Chapter 92: Sleep Disorders

John M. Dopp; Bradley G. Phillips

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 70, Insomnia.

KEY CONCEPTS

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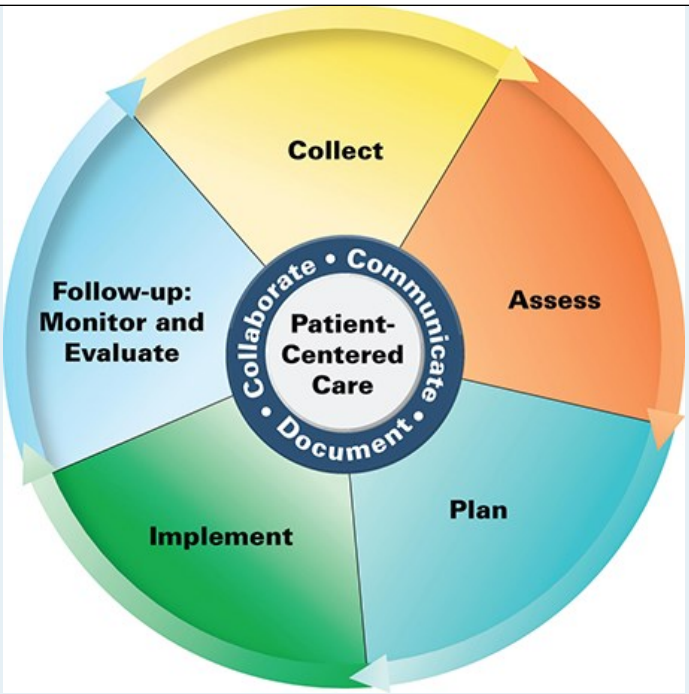
1. Common causes of insomnia include concomitant mental illness, significant psychosocial stressors, alcohol use, caffeine intake, and nicotine use.
2. Good sleep hygiene, including relaxing before bedtime, exercising regularly, establishing a regular bedtime and wake-up time, and discontinuing alcohol, caffeine, and nicotine, alone and in combination with pharmacotherapy, should be part of patient education and treatments for insomnia.
3. Long-acting benzodiazepines should be avoided in older individuals.
4. Benzodiazepine receptor agonist tolerance and physical dependence are avoided by using low-dose therapy for the shortest possible duration.
5. Obstructive sleep apnea may be an independent risk factor for the development of hypertension. When hypertension is present, it is often refractory to pharmacotherapy until sleep-disordered breathing is alleviated.
6. Nasal continuous positive airway pressure is the first-line therapy for obstructive sleep apnea, and weight loss should be encouraged in all obese patients.
7. Pharmacologic management of narcolepsy is focused on two primary areas: treatment of excessive daytime sleepiness and rapid eye movement (REM) sleep abnormalities.
8. Short-acting benzodiazepine receptor agonists, ramelteon, or melatonin taken at appropriate target bedtimes for east or west travel reduce jet lag and shorten sleep latency.
9. The alpha-2-delta ligands, gabapentin, gabapentin enacarbil, and pregabalin, are standard therapy for chronic restless legs syndrome and have not caused symptom augmentation during chronic therapy.

PATIENT CARE PROCESS

Patient Care Process for Sleep–Wake Disorders



Collect

- Patient characteristics (eg, age, sex, concomitant medical conditions, environmental or social stressors)
- Information about nighttime sleep complaints and daytime consequences from patient and bed partner
- Detailed medication history of prescription, over the counter (OTC), and complementary/alternative medication use
- Subjective and objective data about daytime sleepiness, sleep quality, limb movements, snoring, witnessed apneas, and parasomnias
- Information about sleep routine, sleep hygiene, and social history (eg, caffeine, alcohol, and tobacco use)
- Results from sleep testing (if available)

Assess

- Evaluate if individual environmental or social issues are contributing to sleep difficulties.
- Assess medications to determine if any may be contributing to sleep and/or daytime complaints.
- Assess any laboratory or sleep study test results that aid in assessment/treatment of sleep complaints (eg, serum ferritin, TSH, and so on).
- Concomitant mental illness or other medical conditions that should be addressed as part of sleep evaluation (eg, presence of anxiety, depression, chronic pain).

Plan*

- Optimize sleep hygiene and related behaviors (Tables 92-1 and 92-2) that may influence sleep and daytime symptoms.
- For insomnia, if sedative-hypnotic therapy is prescribed, match the agent's duration of action to sleep complaint (eg, short-duration agents for difficulty initiating sleep and moderate duration agents for difficulty maintaining sleep) (Table 92-3).
- Ensure that lowest doses of medication are used, but if response is inadequate, consider increasing dose or adding complementary medication.

- For narcolepsy or sleepiness disorders, consider use of long-acting stimulants to increase wakefulness throughout the day. Add as needed short-acting stimulants for late afternoon or evening periods requiring wakefulness (Table 92-4).

Implement*

- Provide patient education regarding all elements of treatment plan.
- Use motivational interviewing and coaching strategies to maximize adherence.
- Answer patient questions about medications and potential adverse effects.

Follow-up: Monitor and Evaluate

- Evaluate improvement in the specific sleep complaint (eg, how has therapy affected sleep latency or sleep maintenance?).
- Monitor daytime sleepiness, sleep diaries, and diaries of sleep events (eg, periodic limb movements of sleep [PLMS], hallucinations, snoring, apneas, and so on) and monitor cataplexy and other daytime symptoms to determine if therapy is effective.
- Make appropriate changes to therapy to address inadequately controlled symptoms and reported adverse effects (Tables 92-4 and 92-5).

**Collaborate with patients, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

Construct a table of medications used for insomnia, list the half-lives of their parent compound, and whether they are used for difficulty initiating or maintaining sleep.

Medication	Parent Medication Half-Life (hours)	Insomnia Use
Amitriptyline	15	Difficulty maintaining sleep
Zaleplon	1	Difficulty initiating sleep

INTRODUCTION

Approximately 70 million Americans suffer with a sleep-related problem, and as many as 60% of those experience a chronic disorder.[1] More than 80% of patients aged 65 years and older report a sleep-related disturbance..[1]

Sleep Cycles

Sleep is divided into two phases: nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Each night humans typically experience four to six cycles of NREM and REM sleep, with each cycle lasting between 70 and 120 minutes.[2] There are three stages of NREM sleep. Healthy sleep will typically progress through the three stages of NREM sleep prior to the first REM period. From wakefulness, sleep typically progresses quickly through stages 1 and 2. Stage 1 of NREM sleep is the stage between wakefulness and sleep, and individuals describe this experience as being awake, being drowsy, or being asleep. During stage 3 NREM, both metabolic activity and brain waves slow. This slow-wave sleep occurs most frequently early in the sleep period. Stage 3 sleep is called *delta sleep*, as the sleep is characterized by high amplitude and slow activity waves known as delta waves (0.5–3 Hz)

with no eye movements and low tonic muscle activity.

REM sleep involves a dramatic physiologic change from NREM sleep to a state in which the brain becomes electrically and metabolically activated.[2] REM occurs in bursts and is accompanied by a 62% to 173% increase in cerebral blood flow, generalized muscle atonia, bursts of bilateral REMs, poikilothermia, dreaming, and fluctuations in respiratory and cardiac rate.[2] REM cycles tend to lengthen in the later stages of the sleep cycle.[2]

Circadian Rhythm

At birth, human infants spend up to 20 hours a day sleeping with differentiation between REM and NREM sleep occurring at 3 to 6 months of age and the ultradian sleep–wake rhythm changing to a circadian pattern by age 3. Key to this is the suprachiasmatic nucleus of the brain which serves as the biologic clock and paces the circadian rhythm; although the length of a day is 24 hours, in environments devoid of light cues, the sleep–wake cycle lasts about 25 hours.[3] Through development from childhood into adolescence, the amount of nightly delta sleep declines and amount of REM sleep increases. In midlife, however, there is a gradual decline in sleep efficiency and sleep time,[2] and older persons have lighter and more fragmented sleep, with intermittent arousals, shifts in the sleep stages, and a gradual reduction of slow-wave sleep.

