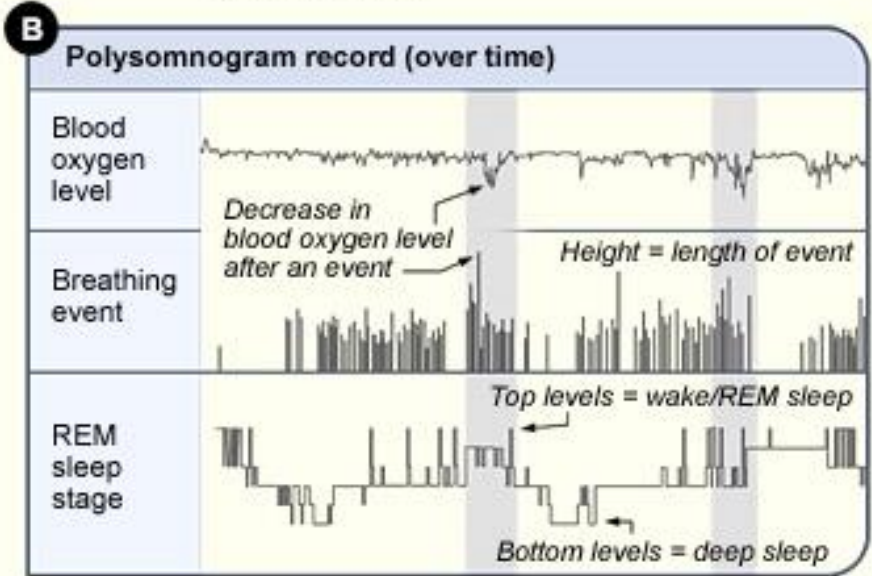
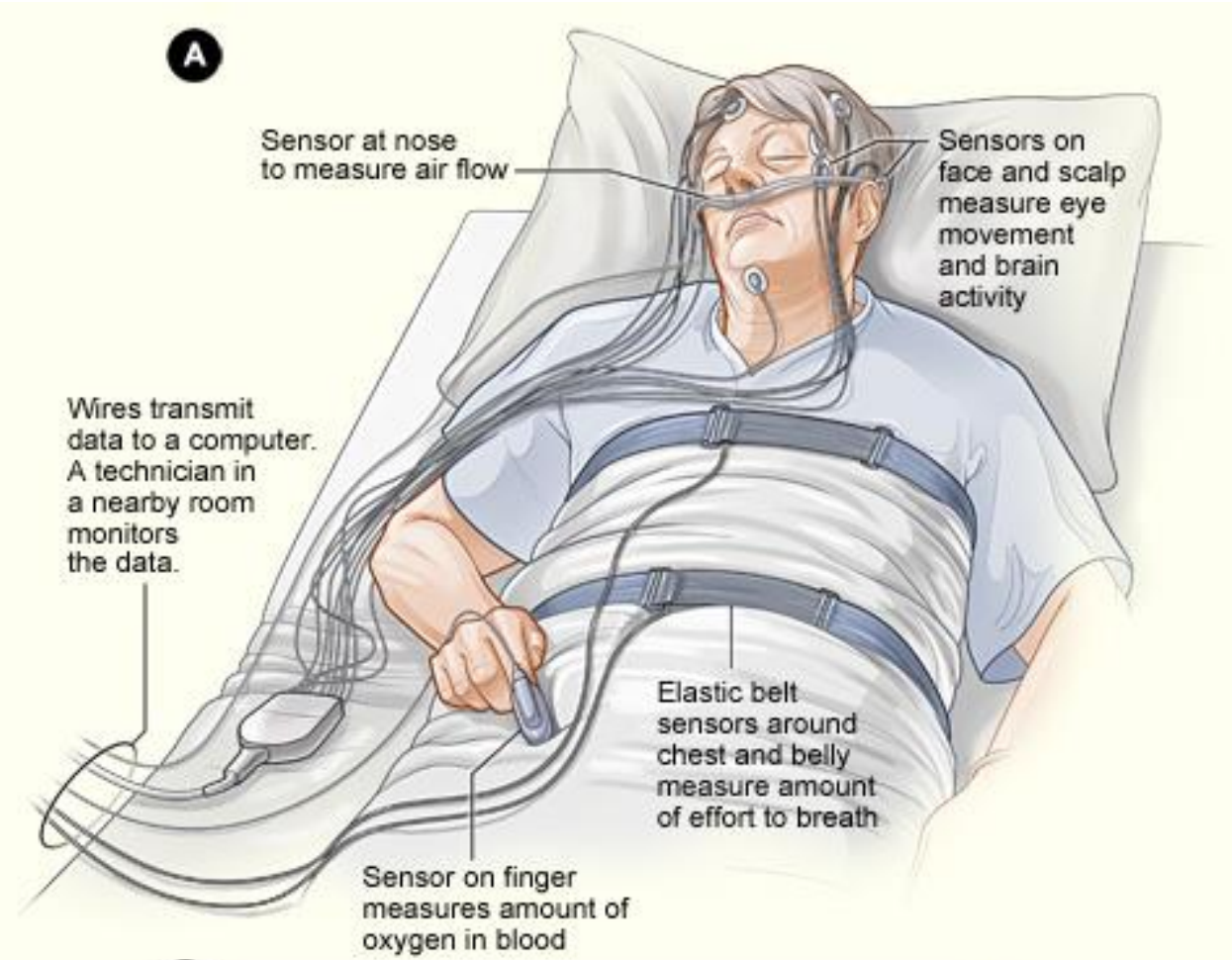




