Insomnia

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Opinion statement

The pathogenesis of insomnia in an individual usually is multifaceted. Effective treatments require a thorough evaluation to determine the factors that need to be addressed. Pharmacologic treatments generally are safe and effective for short-term use. Long-term hypnotic use remains controversial because of the potential risk of tolerance and dependency. Various cognitive and behavioral treatments for insomnia have been shown to be effective in the management of insomnia. For long-term follow-up, multicomponent cognitive behavioral therapy, alone or in combination with hypnotic use, has been shown to be superior to hypnotic use alone.

Introduction

Insomnia generally is defined as a subjective report of difficulty falling sleep, difficulty staying asleep, early awakening, or nonrestorative sleep. It is one of the most common health complaints among the general population. When taking the severity and daytime consequences into consideration, approximately 10% to 20% of the general population reported moderate to severe insomnia [1–3, Class I].

The two most commonly used diagnostic systems, the *International Classification of Diseases, 10th Revision* [4] and *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [5], classify insomnia into primary insomnia (or nonorganic insomnia) and several subtypes of secondary insomnia. The most common cause of secondary insomnia is psychiatric disorders. It was estimated that 35% to 40% of patients with insomnia carry one or more comorbid psychiatric diagnoses, with affective disorders, anxiety disorders, and substance abuse among the most prevalent ones. Evidence also showed that persistent insomnia may predispose patients to the development of psychiatric disorders, especially depression [6,7, Class I]. Difficulty sleeping also may be the result of the discomfort and the pathophysiology associated with medical conditions, such as airway disease, hypertension, musculoskeletal or other painful disorders, heart disease, and prostate problems [8–12, Class II]. In addition to the physiologic conditions associated with the medical or psychiatric illness, the medications prescribed may disrupt sleep and cause insomnia. Examples include antihypertensives, bronchodilators, and activating antidepressants. Other primary sleep disorders, such as restless legs syndrome, periodic limb movement disorders, and sleep apnea syndrome also can lead to insomnia. Therefore, identification and treatment of primary psychiatric and medical disorders or other sleep disorders are essential in the management of insomnia. However, although the primary condition is presumed to be the cause of the sleep disturbances in secondary insomnia, it often is difficult to judge the causal effect in clinical cases. Although the insomnia may be caused originally by the primary condition, sleep-specific pathologies may develop after the onset of insomnia. Therefore, the evaluation and treatment of sleep-specific pathologies may be as important as the evaluation and treatment of the primary condition in these cases.

The pathogenesis of insomnia can be conceptualized as a disruption of the mechanisms that control normal processes of sleep and wakefulness. It has been well recognized that there are at least two physiologically separate processes that regulate sleep: a homeostatic process and a circadian process [13, Class II]. The homeostatic system regulates sleep by increasing sleep propensity by an amount related to the duration of wakefulness, and discharging sleep drive by the amount of sleep. The more sleep drive satiated previously, the

less sleep propensity at a given moment. However, the circadian system generates a near 24-hour rhythm of wakefulness tendency that is independent of prior sleep obtained. These two systems interact with each other, and regulate the level of sleep propensity at a given time. In addition to these two sleep-regulating systems, sleep also is affected by another system that regulates arousal and wakefulness. This arousal system may not modulate sleep directly, but may counteract sleep drive through the promotion of arousal and wakefulness. This system can be boosted by stress and emotional and environmental stimuli, and can interrupt normal sleep processes. Therefore, insomnia can result from dysfunctions of any or a combination of these three regulatory systems: the sleep homeostat, the circadian wakefulness drive, and the arousal system. To understand and treat insomnia, it often is very useful to examine the factors associated with the functioning of these three sleep-wake related domains.

Several etiologic models have been proposed to explain the phenomena associated with insomnia. Many of them focused on the arousal system instead of the sleep systems [14••,15••, Class II]. Characteristics of "hyperarousal" in psychologic or physiologic domains have been reported in previous studies. Individuals with insomnia have been shown to have elevated autonomic system activation indicated by higher metabolic rate, body temperature, heart rate, urinary cortisol, adrenaline excretion, skin conduction, and muscle tension [16,17, Class I], in addition to increased cognitive processing as reflected by faster electroencephalographic frequencies [18–20, Class I]. Another model proposed that the arousal state in insomniacs may be learned through a process of classic conditioning [21, Class II]. Transient sleep disturbances may be triggered by acute stressors. Through repeated waking and worrying in bed, the patient may soon associate the bedtime cues with waking and anxiety, and become aroused around bedtime.

