SLEEP DISORDERS

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.

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, and *non–rapid eye movement (NREM) sleep*, which consists of four substages (stages 1–4). Stage 1 serves as a transition between wake and sleep. Most of the time asleep is spent in stage 2 NREM sleep. Stages 3 and 4 sleep often are grouped together and referred to as *deep sleep*, or *delta sleep*, because prominent delta waves are seen on the electroencephalogram (EEG) during these sleep stages.

Insomnia, restless legs syndrome (RLS), and sleep-related breathing disorders are the most common sleep disorders.

⇨ Insomnia

Insomnia also known as sleeplessness, is a sleep disorder in which people have trouble sleeping. They may have difficulty falling asleep, staying asleep as long as desired, or waking up too early and not be able to get back to sleep. 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).

⇨ Narcolepsy

Narcolepsy is an incurable neurologic disorder characterized by irrepressible sleep attacks typically occurring 3 to 5 times a day. These sleep attacks can intrude at any time during the individual's waking state. Narcolepsy may be present with or without cataplexy.

Cataplexy is the loss of muscle tone in the face or limb muscles and often is induced by emotions or laughter. Cataplexy can be subtle, with the patient limp and not moving, or dramatic, in which the patient collapses to the floor.

⇨ Restless Legs Syndrome and Periodic Limb Movements of Sleep

Restless legs syndrome (RLS), also known as Ekbom disease, is a neurologic medical condition characterized by an irresistible desire to move the limbs.

⇨ Obstructive Sleep Apnea

Sleep apnea is a neurologic disorder characterized by mini-episodes of cessation of breathing, which can occur 10 to 200 times an hour. If there is a reduction in airflow but no cessation of breathing, it is called *hypopnea.*

⇨ Parasomnias

Parasomnias are a category of sleep disorders (eg, sleepwalking, enuresis, sleep talking) that involve abnormal movements, behaviors, emotions, perceptions, and dreams that occur while falling asleep, sleeping, between sleep stages, or during arousal from sleep. Parasomnias are dissociated sleep states which are partial arousals during the transitions between wakefulness, NREM sleep, and REM sleep, and their combinations.

❖ DIAGNOSIS

Although the clinical history guides diagnosis and therapy, only nocturnal polysomnography (NPSG), home sleep studies, and/or multiple sleep latency tests (MSLTs) can definitively diagnose and guide therapy for obstructive sleep apnea (OSA), narcolepsy, and periodic limb movements of sleep (PLMS).

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.

Complete NPSG is the "gold standard" for diagnosing and identifying sleep-disordered breathing, PLMS, parasomnias, and nocturnal sleep irregularities related to narcolepsy. Sleep is observed and monitored in a controlled setting using an EEG, electrooculography, electromyography, electrocardiography, air thermistors, abdominal and thoracic strain belts, and an oxygen saturation monitor. This setup records sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, heart rhythm, airflow, respiratory effort, and oxygen desaturations.

Home sleep studies are increasingly used to diagnose sleep apnea due to their reduced cost and increased patient convenience.

The MSLT is a commonly performed test to assess daytime sleepiness.

❖ CLINICAL PRESENTATION

⇨ Insomnia

Insomnia is often characterized by difficulty falling asleep, frequent nocturnal awakenings, early morning awakenings, and nonrestorative sleep, which may result in daytime impairments in concentration and school or work performance. In comorbid (secondary) insomnia, social factors (eg, family difficulties, bereavement), medications (eg, antidepressants, β-agonists, corticosteroids, decongestants), and coexisting medical (eg, pain, thyroid abnormalities, asthma, and gastroesophageal reflux) or psychiatric conditions (eg, depression, bipolar disorder) may help to explain difficulties in initiating and maintaining sleep.

Insomnia duration may be described as transient (less than 1 week), acute (1–4 weeks), or chronic (greater than 1 month) in duration.

⇨ Narcolepsy

The hallmark of narcolepsy is excessive daytime sleepiness (EDS) and the need for periods of sleep during the day. Patients with narcolepsy may experience repeated nighttime awakenings, terrifying dreams, and difficulty falling asleep. They frequently experience abnormal manifestations of REM sleep, including hallucinations and sleep paralysis that occur on falling asleep and/or awakening. 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).

⇨ Obstructive Sleep Apnea

Common characteristics of OSA include snoring, choking, gasping for air, nocturnal reflux symptoms, and morning headaches. A bed partner or roommate may observe these symptoms and witness apneic episodes where the patient stops breathing. Patients with large neck sizes (greater than 45 cm [~18 in] neck circumference) and a body mass index (BMI) of 30 kg/m^2 or greater are at higher risk for OSA as an extra body weight places pressure on the throat and uvula, narrowing the space into which air must travel; this results in the difficulty in breathing and excessive snoring.

⇨ Periodic Limb Movements of Sleep and Restless Legs Syndrome

Although RLS symptoms can vary, 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 restlessness. Symptoms are worse in the evening and are worse or exclusively present at rest, with temporary relief with movement. Symptoms also can occur during sleep and often lead to semirhythmic PLMS.