Neurochemistry

The neurochemistry of sleep is complex, as sleep cannot be localized to either a specific area of the brain or a specific neurotransmitter. Overall, NREM sleep appears to be controlled by the basal forebrain, the lower brain stem to the thalamus, and hypothalamus with numerous neurotransmitters mediating NREM sleep, including γ-aminobutyric acid (GABA) and adenosine.[3] In contrast, REM sleep appears to be turned on by cholinergic cells in the mesencephalic, medullary, and pontine gigantocellular regions and turned off by the dorsal raphe nucleus, the locus coeruleus, and the nucleus parabrachialis lateralis, the latter two of which are primarily noradrenergic. The ascending reticular activating system and the posterior hypothalamus also facilitate arousal and wakefulness[4] through neurotransmitters such as dopamine, which has an alerting effect.[5] Additional neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex, and histamine and neuropeptides such as substance P and corticotropin-releasing factor in the hypothalamus.[5,6]

Polysomnography

Polysomnography (PSG) is the primary method used to assess and record variables that characterize sleep and aid in diagnosis of sleep disorders. As part of this assessment, sleep is typically measured and observed in sleep laboratories using an electroencephalogram, electrooculograms of each eye, electrocardiogram, electromyogram, air thermistors, abdominal and thoracic strain belts, and oxygen saturation monitor. Variables obtained during PSG include sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, arrhythmias, airflow during sleep, respiratory effort, and oxygen desaturations. Additionally, home sleep monitoring that measures variables such as electrocardiogram, oxygen saturation, airflow, and respiratory effort is increasingly used to diagnose sleep apnea.

Classification of Sleep Disorders

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* classifies sleep–wake disorders into 10 categories: (1) insomnia disorder, (2) hypersomnolence disorder, (3) narcolepsy, (4) breathing-related sleep disorders, (5) circadian rhythm sleep disorders, (6) non-REM sleep arousal disorders, (7) nightmare disorder, (8) REM sleep behavior disorder, (9) restless legs syndrome (RLS), and (10) substance- or medication-induced sleep disorder.[7]

INSOMNIA

Insomnia is one of the most common complaints in general medical practice[8] as it frequently causes distress, due to the fear or a feeling of not being able to fall asleep at bedtime, leading to impaired work-related productivity because of daytime fatigue or drowsiness. Therefore, insomnia disorder is subjectively characterized as trouble initiating sleep, maintaining sleep or waking up early with inability to fall back asleep, that is associated with daytime consequences (insomnia not attributed to environment or limited opportunity for sleep).[7-9] Insomnia is classified as chronic when it has a duration of at least three months, occurring at least three times per week.[7,9]

Primary insomnia usually begins in early or middle adulthood and is rare in childhood or adolescence. Short-term insomnia occurs in 33% to 50% of the adult population,[8] with a year prevalence study of insomnia in the United States reporting that one-third of the individuals surveyed complained of insomnia and 17% reported that the symptoms were serious.[1] Conservative estimates of chronic insomnia range from 9% to 12% in adulthood and up to 20% in older individuals.[1,10] Although young adults are more likely to complain that they have difficulty falling asleep, middle-aged and older adults are more likely to complain that they have middle-of-the-night awakening or early morning awakening. Females complain of insomnia twice as frequently as males and individuals who are older, unemployed, separated, or widowed, and those with a lower socioeconomic status report a significantly higher incidence of insomnia than the general population. Forty per cent of individuals with insomnia also have a concurrent psychiatric disorder (eg, anxiety, depression, or substance use disorder),[11] and a significant percentage of those with insomnia use nonprescription medications or alcohol to self-treat.

Clinical Presentation

Insomnia is considered to be an endogenous disorder caused by either a neurochemical or a structural disorder affecting the sleep–wake cycle. Individuals with primary insomnia can be light sleepers who are easily aroused by noise, temperature, or anxiety. Primary insomnia is a "hyperarousal state," in that insomnia patients have increased metabolic rates compared with controls and thus take longer to fall asleep.[2] Comorbid or secondary insomnia is frequently a symptom or manifestation of another medical disorder. Evaluation of individuals with complaints of transient or short-term insomnia should focus on recent stressors, such as a separation, a death in the family, a job change, or college exams.

1 Chronic insomnia is frequently comorbid with psychiatric or medical conditions. A complete diagnostic examination should be completed in these individuals and should include routine laboratory tests, physical and mental status examinations, as well as ruling out any medication- or substance-related causes.[12] Other sleep disorders that can have a similar presentation should be ruled out, including restless legs syndrome (RLS) periodic limb movement disorder, and sleep apnea. Common causes of insomnia are listed in Table 92-1.

TABLE 92-1

Common Etiologies of Insomnia

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

TREATMENT

Desired Outcomes

The goals of treatment for insomnia are to correct the underlying sleep complaint, consolidate sleep, improve daytime functioning and sleepiness, and avoid adverse effects from selected therapies. Pharmacotherapy should be used in the lowest possible dose, for the shortest possible time period.

General Approach to Treatment

Therapeutic management of insomnia is initially based on whether the individual has experienced a short-term or chronic sleep disturbance. Clinical history should assess the onset, duration, and frequency of the symptoms; effect on daytime functioning; sleep hygiene habits; and history of previous symptoms or treatment.[13] Management of all patients with insomnia should include identifying and correcting the cause, patient education on sleep hygiene, and stress management. Any unnecessary pharmacotherapy that may worsen insomnia should be eliminated.[10] Short-term insomnia, which generally occurs as a result of acute stressors, is expected to resolve quickly and should be treated with good sleep hygiene and careful use of sedative-hypnotics.[11,13] Chronic insomnia requires careful assessment for possible underlying medical causes, nonpharmacologic approaches, and careful use of sedative-hypnotics.[12]

Nonpharmacologic Therapy

2 In many cases, insomnia can be treated without sedative-hypnotics. Education about normal sleep and habits for good sleep hygiene is important for all patients with insomnia. Nonpharmacologic interventions for insomnia frequently consist of short-term cognitive behavioral therapies, most commonly stimulus control therapy, sleep restriction, relaxation therapy, cognitive therapy, paradoxical intention, biofeedback, and education on good sleep hygiene (Table 92-2).[10,14] In patients aged 55 years and older, cognitive behavioral therapy may be more effective than pharmacologic therapy at improving certain measures of insomnia.[15,16]

TABLE 92-2

Nonpharmacologic Recommendations for Management of Insomnia

Stimulus control procedures
1. Establish regular time 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 (eg, read, listen to music) until drowsy. Repeat this as often as necessary. 5. Avoid blue spectrum light from television, smart phones, tablets, and other mobile devices. 6. Avoid daytime naps. 7. Schedule worry time during the day. Do not take your troubles to bed.
Sleep hygiene recommendations
1. Exercise routinely (eg, 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

Antihistamines

Antihistamines exhibit sedating properties and are included in many nonprescription sleep agents. They are effective in the treatment of mild insomnia and generally safe.[13] Diphenhydramine and doxylamine are available in OTC formulations. However, patients quickly experience tolerance to sedative effects, and increasing the dose will not produce a linear increase in response. Antihistamines are considered to be less effective than benzodiazepines, and they have the disadvantages of anticholinergic adverse effects, which are especially troublesome in older individuals.[13,17]

Sedating Antidepressants

For patients with nonrestorative sleep who should not receive benzodiazepines, antidepressants may be an alternative treatment, especially those who have depression, pain, or a history of, or at risk for a substance use disorder. Using antidepressants for insomnia without depression is common but not well studied, and the doses used for treating insomnia are not effective antidepressant doses.[9,13,14] However, low-dose doxepin (3-6 mg) is FDA-approved for the treatment of sleep maintenance insomnia. Other sedating antidepressants such as amitriptyline, doxepin, and nortriptyline are effective in inducing sleep continuity, although daytime sedation and adverse effects can be significant.[9,13] Anticholinergic activity, adrenergic blockade, and cardiac conduction prolongation can be problematic, especially in older individuals and in overdose situations.[9] Mirtazapine is a sedating antidepressant that may help patients sleep, but it may also cause daytime sedation and weight gain.

Trazodone is popular for the treatment of insomnia in patients prone to substance use disorder or in patients with selective serotonin reuptake inhibitor and bupropion-induced insomnia, as physical dependence is not a problem with trazodone.[11] Trazodone in doses of 25 to 100 mg at bedtime is sedating and can improve sleep continuity.[11] Adverse effects associated with trazodone use include carryover sedation and α-adrenergic blockade and orthostasis, which can occur at any age, but it is more dangerous in older individuals. Priapism is a rare but serious adverse effect.[18]

Dual Orexin Receptor Antagonists

Suvorexant and lemborexant are dual orexin A and orexin B receptor antagonists (DORA) that instead of inducing sleepiness, similar to most treatments for insomnia, turns off wake signaling. Suvorexant doses of 10 to 20 mg and lemborexant doses of 5 to 10 mg, at bedtime are indicated for difficulty initiating and maintaining sleep. The most commonly reported adverse effect with DORA use is somnolence, and patients should be counseled that sleep paralysis, cataplexy, and other narcolepsy-like symptoms may rarely occur.[19] Caution should be used in patients with depression as DORA use can worsen mood and trigger thoughts of suicide in a dose-dependent manner.

