Sleep disorders

- The *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., text revision, classifies sleep disorders as primary sleep disorders (dyssomnias), parasomnias and other sleep disorders related to mental disorders. It is shown in Table 1.

- One month of symptoms is required before a sleep disorder is diagnosed.

- ✓ Humans typically have four to six cycles of non–rapid eye movement (NREM) and rapid eye movement (REM) sleep each night, each cycle lasting 70 to 120 minutes. Usually there is progression through the four stages of NREM sleep before the first REM period.

- ✓ Stage 1 of NREM is the stage between wakefulness and sleep. Stage 3 and 4 sleep is called *delta sleep* (i.e., slow-wave sleep).

- ✓ In REM sleep, there is a low-amplitude, mixed-frequency electroencephalogram, increased electric and metabolic activity, increased cerebral blood flow, muscle atonia, poikilothermia, vivid dreaming, and fluctuations in respiratory and cardiac rate.

- ✓ In the elderly, sleep is lighter and more fragmented with more arousals and a gradual reduction in slow-wave sleep.

- Sleep is reduced when there is decreased serotonin activity or destruction of the dorsal raphe nucleus. REM sleep is turned on by cholinergic cells.

- Dopamine has an alerting effect. Neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex and histamine and neuropeptides (e.g., substance P and corticotropin-releasing factor) in the hypothalamus.

- Polysomnography (PSG) is a procedure that measures multiple electrophysiologic parameters simultaneously during sleep (e.g., electroencephalogram, electrooculogram, and electromyogram to characterize sleep and diagnose sleep disorders.

CLINICAL PRESENTATION:

- Patients with insomnia complain of difficulty falling a sleep, maintaining sleep, or not feeling rested in spite of a sufficient opportunity to sleep.

- Transient (two to three nights) and short-term (less than 3 weeks) insomnia is common and is usually related to a precipitating factor.

- Chronic insomnia (greater than 1 month) may be related to medical or psychiatric disorders or medication, or it may be psychophysiologic.

DSM-IV-TR Classification of Sleep Disorders

Primary sleep disorders

Dyssomnias—abnormality in the amount, quality, or timing of sleep

Primary insomnia
Primary hypersomnia
Narcolepsy
Breathing-related sleep disorder
Circadian rhythm sleep disorder
- Delayed sleep phase type
- Jet lag type
- Shift work type
- Unspecified type

Dyssomnia not otherwise specified

Parasomnias—abnormal behavioral or physiologic events associated with sleep

Nightmare disorder
Sleep terror disorder
Sleepwalking disorder
Parasomnia not otherwise specified

Sleep disorders related to another mental disorder

Insomnia or hypersomnia related to another mental disorder

DIAGNOSIS:

- Common causes of insomnia are shown in Table 2. In patients with chronic disturbances, a diagnostic evaluation includes physical and mental status examinations, routine laboratory tests, and medication and substance abuse histories.

- Management includes identifying the cause of insomnia, education on sleep hygiene, stress management, monitoring for mood symptoms, and elimination of unnecessary pharmacotherapy.

- 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, non-pharmacologic treatment, and careful use of sedative-hypnotics (intermittently to prevent tolerance and dependence).

Common Etiologies of Insomnia

Situational
Work or financial stress, major life events, interpersonal conflicts
Jet lag or shift work
Medical
Cardiovascular (angina, arrhythmias, heart failure)
Respiratory (asthma, sleep apnea)
Chronic pain
Endocrine disorders (diabetes, hyperthyroidism)
GI (gastroesophageal reflux disease, ulcers)
Neurologic (delirium, epilepsy, Parkinson's disease)
Pregnancy
Psychiatric
Mood disorders (depression, mania)
Anxiety disorders (e.g., generalized anxiety disorder, obsessive-compulsive disorder)
Substance abuse (alcohol or sedative-hypnotic withdrawal)
Pharmacologically induced
Anticonvulsants
Central adrenergic blockers
Diuretics
Selective serotonin reuptake inhibitors
Steroids
Stimulants

Nonpharmacologic Recommendations for Insomnia

Stimulus control procedures

1. Establish regular times to wake up and to go to sleep (including weekends).
2. Sleep only as much as necessary to feel rested.
3. Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed.
4. Avoid trying to force sleep; if you do not fall asleep within 20–30 minutes, leave the bed and perform a relaxing activity (e.g., read, listen to music, or watch television) until drowsy. Repeat this as often as necessary.
5. Avoid daytime naps.
6. Schedule worry time during the day. Do not take your troubles to bed.