Difficulty sleeping also could result from the disruption of normal functioning of the homeostatic system. This disruption may be physiologically based or caused by maladaptive behaviors. A weak sleep-generating system may be innate, acquired through early developmental problems, or, in elderly patients, associated with aging process. Prolonged napping or frequent dozing off during the daytime also may lead to a decreased sleep drive at night. In addition, the common practice of advancing bedtime and extending time in bed in an attempt to make up sleep loss may additionally exacerbate insomnia attributable to a reduction in sleep drive at bedtime.

Sleep disruption also can be caused by a mismatch between the individual's endogenous circadian sleep-wake system and the exogenous demands regarding the timing and duration of sleep. The sleep per se may not be problematic when patients with circadian rhythm sleep disorders are allowed to choose their preferred sleep schedule. For example, an individual with a delayed endogenous circadian sleep-wake system may tend to have difficulty falling asleep in the evening and may have difficulty getting up in the morning. However, when allowed to sleep at their preferred schedule, such as during the weekend, they usually choose to go to bed late and to sleep-in in the morning without experiencing sleep disruption. This condition is more frequently seen in adolescents or young adults [22,23, Class II]. In contrast, patients with an advanced endogenous circadian rhythm usually have no problem initiating sleep, but complain of early morning awakening. This sleep pattern is more commonly reported by elderly individuals [24,25, Class II]. In clinical cases, mild phase shifting of circadian rhythm may interact with other sleep pathologies, and make the evaluation and treatment of the condition more complicated.

In addition to identifying the physiologic causes of sleep and waking problems, it also is helpful to organize the contributing factors to insomnia into predisposing, precipitating, and perpetuating factors to formulate a comprehensive treatment plan [26, Class II]. Predisposing factors include arousal-prone personality, elevated baseline physiologic arousal, rigid circadian system, and other individual characteristics that make one vulnerable to or set the stage for the development of insomnia. Understanding these risk factors can help one to avoid getting into situations that may lead to poor sleep. Precipitating factors are the events or conditions that trigger the insomnia. Common examples include life stressors and change of sleep-wake schedule. In some cases, resolving the triggering event is the only treatment necessary to address the sleeping problem. However, in many cases, the insomnia persists and becomes chronic over time. The perpetuating factors, such as conditioning of bedtime cues with arousal, maladaptive sleep-wake habits and worries over sleeplessness, then should become the focus of the treatment. lists the common contributing factors of insomnia associated with the sleep and arousal systems along the timeline of the development of insomnia (Table 1).

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Table 1. Common contributing factors for the development of insomnia

Predisposing factors
Homeostatic process
Abnormality or weakness of the central nervous system that generates sleep
Circadian process
Extreme circadian-type functioning better during late evening or early morning as an individual trait
Less flexible circadian system
Arousal system
Anxiety-prone and depressive personality traits and tendencies toward neuroticism and somatization lead to a higher level of emotional arousal such as perfectionism
Personality traits lead to sustained level of arousal such as perfectionism and excessive need for control
Heightened or more sensitive physiologic arousal system
Precipitating factors
Homeostatic process
Lack or decrease in daytime activities such as in retirement; discharge of the sleep drive by sleeping outside of the nocturnal sleep period
Circadian process
Change of sleep-wake schedule, such as in jet lag or shift work
Arousal system
Life stressors or events lead to emotional and physiologic distress
Perpetuating factors
Homeostatic process
Increased resting in bed
Increased daytime naps
Reduced daytime activities
Circadian process
Sleeping-in during weekend to catch up on sleep
Arousal system
Dysfunctional beliefs and attitudes about sleep that lead to increased worries about sleep loss
Conditioning between bedtime cues and arousal

Treatment

- Effective treatment is the result of a thorough evaluation of the particular case to determine the factors that need to be addressed. Pharmacologic treatment for insomnia is safe and effective for short-term usage in most cases. Long-term use remains controversial because of the potential risk of tolerance and dependence [27•, Class II]. Various cognitive and behavioral treatments for insomnia have been shown to be effective in the management of insomnia [28••,29, Class I]. Currently, most behavioral medicine practitioners tend to use a combination of multiple cognitive behavioral techniques rather than a single technique. The multicomponent cognitive behavioral therapy (CBT) alone and CBT in combination with hypnotic use has been shown to be superior to hypnotics in long-term follow-up [30••,31••, Class I]. Pharmacologic treatments and CBT are described in detail in the following sections.

