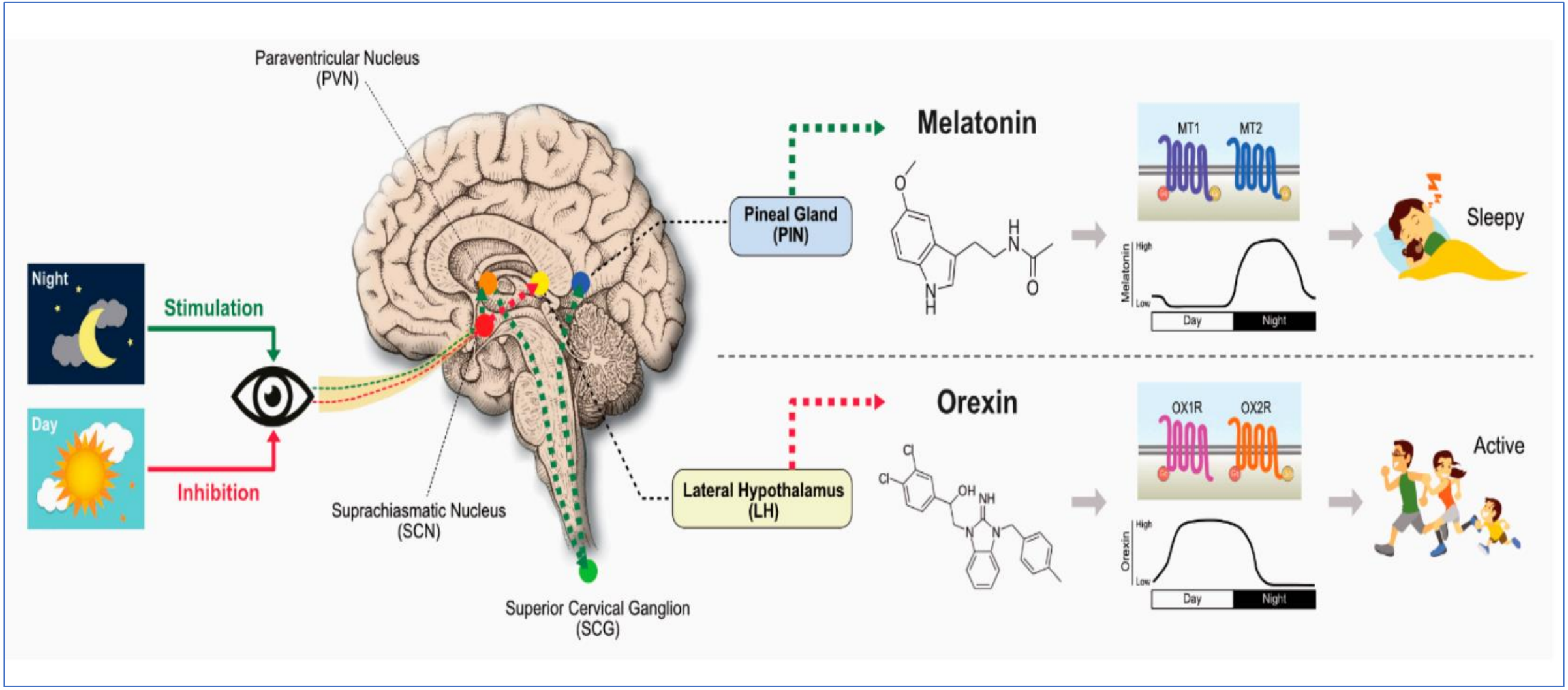
✓**Low-dose doxepin** is approved for sleep maintenance insomnia.

2. Antidepressants

- ✓**Mirtazapine** may improve sleep but may cause daytime sedation and weight gain.

- ✓**Trazodone**, 25–100 mg at bedtime, is often used for **insomnia** induced by **SSRIs** or **bupropion** and in patients prone to substance **abuse**.
- ✓Side effects include **serotonin syndrome** (when used with other serotonergic drugs), **oversedation**, **α-adrenergic blockade**, **dizziness**, and rarely, **priapism**.

PHARMACOLOGIC THERAPY



3. Suvorexant

- ✓ It is an **orexin-A** and **orexin-B antagonist that** turns off wake signaling.
- ✓Doses of 10–20 mg at **bedtime** are indicated for **difficulty initiating** or **maintaining** sleep.
- ✓Side effects include **sedation** and rarely **narcolepsy-like** symptoms.
- ✓Use **caution** in patients with **depression** because suvorexant can **worsen depression** and trigger **suicidal thinking** in a dose-dependent manner.