Sleep hygiene recommendations

1. Exercise routinely (three to four times weekly) but not close to bedtime because this can increase wakefulness.
2. Create a comfortable sleep environment by avoiding temperature extremes, loud noises, and illuminated clocks in the bedroom.
3. Discontinue or reduce the use of alcohol, caffeine, and nicotine.
4. Avoid drinking large quantities of liquids in the evening to prevent nighttime trips to the restroom.
5. Do something relaxing and enjoyable before bedtime.

PHARMACOLOGIC THERAPY:

Nonbenzodiazepine Hypnotics:

- Antihistamines (e.g., diphenhydramine, doxylamine, and pyrilamine) are less effective than benzodiazepines, but side effects are usually minimal. Their anticholinergic side effects may be problematic, especially in the elderly.

- The antidepressants are good alternatives for patients with poor sleep who should not receive benzodiazepines, especially those with depression or a history of substance abuse.

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

- **Trazodone**, 25 to 100 mg, is often used for insomnia induced by selective serotonin reuptake inhibitors or bupropion. Side effects include serotonin syndrome (when used with other serotonergic drugs), over sedation, α- adrenergic blockade, dizziness, and rarely priapism.

- **Ramelteon** 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.

- **Zolpidem**, chemically unrelated to benzodiazepines or barbiturates, acts selectively at the γ-aminobutyric acid A (GABAA)-receptor and has minimal anxiolytic and no muscle relaxant or anticonvulsant effects.

- It is comparable in effectiveness to benzodiazepine hypnotics, and it has little effect on sleep stages. Its duration is approximately 6 to 8 hours, and it is metabolized to inactive metabolites.

- Common side effects are drowsiness, amnesia, dizziness, headache, and GI complaints. Rebound effects when discontinued and tolerance with prolonged use are minimal, but theoretical concerns about abuse exist. It appears to have minimal effects on next-day psychomotor performance.

- The usual dose is 10 mg (5 mg in the elderly or those with liver impairment), which can be increased up to 20 mg nightly. Cases of psychotic reactions and sleep-eating have been reported.

- **Zaleplon** also binds to the GABAA receptor. It has a rapid onset, a half-life of about 1 hour, and no active metabolites. It does not reduce nighttime awakenings or increase the total sleep time. It may be best used for middle- of-the-night awakenings.

- It does not appear to cause significant rebound insomnia or next-day psychomotor impairment. The most common side effects are dizziness, headache, and somnolence. The recommended dose is 10 mg (5 mg in the elderly).

- **Eszopiclone** has a rapid onset and a 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.

- **Valerian**, an herbal product, is also available without a prescription. The recommended dose is 300 to 600 mg. Purity and potency concerns are an issue. It may cause daytime sedation.

Benzodiazepine Hypnotics:

- Benzodiazepines bind to GABA A receptors, and they 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.

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

- **Estazolam and temazepam** are intermediate in their duration of action.
- The effects of **flurazepam** and **quazepam** are long because of active metabolites.

- With the exception of temazepam, which is eliminated by conjugation, all benzodiazepine hypnotics are metabolized by microsomal oxidation followed by glucuronide conjugation.

- N-desalkylflurazepam accounts for most of flurazepam's pharmacologic effects.

- This metabolite may help when daytime anxiety or early morning awakening is present, but daytime sedation with impaired psychomotor performance may occur.