Sleep Disorders



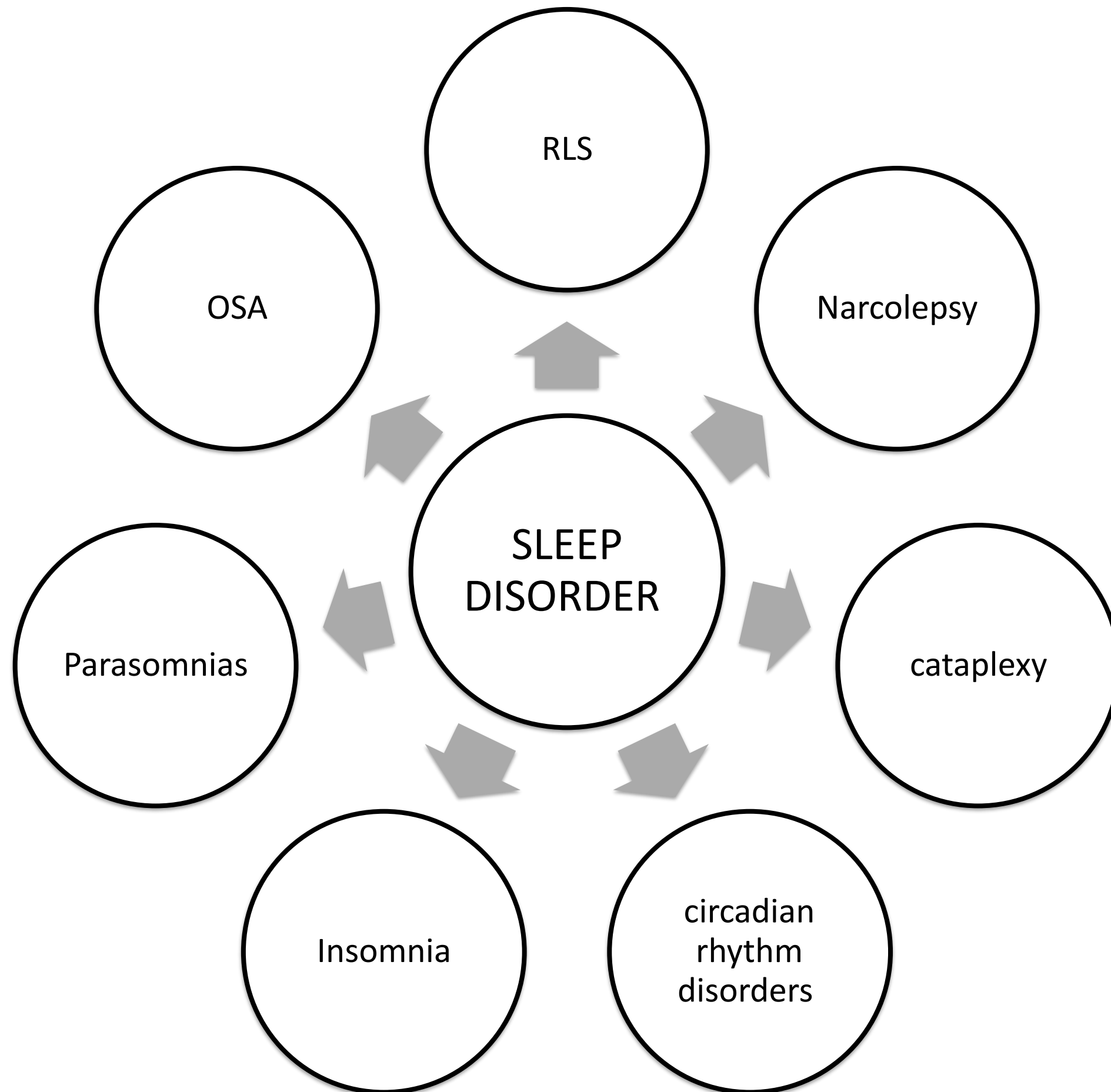
A.Halboup

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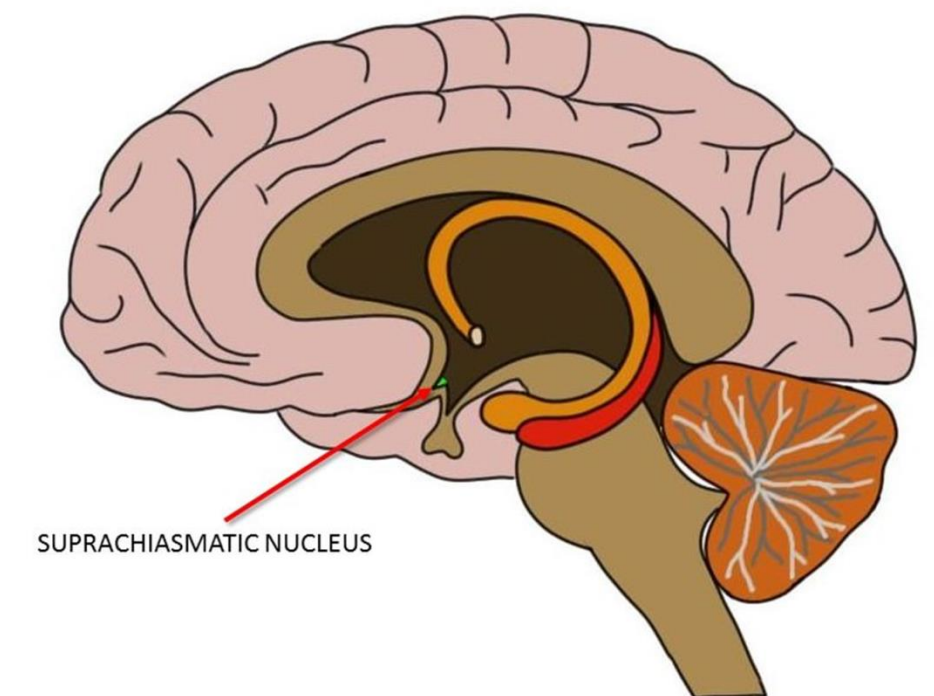

Belsomra.
(suvorexant) **IV**





INTRODUCTION

- Individuals with normal sleep patterns sleep up to **one-third of their lives** and spend more time sleeping than in any other single activity.
- **Sleep is necessary** to enable one to maintain **wakefulness** and **good health**.
- **Disruption of normal sleep** is a major cause of **societal morbidity**, **lost productivity**, and **reduced quality of life**.
- Sleep is governed and paced by the suprachiasmatic nucleus in the brain that regulates circadian rhythm.



There are two main types of sleep:

- **rapid eye movement (REM) sleep**, during which **eye movements** and **dreaming** occur but the body is mostly paralyzed.
 - REM sleep occurs about *every 90 minutes* upon falling asleep.
- **non-rapid eye movement (NREM) sleep**. consists of **four substages** (stages 1–4).
 - Stage 1 serves as a **transition** between **wake and sleep**. Last for *several minutes*
 - stage 2 **most of the time asleep is spent** in stage 2 NREM sleep. It is a *light sleep*
 - Stages 3 is referred to as *deep sleep*, or *delta sleep* (as shown by EEG). Needed to feel *refreshed* in the morning.

EPIDEMIOLOGY AND ETIOLOGY

- Approximately 50% of adults will report a sleep complaint over the course of their lives.
- In general, sleep disturbances increase with age, and each disorder may have gender differences.
- the most common sleep disorders are RLS, and sleep-related breathing disorders
- Other sleep disorders include : insomnia , Narcolepsy, Parasomnias, circadian rhythm disorders , cataplexy.

Insomnia

- The **prevalence of insomnia increases with age** and is **nearly 1.5 times greater in women than in men**.
- Approximately **one-third of patients older than age 65 years have persistent insomnia**.
- *Insomnia is most frequently a symptom or manifestation of an underlying disorder (comorbid or **secondary insomnia**) but may occur in the absence of contributing factors (**primary insomnia**).*
 - secondary) insomnia: are related to
 - **social factors** (eg, family difficulties, bereavement),
 - **medications** (eg, antidepressants, β -agonists, corticosteroids, decongestants), and
 - **coexisting medical or psychiatric conditions** (eg, depression, bipolar disorder).
- **Insomnia duration** may be described as :
 - **transient** (less than 1 week),
 - **Acute** (1–4 weeks), or
 - **chronic** (greater than 1 month) in duration