4. Ramelteon

- ✓It is a **melatonin** receptor **agonist** selective for the **MT1** and **MT2** receptors.
- ✓The dose is 8 mg at bedtime. It is well **tolerated**, but **side effects** include headache, dizziness, and somnolence.
- ✓It is **not a controlled substance** and does **not cause acute drowsiness** similar to other insomnia agents.
- ✓It is **effective** for patients with **COPD** and **sleep apnea**.

5. Valerian

- It is an **herbal** product and is available **without a prescription**.

✓The recommended dose is **300–600 mg**.

✓Purity and potency concerns are an issue.

✓It may cause **daytime sedation**.

6. Benzodiazepine receptor agonists (BZDRAs)

- They are the most **commonly** used drugs for insomnia.
- They include the **newer nonbenzodiazepine** GABA-A agonists and the **traditional benzodiazepines**, which also bind to GABA-A.
- The FDA requires **labeling** regarding anaphylaxis, facial angioedema, and complex sleep behaviors (eg, sleep driving, phone calls, and sleep eating).
- Benzodiazepines have **sedative, anxiolytic, muscle relaxant, and anticonvulsant** properties.
- They **increase stage 2** sleep and **decrease REM and delta sleep**.
- Overdose fatalities are **rare** unless benzodiazepines are taken with other CNS depressants.

6. Benzodiazepine receptor agonists (BZDRAs)

- **Triazolam** is distributed **quickly** because of its high **lipophilicity**, and it has a **short** duration of effect.
- Erythromycin, nefazodone, fluvoxamine, and ketoconazole **reduce the clearance** of triazolam and **increase plasma concentrations**.

6. Benzodiazepine receptor agonists (BZDRAs)

- The effects of **flurazepam** and **quazepam** are **long** because of active metabolites and therefore they should **not** be used as **first-line agents**.
- **Side effects** include drowsiness, psychomotor incoordination, decreased concentration, cognitive deficits, and anterograde amnesia, which are minimized by using the lowest dose possible.
- **Tolerance** to daytime CNS effects (eg, drowsiness, decreased concentration) may **develop** in some individuals.
- **Rebound insomnia** is minimized by using the lowest effective dose and tapering the dose upon discontinuation.
- Long elimination half-life benzodiazepines are associated with **falls and hip fractures**; thus, flurazepam and quazepam should be **avoided** in older individuals.

7. Nonbenzodiazepine GABAA Agonists

- In general, non-benzodiazepine hypnotics do **not have significant active metabolites**, and they are associated with **less withdrawal, tolerance, and rebound insomnia** than benzodiazepines.
- Common examples include:

✓**Zolpidem**

✓**Zaleplon**

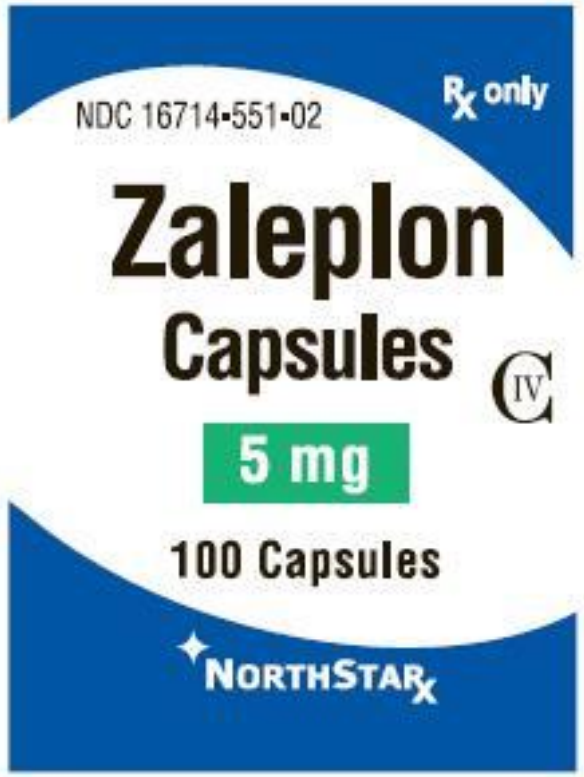
✓**Eszopiclone**

7. Nonbenzodiazepine GABAA Agonists

- **Zolpidem** is **comparable** in effectiveness to benzodiazepine hypnotics, and it has **little** effect on sleep stages with a duration of approximately **6–8 hours**.
- Common **side effects** are drowsiness, amnesia, dizziness, headache, and GIT complaints.
- It appears to have **minimal effects** on next-day psychomotor performance.
- The usual dose is **5 mg** in **women**, **older** persons, and those with liver impairment, and **5–10 mg in men**.
- **Sleep eating** has been reported.
- It should be taken on an **empty stomach**.