Benzodiazepine Adverse Effects:

- Side effects include drowsiness, psychomotor incoordination, decreased concentration, and cognitive deficits. Tolerance to the daytime CNS effects (e.g., drowsiness, psychomotor impairment, decreased concentration) may develop in some individuals.

- Tolerance to hypnotic effects develops after 2 weeks of continuous use of triazolam. Efficacy of flurazepam, quazepam, and temazepam lasts for at least 1 month of continuous nightly use. Estazolam reportedly maintains efficacy at maximum dosage (2 mg nightly) for up to 12 weeks.

- Anterograde amnesia has been reported with most benzodiazepines. Using the lowest dose possible minimizes amnesia. Rebound insomnia occurs frequently with high doses of triazolam, even when used intermittently.

- Rebound insomnia can be minimized by utilizing the lowest effective dose and tapering the dose upon discontinuation. There is an association between falls and hip fractures and the use of long- elimination half-life benzodiazepines; thus, flurazepam and quazepam should be avoided in the elderly.

SLEEP APNEA:

- Apnea is repetitive episodes of cessation of breathing during sleep. The goals of therapy are to alleviate sleep disordered breathing.

OBSTRUCTIVE SLEEP APNEA:

- Obstructive sleep apnea (OSA) is potentially life threatening and characterized by repeated episodes of nocturnal breathing cessation.

- It is caused by occlusion of the upper airway, and blood oxygen (O2) desaturation can occur.

- In severe episodes, there is heavy snoring, severe gas exchange disturbances, and respiratory failure, causing gasping. These episodes may occur up to 600 times/night.

- Episodes may be caused by obesity or fixed upper airway lesions, enlarged tonsils, amyloidosis, and hypothyroidism. Complications include arrhythmias, hypertension, corpulmonale, and sudden death.

- The apneic episode is terminated by a reflex action in response to the fall in blood O2 saturation that causes a brief arousal during which breathing resumes.

- OSA patients usually complain of excessive daytime sleepiness. Other symptoms are morning headache, poor memory, and irritability.

Treatment:

- Patients with severe apnea (greater than 20 apneas per hour on PSG) and moderate apnea (five to 20 apneas per hour on PSG) have shown significant improvement and reduction in mortality with treatment.

- Nonpharmacologic approaches are the treatments of choice (e.g., weight loss [which should be implemented for all overweight patients], tonsillectomy, nasal septal repair, and nasal positive airway pressure [PAP], which may be continuous or bilevel PAP).

- Other surgical therapies, uvulo- palate pharyngoplasty and tracheostomy, may be necessary in severe cases.

- The most important pharmacologic intervention is avoidance of all CNS depressants, which can be lethal.

- **Modafinil** is approved by the FDA to improve wakefulness in those who have residual daytime sleepiness while treated with PAP. It should be used only after patients are using optimal PAP therapy to alleviate sleep- disordered breathing.

CENTRAL SLEEP APNEA:

• Central sleep apnea (CSA; less than 10% of all apneas) is characterized by repeated episodes of apnea caused by temporary loss of respiratory effort during sleep.

It may be caused by autonomic nervous system lesions, neurologic diseases, high altitudes, and congestive heart failure.

Treatment:

• The primary treatment approach for CSA is PAP therapy with or without supplemental O2.

• Acetazolamide causes a metabolic acidosis that stimulates respiratory drive and may be beneficial for high altitude, heart failure, and idiopathic CSA.

NARCOLEPSY:

• The essential features are sleep attacks, cataplexy, hypnagogic hallucinations, and sleep paralysis. Individuals with narcolepsy complain of excessive daytime sleepiness, sleep attacks that last up to 30 minutes, fatigue, impaired performance, and disturbed nighttime sleep. They have multiple arousals during the night.

• **Cataplexy** is sudden bilateral loss of muscle tone with collapse, which is often precipitated by highly emotional situations.

• The hypocretin/orexin neurotransmitter system may play a central role in narcolepsy. An autoimmune process may cause destruction of hypocretin-producing cells.