Diet and lifestyle

- Sleep disturbances may be caused by inadequate sleep hygiene and maladaptive daily life activities. Adjusting lifestyle may help with the sleep problem. Because sleep hygiene education usually is considered to be a

component of nonpharmacologic treatment of insomnia. Details of lifestyle changes to promote improved sleep are described in the sleep hygiene section of this article.

Nonpharmacologic treatment

- Scientifically validated nonpharmacologic treatments of insomnia fall into two treatment categories: cognitive therapy that targets the patients' beliefs or thought processes, and behavioral therapy that institutes changes through behavioral practices. Therefore, they generally are referred to as cognitive behavioral therapy (CBT).
- CBT can be applied individually or in the format of group therapy. Individual treatment usually is tailored according to the individual's condition. Therefore, a thorough evaluation to determine the factors associated with the individual's sleep condition is crucial to gain successful treatment results. Group CBT is more structured and includes components of cognitive therapy and behavioral interventions.
- CBT sessions usually are scheduled on a weekly or biweekly basis. The entire program usually takes 4 to 6 weeks. Recently, abbreviated, two-session CBT also has been reported to be effective for the treatment of insomnia in primary care setting [32••, Class II].
- The different techniques used in CBT can be used alone and have been shown to generate good results [28••,29, Class I]. They also can be used in combination to address different factors leading to insomnia. Different techniques that compose a typical CBT program are described below.

Stimulus control therapy

- Stimulus control therapy is designed to break the association between cues contained in the bed and bedroom and long periods of wakefulness. A set of instructions guides the patients to get out of bed if they are unable to fall asleep, and return to bed when they feel ready to fall asleep [21, Class II]. Specific patient instructions are as follows:
  - Lie down to sleep only when you feel sleepy.
  - Do not use your bed or bedroom for anything except sleep (sexual activity is the only exception).
  - If you are not falling asleep within approximately 20 minutes, get up and go into another room. Do something relaxing and go back to bed only when feeling sleepy again.
  - If you still are not falling asleep or if you are awakening from sleep, repeat the third step.
  - Set the alarm for the same time each morning and get up then regardless how much sleep you have had.
- Indications for this approach are signs of maladaptive association of bedtime cues with anxiety and wakefulness, such as feeling tense when anticipating retiring or getting into bed or sleeping better at places other than one's bedroom.
- Initially, patients will spend considerable time out of bed and will suffer some sleep loss and daytime consequences. The patient needs to be educated that short-term sacrifice will produce long-term gains.

Sleep restriction therapy

- Sleep restriction therapy, based on the assumption that the homeostatic process of sleep can self-correct sleep when it is deprived, promotes sleep by inducing a mild sleep loss initially and gradually enhances sleep time after sleep is stabilized. This procedure also can prevent or break the maladaptive association between wakefulness and bedtime cues by decreasing wakefulness in bed [33,34, Class II].
  - Patients complete a sleep log that records their daily sleep pattern over a 2-week period.
  - Use the average total sleep time of this 2-week period as the prescribed time in bed for the following week. Time of arising from bed is set to the time when the patient is required to wake up or when the patient generally awakens, and time of retiring is calculated accordingly. To avoid the effects of severe sleep deprivation, the minimum time in bed is never set below 4.5 hours. Lying down or napping outside of the scheduled bedtime is not permitted.
  - Patients fill out a sleep log to report bedtimes and their estimated total sleep time. Averaged sleep efficiency (estimated total sleep time/time in bed × 100%) is evaluated weekly.
- Adjust the prescribed time in bed weekly according to the following rules:
  - Prescribed time in bed is adjusted by three criteria: 1) if mean sleep efficiency is greater than 90% (85% in seniors), then increase time in bed by 15 minutes by setting the retiring time earlier; 2) if mean sleep efficiency is less than 85% (80% in seniors), then decrease time in bed by 15 minutes; and 3) if mean sleep efficiency is greater than 85% and less than 90% (80% to 85% in seniors) then the time in bed should remain the same.
  - Increase time in bed progressively by 15 or 30 minutes each week until the patient is spending 7 hours in bed. Additional changes may be made based on daytime functioning, fatigue, and sleepiness [35, Class III].
- This treatment is indicated when the patients normally spend prolonged time in bed awake.
- Special considerations are the same as for stimulus control therapy.