7. Nonbenzodiazepine GABAA Agonists

- **Zaleplon** has a **rapid onset**, a half-life of **~1 hour**, and **no** active metabolites.
- It **decreases** the time to sleep onset but does **not reduce** nighttime awakenings or **increase** the total sleep time.
- It does **not appear** to cause next-day psychomotor impairment.
- The most common **side effects** are dizziness, headache, and somnolence.
- The recommended dose is **10 mg** (**5 mg** in older patients).



7. Nonbenzodiazepine GABAA Agonists

- **Eszopiclone** has a **rapid onset** and duration of action of up to **6 hours**.
- The most common **adverse effects** are somnolence, unpleasant taste, headache, and dry mouth.
- It may be taken **nightly** for up to **6 months**.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess patients with short-term or chronic insomnia **after 1 week** of therapy for drug **effectiveness**, **adverse** events, and **adherence** to nonpharmacologic recommendations.
- Patients should maintain a **daily recording** of awakenings, medications taken, naps, and an index of sleep quality.

Obstructive Sleep Apnea

PATHOPHYSIOLOGY

- OSA is potentially **life-threatening** and characterized by **repeated** episodes of nocturnal breathing cessation **followed** by blood oxygen desaturation.
- It is **caused** by **occlusion** of the **upper airway**, and blood oxygen (O2) **desaturation** can occur.
- Episodes may be caused by **obesity** or fixed upper airway **lesions**, enlarged **tonsils**, **amyloidosis**, and **hypothyroidism**.
- OSA is **associated** with motor vehicle accidents, depression, increased cancer risk, stroke, arrhythmias, hypertension, cor pulmonale, and sudden death.
- The **apneic episode** is terminated by **reflex action** in response to the **fall in blood O_2 saturation** that causes **arousal** with resumed breathing.

CLNICAL PRESENTATION AND DIAGNOSIS

- Heavy **snoring**, severe **gas** exchange **disturbances**, **respiratory failure**, and **gasping** occur in severe episodes.
- Patients with OSA usually complain of **excessive daytime sleepiness** (**EDS**).
- Other symptoms are **morning headache**, **poor memory**, and **irritability**.

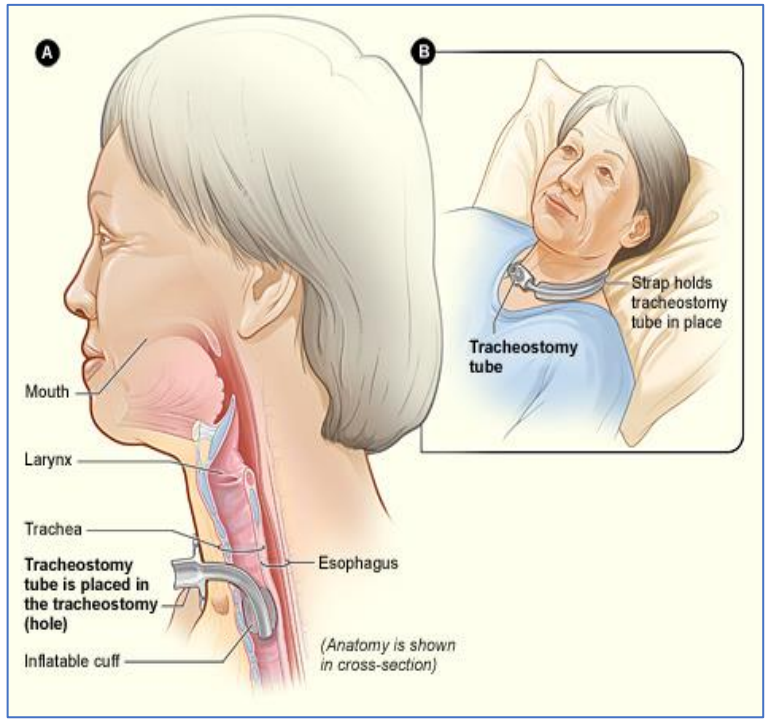
TREATMENT

Goals of Treatment:

- The goal is to **alleviate** sleep-disordered breathing and **prevent Complications**.