Melatonin Receptor Agonists

Ramelteon is a melatonin receptor (MT) agonist approved for the treatment of sleep-onset insomnia. It is selective for the MT1 and MT2 melatonin receptors that are thought to regulate the circadian rhythm and sleep onset. The recommended dose is 8 mg taken at bedtime to induce sleep, and although generally well tolerated, the most common adverse events reported are headache, dizziness, and somnolence. Ramelteon is not a controlled substance and can be a viable option for patients with a history of, or at risk for a substance use disorder; however, patients may not feel that it is as effective, as it does not cause the acute drowsiness associated with other insomnia agents. It does, however, effectively treat sleep-onset difficulties in patients with chronic obstructive pulmonary disease and sleep apnea.[20,21]

Miscellaneous

Valerian is a herbal sleep remedy that is purported to effectively treat insomnia but is not recommended by American Academy of Sleep Medicine based on a lack of high quaility evidence supporting its use.[8] The mechanism of action is not fully understood but may involve increasing concentrations of GABA. Doses range from 300 to 600 mg. Although frequently used by patients to help with sleep, melatonin has weak evidence supporting its use for treatment of insomnia.

Benzodiazepine Receptor Agonists

The most commonly used treatments for insomnia have been the benzodiazepine receptor agonists (BZDRAs) which are FDA-labeled for the treatment of insomnia (Table 92-3). The Food and Drug Administration (FDA) requires BZDRA labeling to include a caution regarding anaphylaxis, facial

angioedema, and complex sleep behaviors (eg, sleep driving, phone calls, sleep eating, and so on). The BZDRAs consist of the newer nonbenzodiazepine $GABA_A$ agonists and the traditional benzodiazepines. All BZDRAs bind to $GABA_A$ receptors in the brain, resulting in agonist effects on GABAergic transmission and hyperpolarization of neuronal membranes. Traditional benzodiazepines have sedative, anxiolytic, muscle relaxant, and antiseizure medication properties; newer nonbenzodiazepine GABA agonists possess only sedative properties.

TABLE 92-3

Pharmacokinetics of Benzodiazepine Receptor Agonists

Generic Name (Brand Name)	t_{max} (hours)[a]	Half-Life[b] (hours)	Daily Dose Range (mg)	Metabolic Pathway	Clinically Significant Metabolites
Estazolam (ProSom)	2	12-15	1-2	Oxidation	–
Eszopiclone (Lunesta)	1-1.5	6	2-3	Oxidation	–
				Demethylation	
Flurazepam (Dalmane)	1	8	15-30	Oxidation	Hydroxyethylflurazepam, flurazepam aldehyde
				N-dealkylation	*N*-desalkylflurazepam[c]
Quazepam (Doral)	2	39	7.5-15	Oxidation, *N*-dealkylation	2-Oxo-quazepam, *N*-desalkylflurazepam[c]
Temazepam (Restoril)	1.5	10-15	15-30	Conjugation	–
Triazolam (Halcion)	1	2	0.125-0.25	Oxidation	–
Zaleplon (Sonata)	1	1	5-10	Oxidation	–
Zolpidem (Ambien; Intermezzo)	1.6	2-2.6	1.75-10[d]	Oxidation	–

[a]Time to peak plasma concentration.

[b]Half-life of parent medication.

[c]*N*-desalkylflurazepam, mean half-life 47 to 100 hours.

[d]Oral and sublingual dosing 5 to 10 mg; sublingual tablets for middle-of-the-night dosing 1.75 to 3.5 mg (1.75 for females, 3.5 for males).

Benzodiazepines relieve insomnia by reducing sleep latency and increasing total sleep time by increasing stage 2 sleep while decreasing delta sleep.[11] Benzodiazepine hypnotics should not be prescribed for individuals who are pregnant or who have untreated sleep apnea or a history of substance use disorder, and patients should be instructed to avoid alcohol and other central nervous system (CNS) depressants.

Adverse effects

Adverse effects are dose dependent and vary according to the pharmacokinetics of the individual benzodiazepine. High doses with long or

intermediate elimination half-lives have a greater potential for producing daytime sedation, psychomotor incoordination, and cognitive deficits. Most traditional benzodiazepines maintain hypnotic efficacy for 1 month. However, tolerance can develop with time.

Anterograde amnesia, an impairment of memory and recall of events occurring after the dose is taken, has been reported with most BZDRAs, and is more likely to occur with short-acting agents.[11] Additionally, after abrupt discontinuation of BZDRAs, rebound insomnia, characterized by increased wakefulness beyond baseline amounts, may occur and last for a few nights. Therefore, the lowest effective dosage should be used to minimize rebound insomnia and avoid adverse effects on memory.

3 Benzodiazepine half-lives are prolonged in older patients, increasing the potential for medication accumulation and the incidence of CNS adverse effects, including prolonged sedation and cognitive and psychomotor impairment. BZDRAs with long elimination half-lives (eg, flurazepam and quazepam) are generally not first-line agents in older patients. Benzodiazepine use is also associated with increased risk of falls and hip fractures in older individuals, but since insomnia itself increases fall and fracture risk, it is unclear if benzodiazepines increase risk independent of sleep problems.[22]

Nonbenzodiazepine $GABA_A$ Agonists

Zolpidem, zaleplon, and eszopiclone are nonbenzodiazepine hypnotics that selectively bind to $GABA_A$ receptors and effectively induce sleepiness.

Zolpidem has a duration of action of 6 to 8 hours[23] and is comparable in efficacy to benzodiazepine hypnotics, in that it is effective in reducing sleep latency and nocturnal awakenings, and increasing total sleep time. It does not have significant effects on next-day psychomotor performance. Sustained-release, sublingual, and reduced-strength (1.75 and 3.5 mg) formulations of zolpidem are available and are used to increase total sleep time, to reduce sleep latency, and for middle-of-the-night rescue dosing, respectively.

Zolpidem is less disruptive of sleep stages than benzodiazepines and adverse effects include drowsiness, amnesia, dizziness, headache, and gastrointestinal complaints, which are dose-related.[23] Sleep eating during zolpidem therapy can result in significant weight gain. The recommended daily dose of zolpidem is 10 mg in male patients, or 5 mg in female patients, older patients, and those with hepatic impairment. Because food decreases its absorption, zolpidem should be taken on an empty stomach.[24]

Zaleplon has a rapid onset of action with a half-life of 1 hour, and is metabolized to inactive metabolites.[25] It is effective in decreasing time to sleep onset but not for reducing nighttime awakening or for increasing total sleep time.[26] Because of its short half-life, zaleplon has no effect on next-day psychomotor performance and can be used as a sleep aid for middle-of-the-night awakenings.[27] The recommended dose is 10 mg in adults and 5 mg in older individuals.[25] The most common adverse effects with zaleplon are dizziness, headache, and somnolence. There are two interactions of note: zaleplon plasma levels increase when combined with cimetidine and decrease with rifampin.[23]

Eszopiclone is effective in reducing time to sleep onset, wake time after sleep onset, and number of awakenings, and increasing total sleep time and sleep quality. Eszopiclone's duration of action is up to 6 hours.[28] It can be a good option for treatment of sleep maintenance insomnia or early morning awakenings. The most common adverse effects with eszopiclone are somnolence, unpleasant taste, headache, and dry mouth.[28] Eszopiclone is labeled for long-term use and may be taken nightly for up to 6 months.[28,29]

In general, nonbenzodiazepine hypnotics seem to be associated with less physical withdrawal, tolerance, and rebound insomnia than benzodiazepine hypnotics. None of the nonbenzodiazepine $GABA_A$ agonists have significant active metabolites.