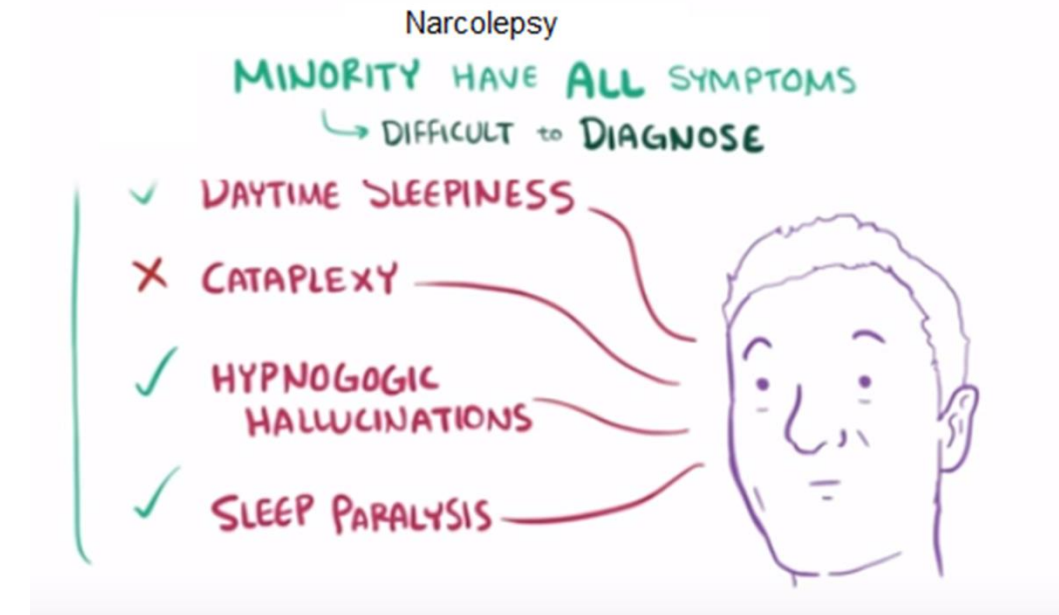
Narcolepsy

Narcolepsy is a **neurological disorder** that affects the control of sleep and wakefulness.

❖ Inability to control sleep-wake cycle

Narcolepsy is characterized by the classic tetrad of:

- excessive daytime sleepiness (**EDS**),
 - **cataplexy**, 50%-80%
 - Hallucinations (dream-like images)
 - **sleep paralysis** (early before sleeping or right after a waking up)
- **Cataplexy** is a weakness or loss of skeletal muscle tone in the jaw, legs, or arms that is elicited by emotion (eg, anger, surprise, laughter, or sadness).
 - narcolepsy results from autoimmune insult to the CNS. Concentrations of **hypocretin** (a wake-promoting neuropeptide) in the cerebrospinal fluid of patients with narcolepsy are **reduced significantly**.
 - The occurrence of a REM onset period during two naps with short sleep latency is indicative of a diagnosis of narcolepsy.



Restless Legs Syndrome

- RLS is a **neurologic medical condition** characterized by an **irresistible desire to move the limbs**.
- RLS occurs **in 6% to 12% of the population**. Prevalence increases with age and in various medical conditions, such as end-stage renal disease, pregnancy, PD, and iron deficiency.
- RLS appears to be **more common in women than in men** and has a **genetic link** in a majority of patients.
- It is thought that these abnormal sensations are a result of **iron deficiency in the brain** and iron-handling abnormalities in the CNS.
- **These iron abnormalities lead to dysfunction of dopaminergic transmission in the substantia nigra.**
 - patients commonly report “creepy-crawly,” burning, tingling, or achy feelings in the legs or arms.
 - These sensations create a desire to move the limbs and may produce motor agitation.

Obstructive Sleep Apnea

- OSA affects **4%** of middle-aged white **men** and **2%** of middle-aged white **women**. Male to female ratio is 4:1.
- **In women**, the frequency increases **after menopause**.
- The risk for OSA increases with **age** and **obesity**.
- Individuals with OSA experience **repetitive upper airway collapse during sleep**, which decreases or **stops airflow**, with **subsequent arousal from sleep to resume breathing**.
 - Severity is determined by **nocturnal polysomnography (PSG)** and is **graded by the number of episodes of apnea** (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation).
- OSA can cause **excessive daytime sleepiness (EDS)** and **neurocognitive deficits**.
- **OSA** is also associated with **systemic disease** such as **hypertension**, **heart failure**, and **stroke**. Furthermore, when hypertension is present, it is often **resistant to antihypertensive therapy**.
- **Common characteristics of OSA** include **snoring**, **choking**, **gasping for air**, and **morning headaches**.

Parasomnias

- Parasomnias are disruptive **sleep disorders** that can occur during arousals from rapid eye movement (REM) sleep or arousals from non-rapid eye movement (NREM) sleep. They can result in undesirable *physical* or **verbal behaviors**, such as walking or talking during sleep.
- Sleep talking, sleepwalking, sleep eating, bruxism(grinding of teeth),, sleep terrors, and enuresis occur more frequently in childhood than in adulthood..
- Nightmares appear to occur with similar frequency in adults and children.
 - Sleep terrors are episodes of screaming, intense fear and flailing while still asleep...

Circadian Rhythm Disorders

- The most common circadian rhythm disorders (CRDs) include:
 - ❖ jet lag,
 - ❖ shift-work sleep disruption,
 - ❖ Delayed sleep-phase disorder, and
 - ❖ advanced sleep-phase disorder.
- Jet lag occurs when a person travels across time zones, and the external environmental time is mismatched with the internal circadian clock.
- Delayed and advanced sleep-phase disorders occur when bed and wake times are delayed or advanced (by 3 or more hours) compared with socially prescribed bed and wake times.