Sleep hygiene education

- Sleep hygiene refers to practices of everyday living and sleep-related activities that promote good quality sleep or that make sleep more resistant to disruption.
- Basic knowledge about sleep and sleep disorders should be provided. The basic knowledge provided usually includes information about the processes and function of normal sleep, the influence of biological rhythms on sleep, the variability of sleep from night to night, developmental changes of sleep, the effect of daily activities on sleep, and the effect of sleep disturbances on daytime function. This understanding empowers the patient, eliminates unnecessary worry about the consequences of sleep loss, and provides the rationale for specific treatments and sleep hygiene prescriptions.
- Sleep hygiene education helps the patients identify and modify their daily living practices that are counterproductive. The patient is asked to refrain from maladaptive activities and, in some cases, engage in sleep-promoting behaviors. Common practices that are incompatible with good sleep are listed in Table 2.
- Sleep hygiene education is indicated when the evaluation of the patient's daily life style and sleep-wake habits show poor sleep hygiene.

Table 2. Poor sleep hygiene: sleep-wake and lifestyle habits that interfere with sleep

Daytime and evening habits	Nighttime and morning habits
Excessive or late caffeine consumption	Irregular sleep-wake schedule
Smoking in the evening	Spending too much time in bed
Alcohol consumption in the evening	Falling asleep with the television or radio on
Napping, nodding, or dozing	Trying too hard to sleep
Exercising in the late evening	Watching the clock during the night
Evening apprehension of sleep or preparations for bed are arousing	Remaining in bed during awakening
Insufficient wind-down in the evening	Lingering in bed awake in the morning
No regular presleep ritual	Extra sleep during the weekends
Distressing pillow talk	Environmental interferences, such as noises, morning sunlight, and pets
Late evening meal or fluid*	
Watching television, reading, or engaging in other behaviors incompatible with sleep in bed before retiring	

*May cause frequent urination

- Sleep hygiene education has been shown to be less effective than the other behavioral treatments. It usually is part of a more comprehensive treatment program in the treatment of most patients with insomnia.
- It is important to convey to the patients that insomnia is the result of numerous factors coming together. Eliminating poor sleep hygiene may not solve the problem. However, successful treatment may be prevented or delayed because of these practices.

Relaxation training

- Activities resulting in arousal or perturbing the mind may interfere with sleep. For the same reasons, activities reducing arousal may facilitate sleep. Various relaxation techniques have been developed to assist in the reduction of tension and anxiety, such as progressive muscle relaxation that reduces muscle tension by sequential tensing and relaxing of the main muscle groups, autogenic training that produces somatic relaxation by inducing sensations of warmth and heaviness of the body, and guided imagery that aims to channel mental processes into a vivid story line [36–38, Class II]. Biofeedback may be used to assist monitoring and learning of relaxation training [39,40, Class II].
- Training usually starts with a demonstration by the clinician during an office visit. The patient then practices the technique at home once or twice a day in between sessions. The instructions of the trainings can be recorded, or commercial relaxation training tapes can be used to facilitate the practice at home.
- This treatment is indicated in patients with signs of hyperarousal, such as muscle tensions, excessive worries, and uncontrollable racing thoughts.
- It may take weeks for some individuals to develop the skill to relax on cue. Only after mastering the procedure, the patient is told to use it to facilitate falling asleep.

Cognitive therapy

- Worrying about sleeplessness is a self-fulfilling prophecy that may promote arousal and may additionally exacerbate sleep difficulties. Faulty beliefs and attitudes about sleep have been shown to be associated with the symptoms of insomnia [41, Class I]. Change of dysfunctional thoughts can

reduce the worry about sleeplessness and therefore break the vicious cycle that leads to arousal. Common dysfunctional cognitions about sleep have been classified into five categories: 1) misconceptions of the causes of insomnia, 2) misattributions or amplifications of its consequences, 3) unrealistic sleep expectations, 4) diminished perceptions of control, and 5) predictability of sleep [42, Class II].