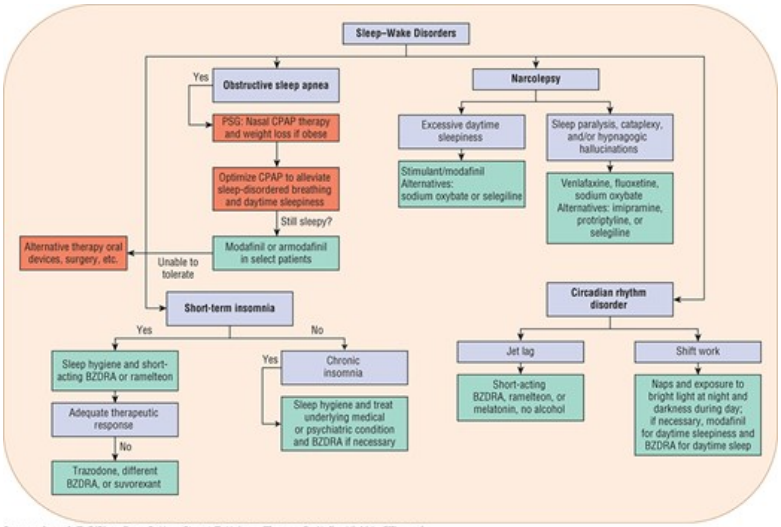
EVALUATION OF THERAPEUTIC OUTCOMES

An algorithm for the evaluation and treatment of sleep–wake disorders is shown in Fig. 92-1. Patients with short-term or chronic insomnia should be evaluated after 1 week of therapy to assess for medication efficacy, adverse effects, and adherence to nonpharmacologic recommendations. For the treatment of insomnia, the choice of a particular BZDRA can be based on its pharmacokinetic profile. When used as a single dose, the extent of distribution and elimination half-life are important in predicting the duration of action. However, after multiple doses, the elimination half-life and formation of active metabolites determine the extent of medication accumulation and resultant clinical effects.[11] Advanced age, liver dysfunction, and

medication interactions can prolong medication effects. The pharmacokinetic profiles of BZDRAs are summarized in Table 92-3.

FIGURE 92-1

Algorithm for treatment of sleep and wake disorders. (BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure) *(Adapted, with permission, from Reference 70.)*



Patients should be instructed to keep a sleep diary that includes daily recording of bedtime, wake time, latency of sleep onset, number and duration of awakenings, medication ingestion, naps, and an index of sleep quality. For patients with chronic insomnia, possible medical, psychiatric, and pharmacologic causes should be identified and managed.[11] Patients with insomnia should receive education about possible medication adverse effects and their management.

4 Clinicians should educate patients about the concepts of tolerance, physical withdrawal, and rebound insomnia. Tolerance and physical dependence can be avoided by using hypnotics at the lowest possible dose, intermittently, and for the shortest duration possible. Patients should also receive instruction about frequency of medication use and the expected duration of therapy to help prevent development of physical dependence. Withdrawal symptoms can be diminished by tapering the dosage gradually.

SLEEP APNEA

Sleep apnea is a common disease, affecting 20 to 25 million Americans. It has a higher prevalence in males, particularly in African American and Hispanic populations.[30,31] It also occurs in children and adolescents. It is characterized by repetitive episodes of cessation of breathing during sleep followed by blood oxygen desaturation and brief arousal from sleep to restart breathing. As a result, individuals with sleep apnea experience fragmented sleep, poor sleep architecture, and periods of apnea and hypopnea. PSG, or a home sleep study, is used to diagnose and quantify sleep apnea as central, obstructive, or mixed. Central sleep apnea (CSA) involves impairment of the respiratory drive, whereas obstructive sleep apnea (OSA) is caused by upper airway collapse and obstruction. Patients with mixed sleep apnea experience both CSA and OSA. The overall severity of sleep apnea is determined by the number of apnea (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation) episodes documented by PSG, which is expressed as the respiratory disturbance index (RDI). Patients with mild sleep apnea have an RDI of between 5 and 15 episodes/hour, and those with moderate apnea have an RDI between 15 and 30 episodes/hour, whereas individuals with severe OSA exhibit more than 30 episodes/hour.

OSA is associated with a greater risk for motor vehicle accidents, depression, increased cancer risk, stroke, and cardiovascular disease.[32-35] Therefore, alleviation of sleep-disordered breathing may improve patient outcomes, particularly those related to cardiovascular disease.[35]

Obstructive Sleep Apnea

OSA is characterized by partial or complete closure of the upper airway, posterior from the nasal septum to the epiglottis, during inspiration. The reason for the loss of upper airway patency is not fully understood and is likely caused by several competing factors. Anatomical factors including neck obesity, narrow airway, and fixed upper airway lesions (eg, polyps, enlarged tonsils) can narrow the upper airway. The intraluminal negative pressure generated during each inspiration also promotes collapse of the upper airway that competes with dilating forces, primarily the pharyngeal dilator muscle. Acromegaly, amyloidosis, and hypothyroidism as well as neurologic conditions that impair upper airway muscle tone may cause OSA. The hallmarks of OSA are witnessed apneas, gasping, or both. Other recognized signs, symptoms, and considerations of sleep apnea include obesity, snoring, daytime sleepiness, family history, and hypertension.

5 OSA is increasingly linked to cardiovascular and cerebrovascular morbidity and mortality, independent of other risk factors.[35] Individuals with OSA are at risk for developing hypertension, and when hypertension is present, it is often resistant to medication therapy.[36] Alleviation of sleep-disordered breathing with nasal positive airway pressure (PAP) only modestly improves blood pressure (2-3 mmHg), but increased use of PAP correlates with greater blood pressure reductions.[37,38]

Central Sleep Apnea

CSA causes fragmented sleep and consequent daytime somnolence. However, unlike OSA, arousals from sleep are not required to initiate airflow. During PSG, there is an absence of airflow out of the mouth and nose with no activation of the inspiratory muscles. The prevalence of CSA is not well established and is less than OSA. CSA can be idiopathic but more commonly is caused by underlying autonomic nervous system lesions (eg, cervical cordotomy), neurologic diseases (eg, poliomyelitis, encephalitis, and myasthenia gravis), high altitudes, opioid use disorder, and congestive heart failure. For these reasons, potential underlying causes for CSA should be evaluated and treated. For example, worsening CSA in heart failure patients can signal the need to optimize heart failure therapies. Practice parameters for the treatment of CSA have been published by the American Academy of Sleep Medicine.[45]

TREATMENT

Desired Outcomes

In the absence of an underlying cause (eg, hypothyroidism, acromegaly), alleviation of sleep-disordered breathing and prevention of associated complications are the primary goals of treatment. Nonpharmacologic measures are the treatments of choice. There is no medication therapy for OSA. However, medications that worsen sleep should be avoided. Practice parameters for the medical treatment of OSA have been published by the American Academy of Sleep Medicine.[39]

Nonpharmacologic Therapy

Positive Airway Pressure

6 Nasal PAP during sleep is the standard treatment for most patients with OSA. This procedure produces a positive pressure column in the upper airway using room air to maintain patency by using a flexible tube that connects the PAP machine to a mask that covers the nose or nose and mouth.

PAP delivery may be continuous (CPAP), bi-level (providing a reduced applied pressure during expiration), or auto-titrating continuous positive airway pressure therapy (AutoPAP). The AutoPAP machines may be programmed to a pressure range allowing the machine to provide individualized pressure based on breath-to-breath analysis of the necessary pressure to keep the airway open. The CPAP pressure may be identified during PSG as the pressure setting that results in elimination of sleep-disordered breathing up to 20 cm H_2O (2.0 kPa). Alternatively, the CPAP pressure may also be identified as the pressure used by the AutoPAP machine 90% to 95% of the time. Barriers to PAP adherence, such as ill-fitted mask and nasal dryness, can be managed; however, PAP nonadherence for one night results in a complete reversal of the gains made in daytime alertness.[40]

Weight Reduction

Obesity can worsen sleep apnea, and weight management should be implemented for all overweight patients with OSA. Additionally, OSA can predispose patients to weight gain, and in obese patients with mild OSA weight loss alone can be effective.[41] Individuals who are morbidly obese and

have severe OSA may consider bariatric surgery for weight loss.

Surgery

Surgical therapy (uvulopalatopharyngoplasty) opens the upper airway by removing the tonsils, trimming and reorienting the posterior and anterior tonsillar pillars, and removing the uvula and posterior portion of the palate. Due to the invasive nature of surgical treatment, this is not a first-line option. In very severe cases, a tracheostomy may be necessary. This procedure can be indicated for select individuals who are morbidly obese, have severe facial skeletal deformity, experience severe drops in oxygen saturation (eg, less than 70% [0.7]), or have significant cardiac arrhythmias associated with their OSA.