TREATMENT:

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

- Good sleep hygiene, as well as two or more brief daytime naps daily (as little as 15 minutes), should be encouraged. Pharmacotherapy focuses on excessive daytime sleepiness and cataplexy.

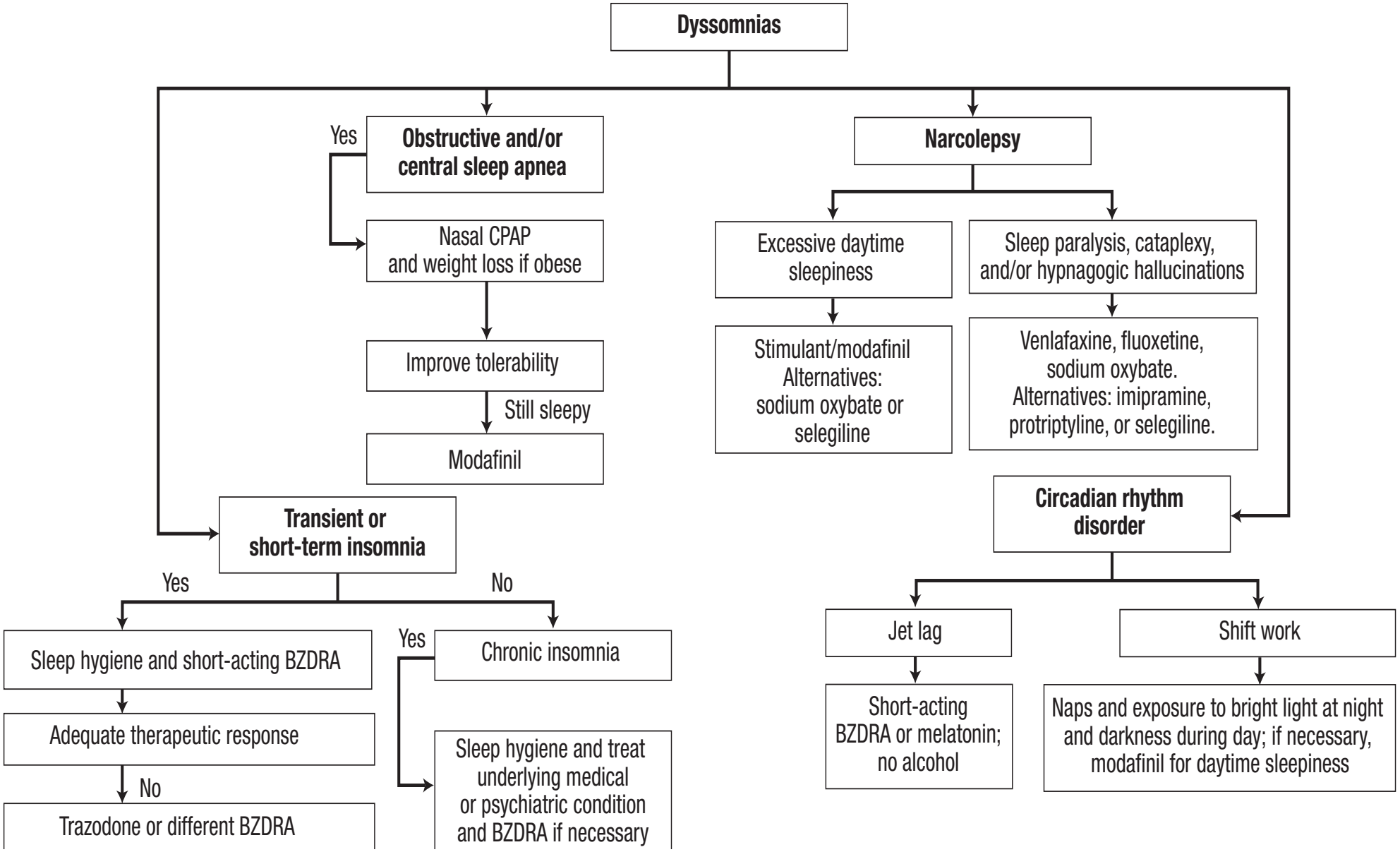
- **Modafinil** is considered the standard for treatment of excessive daytime sleepiness. Plasma concentrations peak in 2 to 4 hours, and the half-life is 15 hours. Preliminary evidence suggests no tolerance or withdrawal after abrupt discontinuation and no risk of abuse.