PATHOPHYSIOLOGY

- **certain neurotransmitters** promote sleep and wakefulness in different areas of the central nervous system (CNS).
- Whereas **serotonin** is thought to control NREM sleep, cholinergic and adrenergic transmitters mediate REM sleep.
- Dopamine, norepinephrine, hypocretin (orexin), substance P, and histamine all play a role in wakefulness.
- **Perturbations** of various neurotransmitters are responsible for some sleep disorders

Clinical Presentation and Diagnosis

KEY CONCEPT *Patients with sleep complaints should have a careful sleep history performed to assess their possible sleep disorder in order to guide diagnostic and therapeutic decisions.*

Daytime symptoms and associated characteristics: EDS is the primary symptom described by patients with sleep disorders. It is usually described as not waking up refreshed in the morning or falling asleep or fighting the urge to sleep during the day despite a night of sleep. Other daytime characteristics of sleep disorders include:

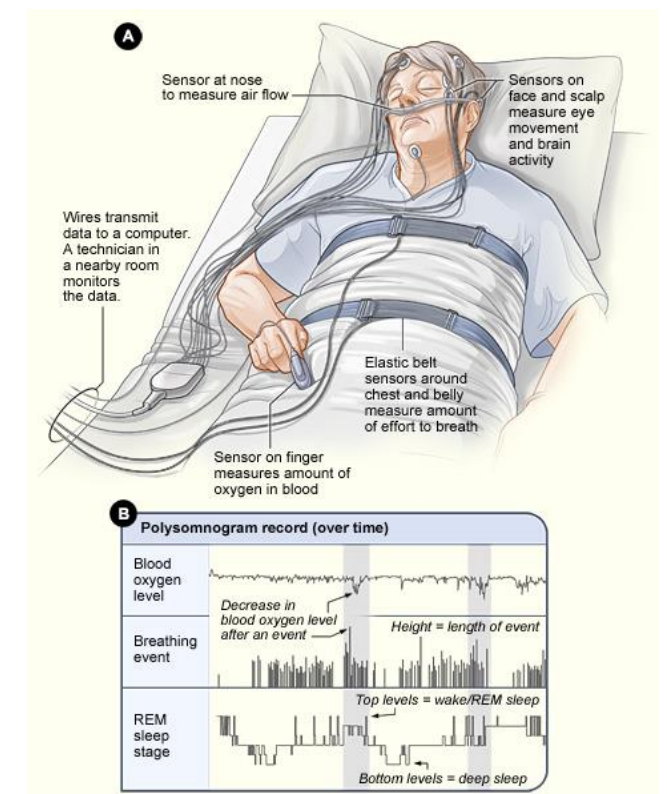
- Irritability, fatigue, or depression
- Confusion or impaired performance at work or school
- Cataplexy
- Hypertension

Nighttime sleep complaints: Depending on the sleep disorder, patients may exhibit or experience various nocturnal complaints during sleep. Some complaints can be uncovered by clinical history alone (eg, hallucinations, RLS, snoring), but others can be diagnosed during sleep studies (eg, OSA, nighttime awakenings, somnambulism, PLMS, etc). Frequent complaints include:

- Inability to fall asleep, nighttime awakenings
- Sleep walking (somnambulism), sleep talking (somniloquy)
- Cessation of breathing (apnea), snoring
- Sleep paralysis or hallucinations when waking or falling asleep
- Restlessness (PLMS or RLS)

Sleep Diagnostics

- Diagnosis depends on :
 - Patient clinical presentation
 - Family history
 - Medication history or substance disorder
 - Complete **nocturnal polysomnography** PSG is the “**gold standard**” for diagnosing .
- *multiple sleep latency tests (MSLT) to assess daytime sleepiness.*



TREATMENT

Desired Outcomes:

- I. restoration of normal sleep patterns,*
- II. Elimination of daytime sequelae,*
- III. improved quality of life, and*
- IV. Prevention of complications and adverse effects from therapy.*

General Approach to Treatment:

- **Sleeping disorders can be treated using non-pharmacologic and pharmacologic approaches**

Nonpharmacologic interventions

Table 41–1

Nonpharmacologic Therapies for Insomnia

Sleep Hygiene

- Keep a regular sleep schedule.
- Exercise frequently but not immediately before bedtime.
- Avoid alcohol and stimulants (caffeine, nicotine) in the late afternoon and evening.
- Maintain a comfortable sleeping environment that is dark, quiet, and free of intrusions.
- Avoid consuming large quantities of food or liquids immediately before bedtime.