- Misunderstandings about sleep may be corrected with sleep hygiene education. Relaxation training also can be helpful to distract the patients from excessive worries or to reduce the physical arousal, thereby helping to break the vicious cycle of sleeplessness. However, cognitive restructuring addresses the sleep-disturbing cognitions directly, and replaces the thoughts with more realistic thoughts and positive ideas. The procedure of cognitive restructuring is as follows:
  - Discuss with the patients their general beliefs regarding sleep and their sleep problems.
  - Identify the counterproductive beliefs.
  - Provide correct information to help the patients develop more positive and less disruptive ideas about their sleep problems.
  - A cognitive behavioral strategy may be used by enlisting the patient as a co-investigator to help gather data that will address the validity of specific beliefs.
- This treatment is indicated when the patients reveal faulty beliefs and attitudes about sleep that lead to excessive worry or maladaptive daily living practices.
- A subjective rating scale on the dysfunctional beliefs commonly reported by the patients, such as the Dysfunctional Beliefs and Attitudes Scale [42], can be used to help with the evaluation of the patient's sleep cognitions.

Light therapy

- Bright light has been identified as the most potent stimulus to shift the phase of human circadian rhythms [43, Class I]. There is a relationship between the timing of light exposure and the size and direction of the phase shift induced. Light exposure in late subjective night and early subjective day produces a phase advance in circadian rhythms; in contrast, light exposure in late subjective day and early subjective night induces a phase delay [44, Class I]. Therefore, for patients with a delayed endogenous circadian rhythms, as indicated by complaints of difficulty falling asleep in the evening and difficulty getting up in the morning, bright light administration on awakening in the morning can advance the patients' circadian rhythms to the desired time [45••, Class I]. Light therapy also has been used to treat patients who report early evening sleepiness and early morning awakening. Because endogenous circadian oscillators are most likely to be advanced in time in these individuals, bright light exposure in the evening should be applied to delay their circadian rhythms [45••,46, Class I]. The treatment procedure is as follows:
  - Patients are asked to set a baseline sleep-wake schedule close to an estimated endogenous sleep phase based on history or sleep log data.
  - As the treatment proceeds, the wake-up time is progressively shifted to an earlier time for patients with a delayed circadian phase; in contrast, the retiring time is gradually shifted to a later time for patients with an advanced sleep phase. Most patients can shift their circadian phase by a half hour to an hour each week with little difficulty with the help of light exposure.

  - For patients with delayed sleep-wake pattern, bright light exposure is administered in the morning as close to the patients' scheduled arising time as possible. However, for patients with advanced sleep-wake pattern, bright light should be administered in the early evening, a couple of hours before their scheduled bedtime.
  - The source of bright light can be an artificial light therapy device or natural outdoor sunlight. Illuminance of approximately 2500 lux or more at eye level usually is required to obtain successful results. A 1- to 2-hour period of treatment each day usually achieves adequate effect. Scheduling constraints may necessitate a shorter exposure duration that will result in slower treatment response.
- This treatment is indicated in patients with symptoms suggestive of a shift of endogenous circadian rhythms.
- Some individuals get so activated by the bright light at night that they have trouble falling asleep. In these individuals we either shorten the exposure duration or move the exposure envelope to an earlier time.
- Patients with eye pathology should consult with an ophthalmologist before receiving light therapy.

Chronotherapy

- It has been reported that the sleep-wake cycle assumes a period length of slightly greater than 24 hours when subjects were kept in special facilities that kept them from knowing the time of day [47, Class I]. Therefore, there is a tendency for humans to have a free-running rhythm of greater than the sidereal day, which favors the delay of endogenous circadian phase over an advance. Based on this finding, chronotherapy was invented as a treatment for individuals with delayed sleep phase by gradually shifting the sleep-wake schedule later in time until it reaches the desired schedule [48, Class II]. The standard procedure for chronotherapy is as follows:
  - Set the baseline retiring time and arising time according to the estimate circadian phase based on sleep log data.
  - Delay retiring time and arising time by 2 or 3 hours each day until it matches the desired sleep schedule.
  - After the desired sleep schedule is achieved, the patients should be instructed to avoid sleeping late to prevent relapse.
- Patients with symptoms suggestive of a delay of endogenous circadian rhythms are candidates for chronotherapy.
- Patients usually need to take several days off from work to follow the odd sleep-wake schedule. They also must ensure that they are not disturbed while they are sleeping.
- Because patients with delayed sleep phase often relapse after successful treatment, morning exposure to bright light can be institute to assist the maintenance of a stable circadian phase.