- Side effects of modafinil include headache, nausea, nervousness, and insomnia.
- Amphetamines and methylphenidate have a fast onset of effect and durations of 3 to 4 hours and 6 to 10 hours, respectively, for excessive daytime sleepiness.
- Divided daily doses are recommended, but sustained- release formulations are available.
- Amphetamines are associated with more likelihood of abuse and tolerance. Side effects include insomnia, hypertension, palpitations, and irritability.

- The most effective treatment for cataplexy is the tricyclic antidepressants, fluoxetine, or venlafaxine. Imipramine, protriptyline, clomipramine, fluoxetine, and nortriptyline are effective in about 80% of patients.

- **Sodium oxybate** (γ-hydroxybutyrate; a potent sedative-hypnotic) improves excessive daytime sleepiness and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations.

- It is taken at bedtime and repeated 2.5 to 4 hours later. Side effects include nausea, somnolence, confusion, dizziness, and incontinence.


Dyssomnias
Yes
Obstructive and/or central sleep apnea
Nasal CPAP and weight loss if obese
Improve tolerability
Still sleepy
Modafinil
Narcolepsy
Excessive daytime sleepiness
Stimulant/modafinil Alternatives: sodium oxybate or selegiline
Sleep paralysis, cataplexy, and/or hypnagogic hallucinations
Venlafaxine, fluoxetine, sodium oxybate. Alternatives: imipramine, protriptyline, or selegiline.
Transient or short-term insomnia
Yes
No
Sleep hygiene and short-acting BZDRA
Adequate therapeutic response
No
Trazodone or different BZDRA
Yes
Chronic insomnia
Sleep hygiene and treat underlying medical or psychiatric condition and BZDRA if necessary
Circadian rhythm disorder
Jet lag
Short-acting BZDRA or melatonin; no alcohol
Shift work
Naps and exposure to bright light at night and darkness during day; if necessary, modafinil for daytime sleepiness

Drugs Used to Treat Narcolepsy

Generic Name	Trade Name	Daily Dosage Range (mg)
Excessive daytime somnolence		
Dextroamphetamine	Dexedrine	5–60
Dextroamphetamine/Amphetamine salts[a]	Adderall	5–60
Methamphetamine[b]	Desoxyn	5–15
Methylphenidate	Ritalin	30–80
Modafinil	Provigil	200–400
Sodium oxybate[c]	Xyrem	4.5–9 g per night
Adjunct agents for cataplexy		
Fluoxetine	Prozac	20–80
Imipramine	Tofranil	50–250
Nortriptyline	Aventyl, Pamelor	50–200
Protriptyline	Vivactil	5–30
Selegiline	Eldepryl	20–40

- ✓ Patients with short-term or chronic insomnia should be evaluated after 1 week of therapy to assess for drug effectiveness, adverse events, and compliance with nonpharmacologic recommendations. Patients should be instructed to maintain a sleep diary, including a daily recording of awakenings, medications taken, naps, and an index of sleep quality.

- ✓ Patients with OSA should be evaluated after 1 to 3 months of treatment for improvement in alertness, daytime symptoms, and weight reduction. The bed partner can report on snoring and gasping.

- ✓ Monitoring parameters for pharmacotherapy of narcolepsy include reduction in daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. Patients should be evaluated regularly during medication titration, then every 6 to 12 months to assess adverse drug events (e.g., mood changes, sleep disturbances, and cardiovascular abnormalities). If symptoms increase during therapy, PSG should be done.