Other Therapies

For individuals who experience OSA only during certain sleep positions (eg, when lying on their back), positional therapies can be effective alone, but are usually used in conjunction with PAP therapy. Oral appliances can also be used to advance the lower jawbone and to keep the tongue forward to enlarge the upper airway. Alternatively, hypoglossal nerve stimulators that contract the genioglossus muscle during sleep to maintain airway patency are increasingly being used. These therapies should be considered when PAP therapy cannot be tolerated.[42]

Pharmacologic Therapy

The most important pharmacologic intervention for sleep apnea is the avoidance of all CNS depressants (eg, alcohol, hypnotics) and medications that promote weight gain as both of these worsen OSA. The use of CNS depressants is potentially lethal, as it reduces the brain's reflex ability to cause a mini-arousal and resume breathing. In addition, certain CNS depressants can relax airway muscles, promoting upper airway collapse. Medications that can cause rhinopharyngeal inflammation and cough as an adverse effect of therapy (ie, angiotensin-converting enzyme inhibitor) may also worsen sleep-disordered breathing.

There is no pharmacotherapy for OSA. In clinical trials, serotonergic agents (eg, fluoxetine, paroxetine), tricyclic antidepressants (TCAs) (ie, imipramine, protriptyline), respiratory stimulants (eg, theophylline), medroxyprogesterone, and clonidine have not clinically improved severity of OSA. The effects of antihypertensive agents on sleep apnea are inconsistent and are likely not clinically significant.

Wake-promoting medications (eg, modafinil, armodafinil, and solriamfetol) are FDA-approved to improve wakefulness in patients who have residual excessive daytime sleepiness (EDS) while being treated with PAP. Initiation of therapy should be attempted in patients only after PAP therapy has been optimized to alleviate sleep-disordered breathing and EDS. Wake-promoting medications should be avoided in those with concomitant cardiovascular disease. In patients with concurrent rhinitis, nasal steroids are recommended for use along with PAP therapy.[39]

Medication therapy for CSA is limited and is individualized for each patient, based on underlying etiology. Acetazolamide, which induces a metabolic acidosis that stimulates respiratory drive, and theophylline, which improves severity of CSA, have been studied but have minimal effects on clinical variables.[46,47]

EVALUATION OF THERAPEUTIC OUTCOMES

Individuals with sleep apnea should be evaluated after 1 to 3 months of treatment for improvement in alertness and daytime symptoms (eg, sleepiness, impaired memory, and irritability) and weight reduction. Individuals experiencing symptoms (eg, daytime sleepiness, snoring, loss of blood pressure control) despite PAP therapy should have repeat evaluation of sleep apnea severity. Symptoms can recur if patients gain weight, requiring a higher-pressure setting. Conversely, PAP pressure settings can be decreased if weight loss is achieved. Patient adherence to PAP therapy can be monitored by assessing the built-in compliance meter, which is also uploaded to a cloud database that measures the hours used at effective pressure and residual apnea occurrence.

NARCOLEPSY

Narcolepsy, which is a severely debilitating neurologic disease that affects between 0.03% and 0.06% of adult Americans,[43] often goes undiagnosed or misdiagnosed for years. The prevalence is equal or somewhat higher in males compared to females, and it is commonly recognized in the second

decade of life and increases in severity through the third and fourth decades.[43] Individuals with narcolepsy complain of EDS, and in the sleep laboratory, exhibit impairment of both the onset and the offset of REM and NREM sleep and have arousals and disturbed sleep during the night.

Narcolepsy is classified as narcolepsy type 1 (narcolepsy with cataplexy) and narcolepsy type 2 (narcolepsy without cataplexy).[9] Four characteristic symptoms differentiate narcolepsy from other sleep disorders and are known as the *narcolepsy tetrad*: EDS, cataplexy, hallucinations, and sleep paralysis. Cataplexy is a sudden bilateral loss of muscle tone of varying severity and duration without the loss of consciousness, which occurs in 60% to 70% of people with narcolepsy.[43] Cataplexy is often precipitated by situations characterized by high emotion (eg, laughter, anger, excitement) and can manifest as subtle changes, such as jaw or head slumping, or severe weakness, such as knee buckling or collapsing to the ground. Cataleptic episodes can be brief, lasting seconds, or can last for several minutes. Sleep paralysis is an episodic loss of voluntary muscle tone that occurs when the individual is falling asleep or waking where they are conscious but not able to move or speak. Hallucinations while falling asleep (ie, hypnagogic) and on awakening (ie, hypnopompic) are brief, dream-like experiences that intrude into wakefulness and are experienced by nearly 60% of patients with narcolepsy. Unfortunately, these symptoms sometimes lead to an incorrect mental illness diagnosis.[43] Mechanistically, cataplexy, sleep paralysis, and hypnagogic hallucinations can be attributed to REM sleep disturbances.[43]

Loss of normal function of the hypocretin-orexin neurotransmitter system plays a central role in the pathophysiology of narcolepsy. Neurons containing hypocretin-orexin are found in the lateral hypothalamus and project to various parts of the brain that are thought to regulate sleep. In 75% of patients with narcolepsy, hypocretin-orexin is undetectable in cerebrospinal fluid.[44,45] Since patients with narcolepsy and cataplexy have low concentrations of hypocretin-1 (less than 110 pg/mL [ng/L; 31 pmol/L]),[9] an autoimmune process may be responsible for the destruction of hypocretin-producing cells.[46,47] Molecular studies of human leukocyte antigens (HLA) have found a high prevalence of the HLA-DR2 and HLA-DQ6/DQB1 haplotypes in patients with narcolepsy.[48] However, the HLA-DR2 haplotype is also common in the non-narcolepsy populations and is not diagnostic.[47] As 3% of patients have a first-degree relative with the disorder, there may also be a genetic component associated with this disease.[44] Lastly, as the onset of this disease occurs in adolescence or adulthood, but not at birth, environmental influences also play a role.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Narcolepsy

Symptoms

- Patients may complain of EDS and disrupted nighttime sleep; often they have some accompanying REM sleep abnormality, sleep paralysis, cataplexy, and/or hallucinations.

Laboratory Tests

- Although not routinely tested, there is a high incidence of human leukocyte antigen (HLA) haplotypes DR2 and HLA-DQ6/DQB1 in narcolepsy.
- Cerebrospinal fluid (CSF) concentrations of hypocretin-1 can be measured to confirm a diagnosis. CSF concentrations less than 110 pg/mL (ng/L; 31 pmol/L) positively predict narcolepsy.

Other Diagnostic Tests

- Narcolepsy is diagnosed using the multiple sleep latency test (nap test). The patient takes four to five naps in a day, and narcolepsy is diagnosed if the patient falls asleep quickly, within less than 5 minutes, and goes into REM sleep in two of those nap periods.

TREATMENT

Desired Outcomes

Nonpharmacologic management of narcolepsy includes counseling the patient and family concerning the illness to alleviate misconceptions around

the individual's behavior. Good sleep hygiene should be encouraged, as well as two or more scheduled daytime naps as naps lasting 15 minutes each can help the individual with narcolepsy feel refreshed. The primary objective of pharmacologic treatment of narcolepsy is to reduce symptoms that adversely influence the patient's quality of life and to produce the fullest possible return of normal function for individuals within work, school, home, and social settings.

Pharmacologic Therapy

Pharmacologic management of narcolepsy is focused on two primary areas: treatment of EDS and REM sleep abnormalities. Clinical practice guidelines for treatment of narcolepsy in adults were updated and strongly recommend modafinil, pitolisant, sodium oxybate, and solriamfetol for the treatment of narcolepsy. Armodafinil, dextroamphetamine, and methylphenidate are also suggested as second-line options. Medication therapy for narcolepsy is summarized in Table 92-4.

TABLE 92-4

Dosing of Medications Used to Treat Narcolepsy

Generic Name	Brand Name	Initial Dose (mg)	Usual Dose (mg)	Comments
Excessive daytime somnolence				
Dextroamphetamine	Dexedrine	5-10	5-60	Concurrent use of amphetamines and acidic foods may reduce amphetamine absorption
Dextroamphetamine/Amphetamine salts[a]	Adderall	5-20	5-60	See above
Methamphetamine[b]	Desoxyn	5-15	5-15	See above
Lisdexamfetamine	Vyvanse	20-30	20-70	Prodrug of dextroamphetamine
Methylphenidate	Ritalin	10-40	30-80	May increase risk of bleeding with concomitant warfarin therapy
Solriamfetol	Sunosi	75	75-150	Renally eliminated; specific dosing required for renal impairment
Modafinil	Provigil	100-200	200-400	May reduce effectiveness of hormonal contraceptives
Armodafinil	Nuvigil	150	150-250	May reduce effectiveness of hormonal contraceptives
Sodium oxybate[c]	Xyrem	4.5 g/night	4.5-9 g/night	Do not use with other CNS depressants
Pitolisant[c]	Wakix	8.9	17.8-35.6	May reduce effectiveness of hormonal contraceptives
Agents for cataplexy				
Atomoxetine	Strattera	18-100	40-100	Lower doses in CYP2D6 poor metabolizers
Fluoxetine	Prozac	10-20	20-80	Will see cataplexy benefits sooner than antidepressant benefits
Imipramine	Tofranil	50-100	50-250	Anticholinergic adverse effects
Nortriptyline	Aventyl, Pamelor	50-100	50-200	Anticholinergic adverse effects
Protriptyline	Vivactil	5-10	5-30	
Venlafaxine	Effexor	37.5	37.5-225	May increase blood pressure
Selegiline	Eldepryl	5-10	20-40	Doses less than 10 mg/day do not require dietary tyramine restrictions

[a]Dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.