Pharmacologic treatment

- Insomnia is considered a symptom of a medical or psychiatric condition that may remit with treatment of the underlying condition, or is generated by behavioral factors that would be better addressed with nonpharmacologic treatments. Therefore, hypnotic therapy may not be a first-line treatment for insomnia. When insomnia cannot be adequately treated by directly addressing the underlying factors, then sedative-hypnotic drugs can be used [49,50, Class II].

- Generally, the medication used to improve sleep is recommended for short-term use (approximately 2 to 4 weeks) [50, Class II], although recent studies have reported improved safety and effectiveness of longer-term hypnotic use [49,51••, Class II].
- Several factors determine how medication should be applied, such as the severity of insomnia, the daytime symptoms, and the pattern of insomnia [52, Class II]. For example, a patient with sleep-onset problems only may benefit from a very short-acting agent before retiring. However, longer-acting agents are more suitable for patients who have difficulty maintaining sleep. Unless there is a need for daytime treatment of anxiety, a short- or intermediate-acting agent usually is preferred.

Selective benzodiazepine receptor agonists

- Selective benzodiazepine (BZD) receptor agonists have a rapid onset of action and a short duration. Additionally, because of their selective action on a subclass of BZD receptor, they do not affect cognition, memory, and motor functions to the extent that traditional BZDs do. In addition, rebound insomnia, dependence, withdrawal symptoms, and loss of efficiency were reported to be less likely to occur with time with these agents [53••, Class I].
- Because of the selective effects and better safety profile, selective BZD receptor agonists gradually became the most commonly prescribed agents for the treatment of insomnia. The three most popular selective BZD receptor agonists are zolpidem, zaleplon, and zopiclone (not available in the United States) [49,50,52, Class II]. Zolpidem has a half-life of approximately 1.5 to 3 hours. It has been shown to be effective in the treatment of sleep onset insomnia. Polysomnographic studies showed that zolpidem administration reduced sleep latency, and increased total sleep time, slow wave sleep, and latency to REM sleep [54, Class I]. Regarding the safety of zolpidem, tolerance and rebound insomnia were less reported in patients who have used zolpidem for 6 months [55, Class I]. In addition, one recent study showed that zolpidem could be taken as needed instead of used nightly [56, Class II]. Zaleplon has shorter latency to onset of action (1-hour peak concentration) and shorter half life (1-hour half-life) than zolpidem [57••, Class I]. It is recommended for the treatment of patients with sleep-onset difficulties, and in patients with repeated awakening during the night. Based on the few reports available, no tolerance developed after zaleplon use for 5 weeks [58, Class I]. A polysomnographic study showed that it reduced sleep-onset latency, reduced the number of awakenings, and decreased the amount of REM sleep. Also, no significant rebound insomnia, tolerance and withdrawal symptoms were reported after sudden discontinuation of zaleplon use for up to 12 months [57••, Class I]. Zopiclone is an intermediate-acting agent with a half-life of 5 hours. Compared with traditional BZD hypnotics, zopiclone has equivalent or better effects on chronic insomnia [59••, Class II]. It has been shown to reduce sleep-onset latency, decrease number of awakenings, and increase total sleep time and the slow waves during deep sleep. No tolerance was reported developed after 17 weeks of zopiclone use. One minor problem of this medication is a bitter taste when its concentration in saliva is greater than 50 mg/L.