Stimulus Control

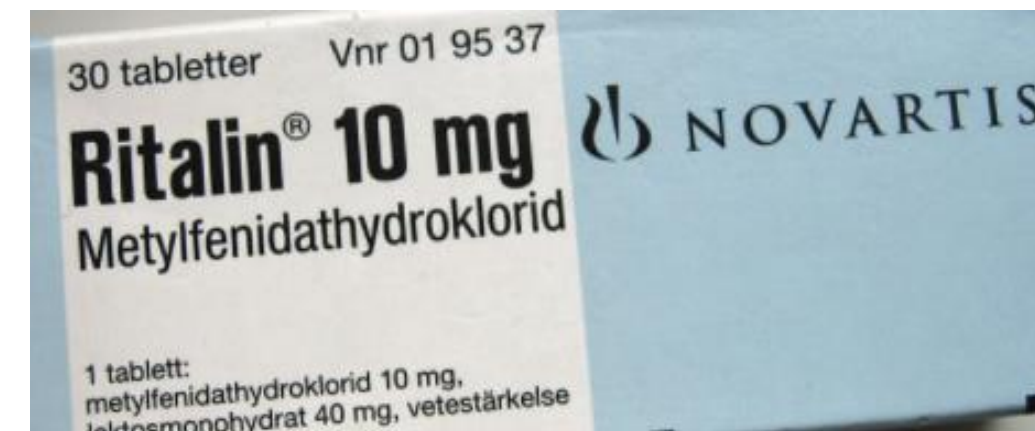
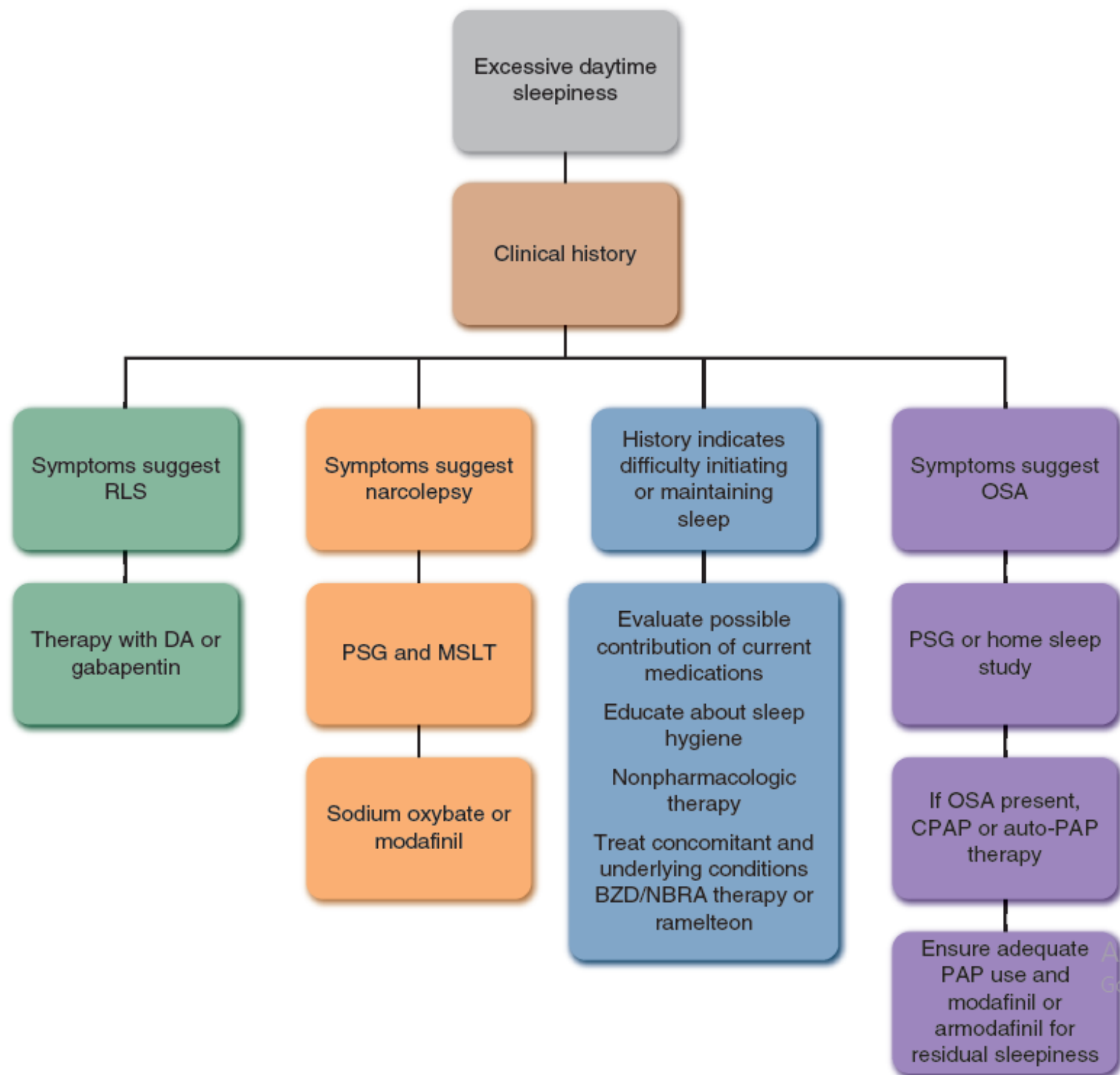
- Go to bed only when sleepy.
- Avoid daytime naps.
- If you cannot sleep, get out of bed and go to another room—only return to your bed when you feel the need to sleep.
- Bed is for sleep and intimacy only (no eating or watching TV in bed).
- Always wake up at the same time each day.

Relaxation Training

- Reduce somatic arousal (muscle relaxation).
- Reduce mental arousal (eg, attention-focusing procedures, imagery training, meditation).
- Use biofeedback (visual or auditory feedback to reduce tension).

Cognitive Therapy

- Alter beliefs, attitudes, and expectations about sleep.



Insomnia

- Early treatment of insomnia may prevent the development of persistent psychophysiologic insomnia.
- The ideal hypnotic drug would be
 - effective at reducing sleep latency,
 - Increasing total sleep time, and
 - would be free of unwanted side effects.
- Benzodiazepine receptor agonists (BZD) and nonbenzodiazepine receptor agonist (NBRA, zolpidem, zaleplon, and eszopiclone) and ramelteon are approved by the FDA for the treatment of insomnia and are first-line therapies.
 - Pharmacologic treatment of insomnia is recommended for transient and acute insomnia.
- Eszopiclone and zolpidem are sedative hypnotic approved by the FDA for chronic use up to 6 months.