[b]Not available in some states.

[C]Also is effective in treating cataplexy.

Data from References 47 and 49.

Modafinil, a racemic compound unrelated to psychostimulants, and armodafinil (its active R-isomer) are FDA-approved for treatment of EDS in narcolepsy. The precise mechanism of action of modafinil and armodafinil is not fully understood. Common adverse reactions are usually mild and include headache, nausea, nervousness, anxiety, and insomnia. The dose of modafinil is between 100 and 400 mg/day, and armodafinil doses are between 150 and 250 mg/day.[50] Although both of these agents are effective in treating EDS, they lack efficacy for the treatment of cataplectic symptoms.[51]

EDS can also be treated with stimulants to improve alertness and to increase daytime performance. Dextroamphetamine and methylphenidate also have FDA approval for the treatment of narcolepsy. Methamphetamine and mixed amphetamine salts have also been used on an off-label basis. Methylphenidate and amphetamines have a fast onset of action and durations of 6 to 10 and 3 to 4 hours, respectively. The doses of methylphenidate and amphetamine formulations can range from 5 to 60 mg daily.

Stimulants improve alertness and daytime performance, and they can elevate mood and prevent sleep. Adverse medication reactions can include insomnia, hypertension, palpitations, and irritability. Tolerance to long-term stimulant therapy can occur, necessitating dosage increases. Amphetamine use is associated with a greater likelihood of a substance use disorder and tolerance, especially when prescribed in high doses. Lisdexamfetamine is an amphetamine prodrug rapidly absorbed and converted in the body to dextroamphetamine, which has a longer duration of action and less risk of a substance use disorder since it is active only when taken orally.

To individualize treatment of narcolepsy many clinicians prescribe both immediate-release and sustained-release stimulants to increase alertness throughout the day. Sustained-release stimulants are prescribed with scheduled administration times, and immediate-release stimulants can be taken as needed when the patient requires alertness (eg, driving). There are no guidelines that recommend pharmacogenomics testing to predict response to simulant medication when being used for the treatment of sleep disorders.

Solriamfetol, a norepinephrine and dopamine reuptake inhibitor, and pitolisant, a histamine-3 antagonist/inverse agonist, are relatively new medications approved for treatment of EDS in narcolepsy. Pitolisant is also approved for treatment of cataplexy, and because it has a completely different mechanism of action, it may be prescribed with other wake-promoting medications. Solriamfetol improves wakefulness and quality of life in patients with narcolepsy.[49]

The most commonly used treatments for cataplexy are tricyclic antidepressants (TCAs), selective norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs). The mechanism of antidepressants in relieving cataplexy, hypnagogic hallucinations, and sleep paralysis is thought to be mediated through blockade of serotonin and norepinephrine reuptake in the locus coeruleus and raphe which subsequently suppresses REM sleep.[52] Imipramine, protriptyline, clomipramine, fluoxetine, and nortriptyline are effective in approximately 80% of patients. Selegiline improves hypersomnolence and cataplexy through REM suppression and an increase in REM latency. Atomoxetine may improve cataplexy and sleepiness in children, but is less effective than other therapies in older teenagers and adults. In contrast to the antidepressants, methylphenidate and amphetamines alone are usually ineffective for complete relief from cataplexy.

Sodium oxybate (γ-hydroxybutyrate, Xyrem) improves symptoms of EDS and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations. A low sodium formulation (Xywav) was developed and has similar dosing to the traditional formulation. Nightly administration of sodium oxybate changes sleep architecture to resemble normal sleep. It increases slow-wave sleep, decreases nighttime awakenings, and increases REM efficiency.[53] Sodium oxybate is available only as a liquid and is taken in two doses; one is taken at bedtime and the second dose is taken 2.5 to 4 hours later. Sodium oxybate is a potent sedative-hypnotic and should not be used concomitantly with any other sedating medications. The most common adverse reactions include nausea, somnolence, confusion, dizziness, and incontinence.

EVALUATION OF THERAPEUTIC OUTCOMES

Patients with narcolepsy should keep a diary of the frequency and severity of cataplexy, sleep paralysis, and sleep hallucinations. Patients should be evaluated regularly during medication titrations and then every 6 to 12 months to assess for adverse medication reactions (eg, sleep disturbances, hypertension, and cardiovascular abnormalities). The healthcare provider should consider the benefit-to-risk ratio for the individual patient, the cost

of medication, the convenience of administration, and the cost of laboratory tests when selecting narcolepsy therapies.[49] One wake-promoting agent may work better than another in an individual patient. Thus, if one agent is not effective at adequate doses, a trial with another agent should be undertaken.

CIRCADIAN RHYTHM DISORDERS

The sleep–wake cycle is under the circadian control of oscillators and can be disrupted by misalignment between an individual's biologic clock and external demands on the sleep cycle. Circadian rhythm sleep disorders usually present with either insomnia or hypersomnia, depending on the individual's performance requirements. Two commonly occurring circadian rhythm sleep disorders are jet lag and shift work sleep problems.

Jet Lag

Jet lag occurs when a person travels across time zones, and the external environmental time is mismatched with the internal circadian clock. Disturbances in sleep due to jet lag typically last for 2 to 3 days, but can last as long as 7 to 10 days if the time zone changes are greater than 8 hours. Compared with westward travel, eastward travel is associated with a longer duration of jet lag. In addition to decrease in alertness and performance, jet lag can also lead to increased incidence of gastrointestinal disturbances.

8 Treatment of jet lag includes nonpharmacologic approaches alone or in combination with medication therapy. Jet lag can be minimized in coast-to-coast travel in the United States if the duration is less than 7 days and the normal sleep–wake cycle is observed. For travel lasting longer than 7 days, jet lag severity can be lessened by 1- to 2-hour adjustments in sleep and wake times prior to departure to the destination time zone. Appropriate timing of light exposure along with short-acting BZDRAs, ramelteon, and 0.5 to 5 mg melatonin, taken at appropriate target bedtimes for east or west travel, reduce jet lag and shorten sleep latency.[54]

Shift Work Sleep Disorder

Shift workers comprise approximately 20% of the workforce.[55] Night shift work causes a misalignment in the sleep–wake cycle and circadian rhythm that is associated with a decrease in alertness, performance, and quality of daytime sleep. More than 65% of workers on rotating shifts complain of insomnia, compared with only 20% who work one shift.[56] Shift workers ultimately are at risk of developing shift work sleep disorder, which is a complaint of insomnia or excessive sleepiness that occurs because of circadian sleep disruption due to working shifts during normal sleep time.[9,55] Shift workers have a higher injury rate, divorce rate, occurrence of on-the-job sleepiness, and incidence of substance use disorder. They may also be at increased risk of developing peptic ulcers, depression, breast cancer, and sleepiness-related accidents.[55-57] Night shift workers are usually in a state of permanent circadian misalignment because of the tendency to revert to conventional sleep schedules on nonwork days.[56]

Treatment for shift work sleep problems includes optimizing sleep hygiene, extending daytime sleep by sleeping in the afternoon, scheduling a 2- to 3-hour nap on days off from work, or switching to a day shift job. Short-acting BZDRAs, ramelteon, and melatonin can consolidate sleep during day sleep periods and reduce lost sleep time. Modafinil and armodafinil are FDA-approved to improve wakefulness in patients with EDS associated with shift work sleep disorder. Scheduled exposure to bright lights at night and darkness in the daytime improves adaptation to night work and daytime sleep.[56]