Zolpidem, zaleplon, and zopiclone

Standard dosage	Zolpidem, 10 mg, given before bed is the recommended dosage. Dosage may increase to 20 mg. Zaleplon, 10 mg, before bed is the recommended starting dosage, but may be increased to 15 to 20 mg. Zopiclone, 7.5 mg, taken 30 to 60 minutes before sleep is the recommended starting dosage, but could be increased to 15 mg.
Contraindications	Severe hepatic impairment, obstructive sleep apnea, acute pulmonary impairment, or respiratory depression. Not recommended for pregnant women and mothers who are breastfeeding.
Main drug interactions	CYP3A4 enzyme activators (*eg*, rifampin, phenytoin, carbamazepine, and phenobarbital), CYP3A4 enzyme inhibitors (*eg*, ketoconazole, nefazodone, fluvoxamine, and cimetidine). Concentration of zopiclone may be increased when combined with carbamazepine, metoclopramide, and erythromycin.
Main side effects	Zolpidem may cause dizziness, headache, sleepiness, and stomach discomfort. Zaleplon may cause headache, dizziness, and sleepiness. Zopiclone may cause daytime sedation, cognitive impairments, respiratory depression, and muscle weakness. The common withdrawal symptoms include insomnia and anxiety.
Cost/cost effectiveness	These drugs are more expensive compared with most BZD hypnotics, but generally are better in terms of safety.

Benzodiazepines

- Based on different reaction times and half-life, BZDs often are divided into three major types: 1) rapid-onset and short-acting BZDs, such as triazolam; 2) delayed-onset, intermediate-acting BZDs, such as temazepam and estazolam; and 3) rapid-onset and long-acting BZDs such as flurazepam and quazepam [60, Class II]. The choice of the type of BZD prescribed depends on the pattern of the sleep disturbance to be treated. Generally, short-acting BZDs are more suitable for patients with sleep-onset difficulty only. However, intermediate-acting agents are more suitable for patients who report difficulty maintaining sleep. Long-acting BZDs are reserved for patients with sleep problems and daytime anxiety.

Triazolam, temazepam, estazolam, flurazepam, and quazepam

Standard dosage	Triazolam, 0.125 mg to 0.250 mg, is given at bed. Temazepam, 7.5 to 30 mg, is given at bed. Estazolam, 1 to 2 mg, is given at bed. Flurazepam, 15 to 30 mg, is given at bed. Quazepam, 7.5 to 15 mg, is given at bed.
Contraindications	These medications should be prescribed with great caution for the elderly, patients with renal or hepatic impairment, patients with obstructive sleep apnea, and patients with chronic obstructive pulmonary disease. Also, patients with substance abuse, cognitive disorders, porphyria, central nervous system depression, and myasthenia gravis should avoid using BZDs.
Main drug interactions	Antacids slow BZD absorption. MAOIs, cimetidine, and oral contraceptives slow metabolism of BZD. Phenytoin and barbiturates reduce BZD half-life. In addition, BZDs increase digoxin levels in the blood and therefore may lead to digoxin toxicity.
Main side effects	Daytime sedation, anterograde amnesia, respiratory depression, ataxia, confusion, and muscle weakness.
Special points	Discontinuation of short-term BZD treatment can cause rebound insomnia. Withdrawal from long-term BZD treatment can cause complex withdrawal symptoms that last for 1 to 2 weeks [50,60, Class II]. Common withdrawal symptoms include anxiety, nervousness, diaphoresis, restlessness, irritability, fatigue, light-headedness, tremor, insomnia, and weakness. Therefore, BZDs should be discontinued by tapering it slowly (approximately 25% per week).
Cost/cost effectiveness	The cost varies for different medications. They usually are less expensive than selective BZD receptor agonists.