Benzodiazepine Receptor Agonists(BZD)

- BZD have become the **first-line agents** for treating insomnia and **sleep-maintenance problems**. They are all efficacious, have wide therapeutic indices, and have a low incidence of abuse.
- Patients should be instructed to take **BZD at bedtime and** avoid activities requiring alertness after ingestion.
 - Estazolam, Flurazepam, Quazepam, Triazolam

- The most **common side effects associated** with BZDs include :
 - **residual sedation** into the waking hours after sleep,
 - **Grogginess (ataxia)**, and
 - **psychomotor impairment**.
 - **anterograde amnesia** (defined as memory loss of activities and interactions after ingestion of the drug).
- On **discontinuation of hypnotic BZD**, patients may experience **rebound insomnia** that may last for a few nights.
- **insomnia occurs more frequently after discontinuation of shorter duration BZDs.**
 - **Patients should be counseled** that rebound insomnia is not necessarily a **return of their original symptoms**, and it may take a **few nights** for rebound symptoms to subside.
- In general, **eszopiclone, zaleplon, and zolpidem** appear to be associated with **lower risk** of **tolerance, rebound insomnia, and withdrawal** than traditional benzodiazepines.



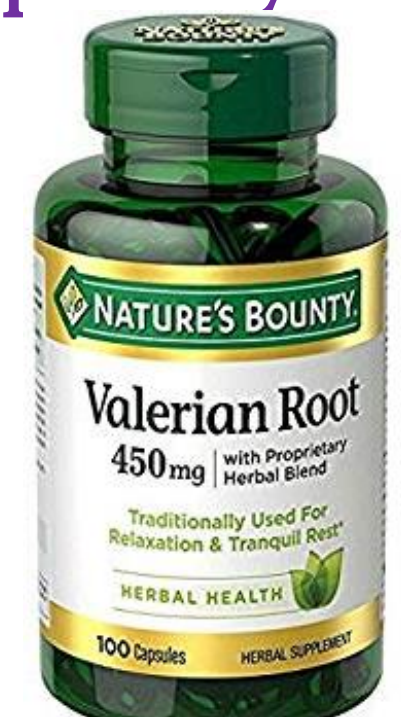
Sedating Antidepressants

- Sedating antidepressants (eg, **trazodone**, **amitriptyline**, **mirtazapine**, **doxepin**) are commonly used for insomnia and may be an **appealing option** in patients with **concomitant depression**.
- quality **clinical studies demonstrating** efficacy for insomnia are lacking. Side effects from antidepressants can be frequent, including **carryover sedation**, **grogginess**, **anticholinergic effects**, and **weight gain**.
- **Mirtazapine** can cause **daytime sedation**, **dizziness**, and **weight gain**, and **trazodone** can cause **hypotension** and **dizziness**.
- **Doxepin** is approved for treatment of **sleep maintenance insomnia** in low doses (3–6 mg).



Over-the-Counter and Other Miscellaneous Agents

- Over-the-counter antihistamines such as **diphenhydramine**, **doxylamine** are frequently used (usual doses, 25–50 mg) for difficulty sleeping.
- **Diphenhydramine** is approved by the FDA for the **treatment of insomnia** and can be effective at **reducing sleep latency** and **increasing sleep time**.
 - However, diphenhydramine produces **undesirable anticholinergic** effects and **carryover sedation** that limit its use, especially in the elderly.
- **Valerian root** is an herb that has inconsistent effects on sleep but may **reduce sleep latency** and increase efficiency at commonly used doses of 400 to 900 mg valerian extract



- Ramelteon, a melatonin receptor agonist, is indicated for insomnia characterized by difficulty with sleep onset.
 - It has documented efficacy treating sleep onset difficulties in those with mild to moderate COPD and OSA.
- Suvorexant (an orexin receptor antagonist) and lemborexant were approved for treatment of insomnia.
- Suvorexant and lemborexant are indicated for both difficulty initiating and maintaining sleep, and like BZD, it is classified as a schedule IV controlled substance. Its Contraindicated in narcolepsy.



Belsomra.
(suvorexant) (IV)
5, 10, 15, 20 mg tablets

Narcolepsy



- Therapy for narcolepsy involves two key principles:
 - ❖ (a) treatment of EDS with **scheduled naps** and **CNS stimulants** and
 - ❖ (b) suppression of cataplexy and **REM-sleep abnormalities** using **aminergic signaling antidepressants** or **sodium oxybate**.
- Modafinil (Provigil), armodafinil (Nuvigil), methylphenidate, and amphetamines are effective FDA-approved drugs for the treatment of EDS with narcolepsy.
 - Traditional CNS stimulants have the potential to **increase blood pressure** and **heart rate** when used long term. However, **newer stimulants are not**.
 - In addition, **excessive CNS stimulation** can cause tremors and tics, **lower the seizure threshold**, and can carry over into evening hours, **disrupting normal nighttime sleep**.