Restless Legs Syndrome

RLS, or Willis-Ekbom syndrome, is characterized by paresthesias that are usually felt deep in the calf muscles resulting in the urge to keep limbs in motion. Additionally, these paresthesias can also appear in the thighs and arms. RLS occurs in both sexes, and it occurs more frequently in older individuals. It has been associated with chronic kidney disease and pregnancy. Additionally, RLS can be caused by iron deficiency in the substantia nigra in the CNS[58] and caffeine, stress, alcohol, and fatigue can worsen symptoms. The diagnosis of RLS is based on patient- or partner-reported symptoms and specific diagnostic criteria that include (a) an urge to move the limbs that are usually associated with uncomfortable and unpleasant sensations, (b) symptoms that begin or worsen during rest or inactivity, (c) symptoms that are exclusively present or worse in the evening or night, (d) symptoms that are temporarily relieved by movement, and (e) occurrence of symptoms is not accounted for as symptoms of another medical condition.[59] The discomfort returns when the person tries to sleep, resulting in insomnia. RLS adversely affects work performance, quality of life, and increased risk for cardiovascular disease.[60-62]

Periodic Limb Movements of Sleep

Periodic limb movements of sleep (PLMS) are stereotypic, repetitive, periodic movements of the legs that occur during sleep every 20 to 40 seconds and last 10 minutes to several hours.[66] The movements usually involve the big toe, but the ankle, knee, and hip can also flex. They can be terminated by a violent kick or other body movements. Often patients will be unaware of these movements and only recognize consequent insufficient sleep and morning leg cramps. A bed partner can describe PLMS. PLMS is diagnosed in the sleep laboratory using electromyogram recordings.

PLMS can occur with RLS or alone because of systemic disease (eg, renal failure) or medication therapy.[72] In fact RLS patients commonly have PLMS, while approximately one-third of patients with PLMS have RLS.[66] TCAs, SSRIs, dopaminergic antagonists, xanthines, nicotine, alcohol, and caffeine can all worsen PLMS.

TREATMENT

Pharmacologic Therapy

For treatment of intermittent symptoms, occurring less than 2 days per week, levodopa or benzodiazepines are recommended for as-needed use. However, for chronic, persistent symptoms, alternative therapies are recommended.

9 The alpha-2-delta ligands gabapentin, gabapentin enacarbil, and pregabalin are standard therapy for chronic RLS and have not caused symptom augmentation during chronic therapy. Gabapentin 100 to 1,800 mg near bedtime may be especially effective for those with paresthetic or painful RLS symptoms.[63] Gabapentin enacarbil (Horizant) is a gabapentin prodrug that is FDA-approved for the treatment of RLS at a dose of 300 to 600 mg taken at 5 pm. Pregabalin has similar or greater efficacy for RLS compared to dopamine agonists. These medications should have the dose slowly increased to achieve therapeutic effect, as their benefit may not be evident until therapeutic doses are reached. Iron studies should be completed in patients with RLS and iron supplementation initiated in those who are deficient. In patients with ferritin concentrations less than 75 mcg/L (ng/mL) or transferrin saturation less than 20%, iron supplementation improves RLS symptoms.[64,65]

The dopamine agonists ropinirole, pramipexole, and rotigotine are FDA-approved for RLS treatment.[66] Lower doses of dopamine agonists are used when treating RLS compared with Parkinson's disease. Providers should caution patients that compulsive behaviors (eg, gambling, shopping, eating, and so on) and sudden periods of extreme sleepiness may emerge during therapy with dopamine agonists. Due to levodopa's short half-life, it may not provide relief over the entire night. Additionally, dopaminergic agents are associated with a high incidence of symptom augmentation, which is a worsening in symptom severity, increase in symptom distribution, emergence of symptoms earlier in the evening, shortening duration of symptom control, and need for escalating dopaminergic doses to control symptoms. Augmentation can be treated by tapering and discontinuing dopaminergic medications, repleting low body iron stores and switching to alternative medications such as gabapentin. Sedative-hypnotic agents can be effective in patients who have frequent awakenings from their RLS symptoms. Clonazepam at doses ranging from 0.5 to 2 mg has been most frequently studied; however, patients may experience carryover sedation because of its long duration of action. Shorter half-life sedative-hypnotics (eg, zolpidem, zaleplon) can improve sleep and reduce daytime sleepiness without carryover sedation. Opioids such as methadone 5 to 20 mg, and prolonged release oxycodone-naloxone are effective in patients with painful RLS; however, the potential for tolerance and physical dependence on opioid therapy should be considered. Patients with RLS or PLMS should be evaluated regularly to monitor for excessive daytime somnolence, tolerance, efficacy, and adverse effects of the medication. Therapy should be monitored for adverse medication reactions found in Table 92-5.

TABLE 92-5

Monitoring Patients Taking Medications for RLS and PLMS

Medication or Medication Class	Adverse Medication Reaction	Monitoring Parameter	Comments
Dopamine agonists	Compulsive behaviors	Frequency and quantity of eating, gambling, shopping, other reward behaviors	May occur at any time during therapy but is dose-related
Levodopa/Carbidopa	Symptom augmentation	Location and timing of RLS symptoms	Appearance of symptoms in other areas of body and earlier in day
Gabapentin/Pregabalin	Dizziness	Subjective dizziness, falls	–
Sedative-hypnotics (eg, clonazepam, temazepam, zolpidem, and so on)	Carryover sedation	Morning sleepiness, grogginess	More likely to occur with longer duration agents
Opioids (eg, oxycodone, codeine, hydrocodone, and so on)	Tolerance, constipation	Patient RLS symptoms and response to ongoing therapy	–
Oral iron therapy (eg, ferrous sulfate, and so on)	Gastrointestinal upset, constipation	Monitor for constipation	Prophylactic stool softeners may be necessary to reduce risk of constipation

The treatment approach for PLMS is similar to that of RLS in that if the PLMS do not cause disruptions for the patient or bed partner or daytime symptoms, they may not require treatment. Symptomatic or problematic PLMS should be treated with dopaminergic medications or alpha-2-delta ligands to suppress limb movements or sedative-hypnotics to reduce awakenings and consolidate sleep.

PARASOMNIAS

Parasomnias are abnormal behavior or physiologic events that either occur during sleep or are exaggerated by sleep. Many of these disorders are considered to be disorders of partial arousal from various sleep stages. Parasomnias can be categorized as disorders of arousal (sleepwalking, sleep terrors), sleep–wake transition disorders (sleep-talking), rhythmic movement disorder, REM parasomnias (REM behavior disorder, nightmares), and miscellaneous parasomnias (enuresis, bruxism). Sleepwalking, sleep terrors, and sleep-talking predominantly occur during NREM sleep, whereas others, such as REM behavior disorder, occur during REM sleep.

Sleepwalking and sleep terrors are found normally in children between the ages of 4 and 12 years and usually resolve in adolescence. These disorders are increasingly recognized to also occur in adulthood, and, contrary to previous beliefs, are not related to psychological or psychiatric pathology.[67] In adults, sleep terrors can begin between the ages of 20 and 30 years. Onset of sleepwalking in adults without a childhood history of sleepwalking should prompt a search for a neurologic or substance use disorder.[68] Sleepwalking and sleep terror disorder involve intrusions of wakefulness into NREM sleep during the first third of the night. In sleepwalking, individuals become ambulatory, are difficult to awaken, and are amnestic for the event. Sleep terrors involve intense fear and autonomic arousal. Individuals are difficult to awaken, inconsolable, and amnestic for the event.[68] Patients with REM behavior disorder act out their dreams, often in a violent manner, and are at risk for injury.

Treatment of sleepwalking involves protecting the individual from harm by putting safety latches on doors and windows, removing hazardous objects from bedrooms, and covering glass doors with heavy curtains. In adult patients, benzodiazepines, SSRIs, or TCAs can be beneficial therapies for

sleepwalking or other NREM disorders of arousal.[67] Benzodiazepines can also be helpful in curtailing sleep terrors in adults.[68] Nightmares are anxiety-provoking dreams characterized by vivid recall and treatment is directed at reducing stress, anxiety, and sleep deprivation. In extreme cases, low-dose benzodiazepines can be indicated. Clonazepam is the treatment of choice for REM behavior disorder. Melatonin (3-12 mg at bedtime) and pramipexole can also be an effective therapy for REM behavior disorder.[69]

CONCLUSION

Sleep and wake disorders are common but they may be challenging to diagnose since clinical presentation and precise symptoms may be unknown to the individual who is asleep. Practitioners need to perform a sleep history that involves both the patient and their bedpartner. Treatments for sleep and wake disorders are effective, but not curative, and need to be monitored carefully for both safety and efficacy. Practitioners should use the lowest doses of medications for the shortest durations possible, and thoroughly investigate potential underlying causes for sleep and wake disturbances.