NONPHARMACOLOGIC THERAPY

- Nonpharmacologic approaches are the **treatments of choice** (eg, weight loss [for all overweight patients], tonsillectomy, nasal septal repair, and nasal positive airway pressure [PAP], which may be continuous [CPAP] or bi-level.
- Other surgical therapies, such as **uvulo-palatopharyngoplasty** and **tracheostomy**, may be necessary in severe cases.
- Avoid all **CNS depressants** and drugs that promote **weight gain**.
- **ACE inhibitors** can also worsen sleep-disordered breathing.



PHARMACOLOGIC THERAPY

- There is **no drug therapy** for OSA, and medications that worsen sleep should be **avoided**.
- **Modafinil** and **armodafinil** are approved by the FDA to **improve wakefulness** in those with **residual daytime sleepiness**.
- They should be **used only** in patients **without** CVS disease who are using optimal PAP therapy.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess patients with OSA after **1–3 months** of treatment for **improvement** in alertness, daytime symptoms, weight reduction, and compliance with PAP therapy.
- **Bed partners** can report **snoring** and **gasping**.

Narcolepsy

PATHOPHSYIOLOGY

- **Narcolepsy** is a **long-term neurological disorder** that involves a **decreased ability to regulate sleep-wake cycles.**
- Narcolepsy **type 1** includes symptoms of **cataplexy** and occurs in **70%–80%** of patients.
- **Cataplexy** is a **sudden bilateral loss of muscle tone with collapse**, which can be precipitated by a **high emotional situation**.
- Narcolepsy **type 2** does **not** include cataplexy.
- **Dysfunction** of the **hypocretin/orexin** neurotransmitter system may play a central role in **narcolepsy**.
- An **autoimmune** process may cause the **destruction** of **hypocretin-producing cells**.

CLINICAL PRESENTATION AND DIAGNOSIS

- Narcolepsy can be **diagnosed** if the patient **goes into REM sleep within 5 minutes of sleep**.
- The narcolepsy **tetrad** includes **EDS**, **cataplexy**, **hallucinations**, and **sleep paralysis**.
- Patients complain of EDS, sleep attacks that last up to **30 minutes**, fatigue, impaired performance, and disturbed nighttime sleep.

CLINICAL PRESENTATION AND DIAGNOSIS

TREATMENT

Goals of Treatment:

- The goal is to **maximize** alertness during waking hours and **improve** quality of life.

NONPHARMACOLOGIC THERAPY

- Provide patient and family **education** about misconceptions about the individual's behavior.
- **Encourage** good sleep hygiene and **two or more daytime naps** daily (as little as **15** minutes).

PHARMACOLOGIC THERAPY

- **Modafinil** is the **standard** for the treatment of EDS and **armodafinil** (the active R-isomer) are **FDA-approved**.
- They do **not treat cataplexy**.
- Evidence suggests **no risk of tolerance**, **withdrawal**, or **risk** of **abuse**.
- **Side effects** include headache, nausea, nervousness, and insomnia.

PHARMACOLOGIC THERAPY

Amphetamines and methylphenidate:

- They have a **fast onset** of effect and durations of **3–4 hours and 6–10 hours**, respectively, for EDS.
- Amphetamines have more risk of **abuse** and **tolerance**.
- **Side effects** include insomnia, hypertension, palpitations, and irritability.
- Clinicians may prescribe **sustained-release** stimulants with scheduled administration times, and **immediate-release** stimulants to be taken as needed when the patient requires alertness (eg, driving, etc.).

PHARMACOLOGIC THERAPY

- The most common treatments for **cataplexy** are **TCAs, SNRIs, & SSRIs**.
- Imipramine, protriptyline, clomipramine, fluoxetine, and nortriptyline are **effective** in approximately **80%** of patients.
- **Selegiline** improves hypersomnolence and cataplexy.

- **Atomoxetine** may improve cataplexy and sleepiness in **children** but appears to be **less effective** than other therapies in **adults** and older **teenagers**.

- **Sodium oxybate** (γ-hydroxybutyrate) improves EDS and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations.
- **Give** at bedtime and repeat 2.5–4 hours later.
- **Side effects** include nausea, somnolence, confusion, dizziness, and **incontinence**.

EVALUATION OF THERAPEUTIC OUTCOMES

- Patients with narcolepsy should **keep** a diary of the frequency and severity of core symptoms.
- **Monitoring parameters** include reduction in daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis.
- Assess patients **regularly** during medication titration, then **every 6–12 months** for side effects (eg, hypertension, sleep disturbances, and cardiovascular abnormalities).

THANK YOU FOR YOUR ATTENTION