- Traditionally, **aminergic signaling antidepressants** have been used effectively to **control** symptoms of **cataplexy**, **sleep paralysis**, and other **REM-sleep manifestations of narcolepsy**.
 - These include **TCAs** and SSRIs and SNRIs.
- Doxepin (3-6 mg), Clomipramine, imipramine, venlafaxine, and fluoxetine are the agents that have been used most frequently.
- Sodium oxybate, a **potent sedative** with a very short duration of action, is FDA approved for the treatment of **narcolepsy** with **cataplexy**.



Restless Legs Syndrome

RLS treatment involves *suppression of abnormal sensations and leg movements and consolidation of sleep.*

- Dopaminergic medication prescribed commonly.
- Dopamine agonists (DAs) successfully treat RLS symptoms and offer many advantages over levodopa–carbidopa, including longer half-lives to cover overnight symptoms, flexible dosing, and a reduced incidence of symptom augmentation.
- Up to 80% of patients who take levodopa–carbidopa eventually will experience symptom augmentation:
 - RLS symptoms appear earlier in the day,
 - previously unaffected body parts become involved,
 - duration of relief gets shorter, and
 - higher doses of medication are required to control symptoms.

- **Ropinirole** (Requip), **pramipexole** (Mirapex), and **rotigotine** (Neupro) are FDA approved for the treatment of RLS.
- **Gabapentin** is an effective treatment for RLS, particularly in patients with painful symptoms.
 - Gabapentin 600 mg can be taken with dinner
- **Iron supplementation** should be prescribed in patients who are iron deficient. Iron supplementation in patients with **serum ferritin concentrations** of less than 50 to 75 mcg/L (ng/mL; 112–169 pmol/L) improves RLS symptoms.

Table 41–3

Frequently Used Medications for Restless Legs Syndrome

Generic Name (Brand Name)	Half-Life (Hours)	Dose Range (mg/day) ^a	Potential Side Effect or Disadvantage
Dopaminergic Agents^b			
Levodopa–carbidopa (Sinemet)	1.5–2	100–200 of levodopa	<u>Nausea or vomiting</u> ; high incidence of symptom <u>augmentation</u>
Pramipexole (Mirapex)	8–12 ^c	0.125–0.5	Nausea or vomiting; risk of <u>compulsive behaviors</u> ^d
Ropinirole (Requip)	6 ^e	0.25–3	Nausea or vomiting; risk of compulsive behaviors ^d
Rotigotine (Neupro)	5–7	1–3	Application site reactions with patch
Anticonvulsants			
Gabapentin (Neurontin, Horizant)	5–7 ^c	300–3600	Dizziness, <u>ataxia</u>
Pregabalin (Lyrica)	5–6.5	50–300	<u>Weight gain</u> , <u>daytime sedation</u>
Hypnotic Agents			
Clonazepam (Klonopin)	30–40	0.5–2	<u>Tolerance</u> , <u>carryover</u> sedation
Temazepam (Restoril)	10–15	7.5–30	Tolerance, carryover sedation
Zolpidem (Ambien)	2–2.6 ^e	5–10	Tolerance
Zaleplon (Sonata)	1 ^e	5–10	Tolerance; may not last entire night
Opioids			
Hydrocodone	3.8–4.5 ^e	5–10	<u>Constipation</u> , <u>nausea</u> , <u>sedation</u>
Codeine	2.5–3.5 ^e	30–60	Constipation, <u>nausea</u> , <u>sedation</u>
Methadone	22 ^e	5–20	Constipation, nausea, sedation
Oxycodone	3.2–12 ^{ce}	5–30	Constipation, nausea, sedation

Obstructive Sleep Apnea

- *The main therapy for OSA is nasal continuous positive airway pressure (CPAP) therapy.*
- CPAP therapy has a favorable impact on blood pressure and attenuates some of the potential hemodynamic and neurohumoral responses that may link OSA to systemic disease.
 - bi-level positive airway pressure (BiPAP) or auto titrating continuous positive airway pressure (AutoPAP) therapy can be used .
- weight management should be implemented for all overweight patients with OSA.



Parasomnias

- **NREM parasomnias** usually **do not require treatment**. If needed, **low-dose BZDs** such as clonazepam can be prescribed.
 - Clonazepam reduces the amount of sleep time spent in stages 3 of NREM sleep, when most NREM parasomnias occur.
- For treating REM-sleep behavioral disorder (RBD), clonazepam 0.5 to 2 mg at bedtime is the drug of choice, although melatonin 3 to 12 mg at bedtime also may be effective.
 - Patients with RBD also should have dangerous objects removed from the bedroom.

Circadian Rhythm Disorders

- Melatonin, 0.5 to 5 mg taken at appropriate target bedtimes for east or west travel, is the drug of choice for jet lag.
 - jet lag :is a temporary sleep problem that can affect anyone who quickly travels across multiple time zones.
- Melatonin significantly **reduces jet lag** and **shortens sleep latency** in travelers.
- **Hypnotic agents** with relatively short durations of action (3–5 hours; Zolpidem) may also be used to **sustain sleep during the initial adaptation** to the new time zone.