ABBREVIATIONS

AutoPAP	auto-titrating positive airway pressure
BZDRA	benzodiazepine receptor agonist
CNS	central nervous system
CPAP	continuous positive airway pressure
CSA	central sleep apnea
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition
DORA	dual orexin receptor antagonist
EDS	excessive daytime sleepiness
GABA	γ-aminobutyric acid
GI	gastrointestinal
HLA	human leukocyte antigen
NREM	nonrapid eye movement
OSA	obstructive sleep apnea
PAP	positive airway pressure
PLMS	periodic limb movements of sleep
PSG	polysomnography
RDI	respiratory disturbance index
REM	rapid eye movement
RLS	restless legs syndrome
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

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SELF-ASSESSMENT QUESTIONS

1. SB is a 28-year-old who complains that they had difficulty sleeping over the last several weeks and that it is beginning to interfere with work. They state that they had been working long hours and feeling stressed, so they participate in aerobics before bed around 10 pm. What would you recommend initially to SB?

   A. Trazodone

   B. Flurazepam

   C. Zolpidem

D. Sleep Hygiene

2. A 35-year-old individual, complains of difficulty with sleep onset for more than 12 weeks. They have appropriately tried sleep-hygiene therapy, but that has not worked. The plan is to initiate medication therapy. If the patient has no contraindications, and no medical causes for these sleep difficulties, which of the following therapies would be best for initial therapy?

   A. Amitriptyline

   B. Fluoxetine

   C. Doxepin

   D. Zolpidem

3. A 42-year-old individual who recently lost their partner tells you that they are not sleeping at night. After further questioning, you determine that they do not have depression or a substance use disorder. What would you recommend?

   A. Educate concerning sleep hygiene.

   B. Recommend a trial of a short-acting BZDRA.

   C. Recommend a trial of fluoxetine.

   D. Recommend a trial of amitriptyline.

4. A 27-year-old individual has trouble due to waking up in the middle of the night. Which of the following is *least* likely to be effective if taken at bedtime?

   A. Zaleplon

   B. Temazepam

   C. Zolpidem CR

   D. Estazolam

5. What is the best way to avoid tolerance and misuse in this patient?

   A. Use high-dose BZDRA therapy for as long as possible.

   B. Use high-dose BZDRA therapy for as short a time as possible.

   C. Use low-dose BZDRA therapy for as long as possible.

   D. Use low-dose BZDRA therapy for as short a time as possible.

6. A 28-year-old individual has a chief complaint of insomnia occurring for the last 5 months. They just graduated from pharmacy school and spends the evening worrying if they made a mistake during their busy days at work. All other mental health and medical conditions have been ruled out. How would you approach treating this patient?

   A. Recommend a short-term trial of lorazepam.

   B. Recommend a short-term trial of clonazepam.

   C. Recommend an approach that would include education concerning good sleep. hygiene, supportive therapy, and trazodone as an adjunct if needed.

D. Recommend cognitive therapy alone.

7. A 34-year-old individual begins working overnight shifts. They find difficulty sleeping during daytime hours. What is the best recommendation you can provide to help with this complaint?

   A. Drink alcohol after their work shift to help with falling asleep.

   B. Take melatonin, ramelteon, or a short-acting BZDRA at bedtime.

   C. Take an SSRI after work to help falling asleep.

   D. Take modafinil prior to going to work to help staying awake overnight.

8. A 54-year-old patient has been having difficulty maintaining sleep. They sleep fine until around 1 am when they wake up and they would like to sleep until 6:30 am. Which of the following would be the most appropriate?

   A. Diazepam 5 mg PO at bedtime

   B. Eszopiclone 3 mg PO when awakening at 1 am

   C. Zolpidem 3.5 mg SL when he awakening at 1 am

   D. Flurazepam 30 mg PO at bedtime

9. A 46-year-old with chronic obstructive pulmonary disease has difficulty falling asleep. Which pharmacologic agent would you recommend in this patient?

   A. Temazepam

   B. Amitriptyline

   C. Ramelteon

   D. Levothyroxine

10. DB is a 58-year-old individual with obstructive sleep apnea and daytime sleepiness but no other medical conditions. What is the best therapy for this patient?

    A. Solriamfetol

    B. Uvulopalatopharyngoplasty

    C. Oral appliances

    D. Positive airway pressure

11. Sleep apnea can lead to all of the following sequelae *except*?

    A. Depression

    B. Stroke

    C. Hypertension

    D. Jet lag

12. Which of the following has a strong recommendation for the treatment of daytime sleepiness associated with narcolepsy according to recent clinical practice guidelines?

A. Methamphetamine

B. Modafinil

C. Zolpidem

D. Imipramine

13. Which of the following is an effective treatment for cataplexy associated with narcolepsy?

A. Methamphetamine

B. Medroxyprogesterone acetate

C. Modafinil

D. Pitolisant

14. It is believed that restless legs syndrome results from:

A. Hypocretin-orexin neuron dysfunction in the hypothalamus

B. Repetitive airway closure during sleep

C. Iron deficiency in the substantia nigra of the CNS

D. Loss of serotonin receptors in the dorsal raphe nucleus

15. Which of the following would be the correct recommendation for a patient with internet addiction disorder and restless legs syndrome who has RLS?

A. Gabapentin

B. Doxepin

C. Ropinirole

D. Pramipexole

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** They should improve sleep hygiene (exercise before bed) before trying medications. For some people, exercising immediately prior to bedtime activates the sympathetic nervous system and produces difficulty with sleep. See Nonpharmacologic Therapy of Insomnia Section.

2. **D.** Zolpidem is indicated for difficulty with sleep onset and is preferred first-line therapy. See subsection "Benzodiazepine Receptor Agonists" under "Pharmacologic Therapy" of the section "Insomnia."

3. **B.** BZDRAs are first-line therapies for short-term treatment of insomnia and in this case a trial of a short-acting BZDRA is indicated. See Fig. 92-1.

4. **A.** Zaleplon has a short duration of action and will not last through the night to prevent middle-of-the-night awakenings if it is taken at bedtime. See subsection "Benzodiazepine Receptor Agonists" under "Pharmacologic Therapy" of the section "Insomnia."

5. **D.** By using the lowest dose BZDRA for the shortest duration you can minimize the risk of tolerance or a substance use disorder. Higher doses and longer durations of treatment will increase these risks. See subsection "Benzodiazepine Receptor Agonists" under "Pharmacologic Therapy" of the section "Insomnia."

6. **C.** A comprehensive approach to sleep hygiene, including supportive therapy, is indicated for this patient to determine the causes of sleep problems. Trazodone may be provided medication therapy if indicated. See the subsection "Sedating Antidepressants" of "Nonpharmacologic Therapy" and "Pharmacologic Therapy" of the section "Insomnia."

7. **B.** Melatonin, ramelteon, or short-acting BZDRA are effective in helping initiate sleep in patients with shift work sleep disorder. See "Circadian Rhythm Disorders" section.

8. **C.** Zolpidem sublingual indicated for middle-of-the-night awakenings. See subsection "Benzodiazepine Receptor Agonists" under "Pharmacologic Therapy" of the section "Insomnia."

9. **C.** Ramelteon is safe and effective in patients with COPD. See "Melatonin Agonist" section under "Pharmacologic Therapy" of the section "Insomnia."

10. **E.** CPAP is first-line therapy for OSA with sleepiness. CPAP is noninvasive, effective, and is universally prescribed as first therapy for OSA. See "Nonpharmacologic Therapy" section under "Sleep Apnea."

11. **D.** Sleep apnea is not associated with development of Jet Lag. Sleep apnea is associated with development of hypertension, risk of stroke, and depression. See "Sleep Apnea" section.

12. **B.** Modafinil is recommended (strong) for treatment of daytime sleepiness with narcolepsy. See "Pharmacologic Therapy" section of "Narcolepsy."

13. **D.** Pitolisant is indicated for cataplexy with narcolepsy. See "Pharmacologic Therapy" section of "Narcolepsy."

14. **C.** Localized CNS iron deficiency has been documented in the cadaver studies of brains of individuals who had RLS and iron deficiency exacerbates and, in some cases, initiates RLS symptoms. See "Restless Legs Syndrome" section.

15. **A.** Gabapentin will not increase risk of impulse control disorders and is first-line therapy for RLS. Dopamine agonists are not the best choice in this patient since they are associated with the development of impulse control disorders which may be particularly problematic in patients with a substance use disorder or other use disorder. See "Pharmacologic Therapy" of the "Restless Legs Syndrome" section.