⇨ Parasomnias

Parasomnias are characterized by undesirable physical or behavioral phenomena that occur during sleep (eg, sleepwalking, sleep eating, sleep talking, bruxism [grinding of teeth], enuresis, night terrors, and REM-sleep behavior disorder [RBD]). People with RBD act out their dreams during sleep, often in a violent manner.

⇨ 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.

❖ TREATMENT

⇨ Desired Outcomes

Treatment goals vary among different sleep disorders but generally include restoration of normal sleep patterns, elimination of daytime sequelae, improved quality of life, and prevention of complications and adverse effects from therapy.

⇨ ` Insomnia

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.

Early treatment of insomnia may prevent the development of persistent psychophysiologic insomnia. The hypnotic drugs are commonly used and the ideal one would be effective at reducing sleep latency, increasing total sleep time, and would be free of unwanted side effects.

Benzodiazepine receptor agonists (BZDRAs) (including traditional benzodiazepines [flurazepam, quazepam, temazepam], zolpidem, zaleplon, and eszopiclone) and ramelteon are approved by the Food and Drug Administration (FDA) for the treatment of insomnia and are first-line therapies.

Pharmacologic treatment of insomnia is recommended for transient and acute insomnia. Eszopiclone is the only sedative hypnotic approved by the FDA for chronic use up to 6 months.

Although not first-line agents for insomnia, sedating antidepressants are also commonly prescribed.

»» *Benzodiazepine Receptor Agonists*

These agents occupy the benzodiazepine site on the γ-aminobutyric acid (GABA) type A receptor complex, resulting in opening of chloride channels that facilitate GABA inhibition and promote sleepiness. BZDRAs 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.

The most common side effects associated with BZDRAs include residual sedation into the waking hours after sleep, grogginess, and psychomotor impairment.

BZDRAs should be initiated at low doses, and agents with active metabolites should be avoided in elderly patients. BZDRAs may cause anterograde amnesia, defined as memory loss of activities and interactions after ingestion of the drug. On discontinuation of hypnotic BZDRAs, patients may experience rebound insomnia that may last for a few nights.

»» ***Sedating Antidepressants***

Sedating antidepressants (eg, trazodone, amitriptyline, mirtazapine, nefazodone, doxepin) are commonly used for insomnia and may be an appealing option in patients with concomitant depression. However, at the doses frequently used for sleep, only mirtazapine exhibits significant antidepressant activity.

Side effects from antidepressants can be frequent, including carryover sedation, grogginess, anticholinergic effects, and weight gain.

»» ***Over-the-Counter and Other Miscellaneous Agents***

Over-the-counter antihistamines such as diphenhydramine 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. Yet, 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. Ramelteon is not a controlled substance and can be a viable option for patients with a history of substance abuse.

Suvorexant (an orexin receptor antagonist) was recently approved for treatment of insomnia. It is the first medication that turns off wakefulness mechanisms instead of stimulating pathways that induce sleepiness.

⇨ **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 with aminergic signaling drugs.

Modafinil (Provigil), *armodafinil* (the active R-isomer of modafinil) (Nuvigil), *methylphenidate*, and *amphetamines* are effective FDA-approved drugs for the treatment of EDS with narcolepsy. *Selegiline*, a selective monoamine oxidase B enzyme inhibitor, is metabolized to amphetamines and can reduce daytime sleepiness.

Treatment of EDS in narcolepsy and other sleep disorders may require sustained- and immediate-release stimulants to promote wakefulness throughout the day and at

key times that require alertness. One potential treatment regimen includes a sustained-release stimulant preparation first thing in the morning and again at noon followed by an immediate-release stimulant preparation as needed in the late afternoon or before driving to maintain wakefulness.
Traditional CNS stimulants have the potential to increase blood pressure and heart rate when used long term. In addition, excessive CNS stimulation can cause tremors and tics and can carry over into evening hours, disrupting normal nighttime sleep.

⇨ Cataplexy

Traditionally, aminergic signaling antidepressants have been used effectively to control symptoms of cataplexy, sleep paralysis, and other REM-sleep manifestations of narcolepsy. These include tricyclic antidepressants (TCAs) and certain selective serotonin and serotonin/norepinephrine reuptake inhibitors (SSRIs and SNRIs). Clomipramine, protriptyline, imipramine, venlafaxine, and fluoxetine are the agents that have been used most frequently. Although not approved by the FDA for treatment of cataplexy, these drugs suppress REM sleep and have been the mainstay of anticataplectic therapy for years.

⇨ Restless Legs Syndrome

RLS treatment involves suppression of abnormal sensations and leg movements and consolidation of sleep. Dopaminergic and sedative–hypnotic medications are 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.
Ropinirole (Requip), *pramipexole* (Mirapex), and *rotigotine* (Neupro) are FDA approved for the treatment of RLS and are available in sustained-release products.
Gabapentin is an effective treatment for RLS, particularly in patients with painful symptoms. The gabapentin prodrug (gabapentin enacarbil) is FDA approved for RLS at a recommended dose of 600 mg taken with food at about 5 pm. BZDRAs such as temazepam, clonazepam, zolpidem, and zaleplon reduce arousals in patients with RLS.