Sedative antidepressants

	Some antidepressants with sedative-hypnotic properties also have been used for the treatment of insomnia, especially in patients with depression and insomnia symptoms [61, Class II]. The most commonly used sedative antidepressant is trazodone. Trazodone has been shown to improve sleep in insomniacs and increase slow-wave sleep [62, Class II]. Some tricyclic antidepressants (TCAs) also have a strong hypnotic effect. However, because the actions of TCAs are relatively nonselective, they tend to lead to more side effects. In addition, nefazodone (a selective serotonergic antidepressant) and mirtazapine (a noradrenergic and specific serotonergic antidepressant) also have been shown to reduce sleep disruptions in depressed patients with significant insomnia [61, Class II].
Standard dosage	There is no standard dosage available for the treatment of insomnia. In comparison to their use in the treatment of depression, only low dosages are needed to treat insomnia.
Contraindications	Great cautions should be taken when using these sedative antidepressants in the elderly patients and in patients with cardiovascular diseases, liver disease, and difficulties in sexual functioning.
Main drug interactions	TCAs may block the actions of b-adrenergic receptor antagonists (propranolol and clonidine), cause severe cardiovascular effects when taken with sympathomimetic drugs, and increase agitation when administered with methyldopa. When combined with antipsychotics, TCAs plasma concentrations may increase. Trazodone has been shown to potentiate the central nervous system depressant effects of alcohol and other centrally acting drugs, and to increases the levels of digoxin and phenytoin. In addition, the use of trazodone, mirtazapine, and nefazodone in combination with monoamine oxidase inhibitors should be avoided. Interactions of nefazodone with triazolam and alprazolam also have been reported.
Main side effects	Side effects of TCAs include: 1) anticholinergic effects such as dry mouth, constipation, difficulties urinating, blurred vision, torsades de pointes, and decrease in cognitive abilities; 2) antihistaminergic effects such as severe drowsiness and increase in appetite; and 3) anti-adrenergic side effects such as postural hypotension, difficulties in ejaculation, and dizziness. The common side effects of trazodone include erectile dysfunction and rarely priapism. Atrial and ventricular arrhythmia and induced QT prolongation also have been reported. The common side effects of mirtazapine are dizziness, sedation, dry mouth, increased appetite, and weight gain. Life-threatening side effects caused by liver failure have been reported after using nefazodone.
Cost/cost effectiveness	TCAs generally are very inexpensive. The atypical antidepressants are more expensive, but have a better side-effect profile and safety properties.

Sedating antihistamines

	Sedating antihistamines (over-the-counter sleep aids) sometimes are used as sleep inducers. These agents can reduce sleep latency, and can be beneficial for patients whose sleep problems are associated with allergic reactions. Because antihistamines have not been shown to have abuse potential, they sometimes are prescribed to help sleep in patients who have abused hypnotics.
Standard dosage	Generally ranges from 50 to 100 mg for diphenhydramine.
Contraindications	Severe hepatic disease.
Main drug interactions	Diphenhydramine may have an additive depressant effect when used in combination with alcohol or with other central nervous system depressants.
Main side effects	Gastrointestinal distress, dry mouth, blurred vision, constipation, and urinary retention; may cause confusion or memory problems in the elderly. These medications should not be taken by patients with closed angle glaucoma.
Cost/cost effectiveness	Very inexpensive.

Melatonin

	Melatonin is a neurohormone secreted by the pineal gland during the dark phase of day-night cycle. It has been shown to have hypnotic effects and [63••, Class I] phase-shifting effects on endogenous circadian rhythm [64••, Class I]. Because there are only mild side effects reported, it has become popular with the general

public. However, studies on the hypnotic effect of melatonin have generated inconsistent results. It has been shown that the hypnotic activity is effective only when given in the absence of endogenous melatonin [63••, Class I].

In terms of its phase-shift effect on the endogenous circadian rhythm, melatonin administration in the early evening has been shown to advance the onset time of endogenous melatonin secretion; conversely, melatonin administration in the early morning was shown to delay endogenous melatonin secretion [64••, Class I].

Standard dosage There is no standard dosage for melatonin administration. The melatonin pills usually are 0.3 to 5 mg.

Contraindications Melatonin should not be given to prepubertal or pregnant women.

Main drug interaction Luteinizing hormone.

Main side effects Drowsiness. Patients with auto-immune disease should consult there physician before taking melatonin.

Cost/cost effectiveness Very inexpensive.

Pediatric considerations

- Insomnia in the children is phenomenologically different from insomnia in the adults. As in the treatment of adult insomnia, a thorough evaluation should be done first to identify the associated factors. Psychologic and social stressors may induce short-term sleep disturbances. The attitude of the parents and their methods of regulating the child's sleep often are crucial. Brief sleep disturbance may be handled with support. More chronic sleep problems may require behavioral or psychosocial intervention [65••, Class I].
- If medication is needed, the lowest dose that could achieve satisfactory results should be chosen. In addition, the medication should be periodically tapered to check if continuation of treatment is needed. Because of the possible side effects, BZDs should be prescribed with great caution. Chloral hydrate (50 to 75 mg/kg up to maximum of 1 to 2 g), promethazine (25 to 100 mg) or clonidine (0.25 to 1 mg), given in a single dose at bedtime, may be beneficial for sleepless children. Melatonin (0.5 to 10 mg) also has been reported to be helpful in the treatment of sleep disturbances in children with circadian rhythm sleep disorders, pervasive developmental delay, neurologic impairments, or congenital syndromes [66••, Class I].

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