⇨ Obstructive Sleep Apnea

The main therapy for OSA is nasal continuous positive airway pressure (CPAP) therapy, which alleviates sleep-disordered breathing by producing a positive pressure column in the upper airway using room air. A flexible tube connects the CPAP machine to a mask that covers the nose. 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.

There is no drug therapy for OSA. Drug therapy for symptoms of OSA may be considered in selected patients.

⇨ Parasomnias

NREM parasomnias usually do not require treatment. If needed, low-dose BZDRAs such as clonazepam can be prescribed for bothersome episodes. Clonazepam reduces the amount of sleep time spent in stages 3 and 4 of NREM sleep, when most NREM parasomnias occur.

⇨ 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. Melatonin significantly reduces jet lag and shortens sleep latency in travelers.

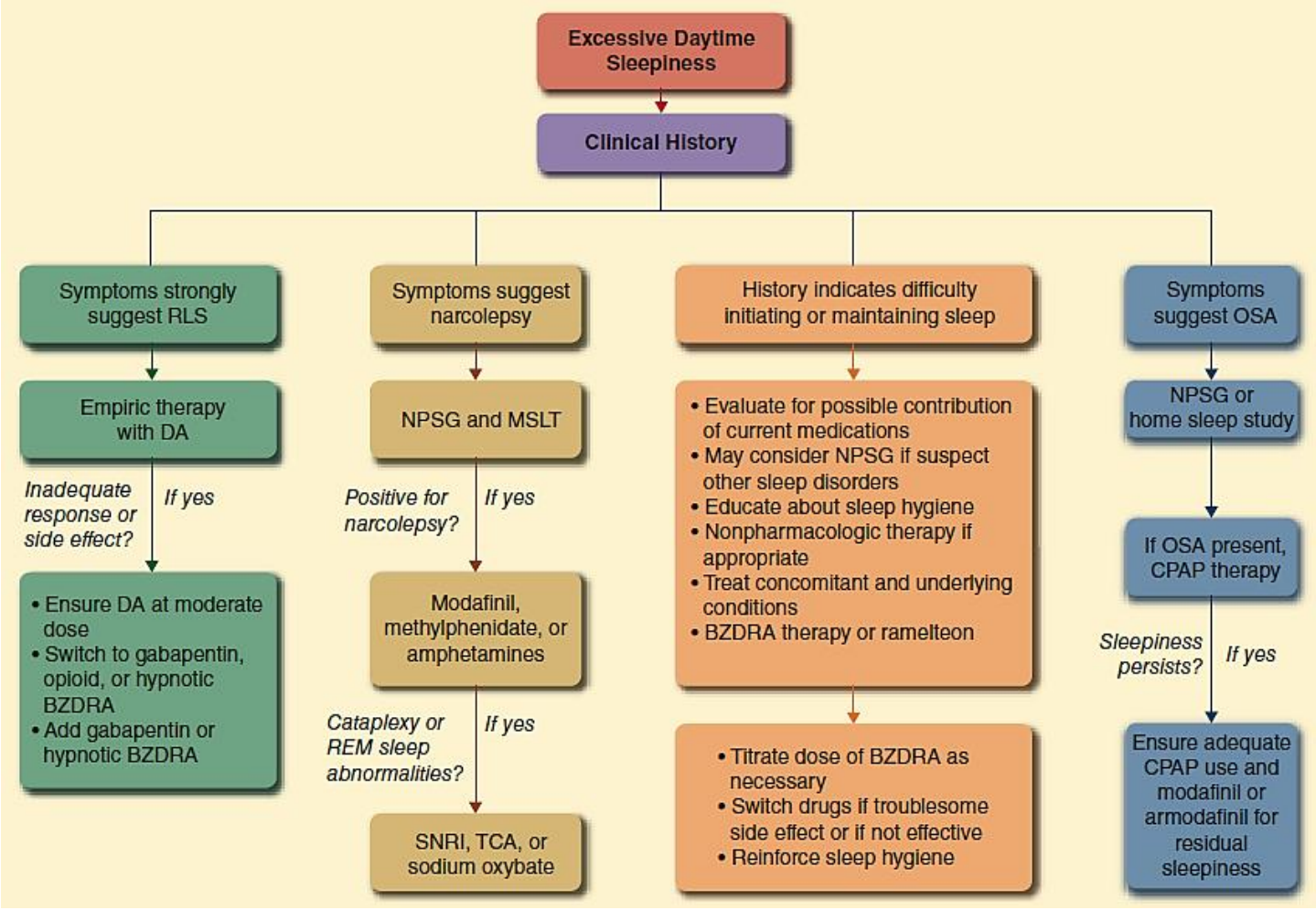

Figure 1: *Primary assessment and initial treatment for complaint of excessive daytime sleepiness. BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure; DA, dopamine agonist; MSLT, multiple sleep latency test; OSA, obstructive sleep apnea; RLS, restless legs syndrome; SNRI, serotonin and norepinephrine reuptake inhibitor; NPSG, nocturnal polysomnography; TCA, tricyclic antidepressant.*