Insomnia

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KEYWORDS
- Chronotype
- Cognitive behavioral therapy for insomnia (CBT-I)
- Hyperarousal
- Primary insomnia
- Restless legs syndrome
- Short sleeper
- Sleep restriction therapy
- Stimulus control

KEY POINTS
- To the general public and in primary care, “insomnia” refers to the symptom of difficulty sleeping; to sleep specialists and researchers, it refers to a subset in which common specific causes have been ruled out.
- Acute insomnia should be treated by addressing the underlying cause (if possible) and with safe, effective sleep medication, in part to prevent the development of chronic insomnia.
- Chronic insomnia is best approached via history and/or questionnaires to identify common specific causes that have specific treatments.
- Restless legs syndrome, sleep apnea, and circadian rhythm disorders such as delayed sleep phase syndrome (night owl) are common causes of insomnia presenting in primary care.
- Cognitive behavioral therapy for insomnia is considered first-line therapy for chronic insomnia that is otherwise unexplained (primary insomnia) or is associated with chronic psychological or medical conditions.

EVALUATION AND TREATMENT OF INSOMNIA

Definitions and Presentation

Insomnia as experienced by people and reported to physicians is, simply, difficulty sleeping. Insomnia is typically described in terms of dissatisfaction with, and distress from, the quality or quantity of sleep obtained, despite attempts to obtain sleep. Insomnia is common, affecting most people at some point in a year and 10% to 20% of people chronically, and is commonly associated with a wide range of psychosocial, psychiatric, medical, and underlying sleep disorders. Both short-term and long-term insomnia can impair daytime functioning, and chronic insomnia is associated bidirectionally with adverse health and social outcomes. As with other symptoms such as dizziness or pain, treatment of the symptom without consideration of the underlying condition can be ineffective and misdirected.
This article focuses on evaluation and treatment of the symptom insomnia as self-reported by patients in primary care settings. History is the key to uncovering underlying patterns and associated symptoms to determine factors contributing to the insomnia (Table 1). In sleep medicine practices, this typically includes a sleep diary and validated questionnaires, but with a framework in mind one can obtain a useful direct history from the patient (Fig. 1). Nocturnal polysomnography (PSG) does not diagnose insomnia, and it does not distinguish between satisfied sleepers and those with chronic unexplained insomnia. However, when sleep is described as fragmented or

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<td>Conditioned insomnia</td>
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1) Is frustration with insomnia (rather than impaired daytime functioning) the primary concern?

2) If yes: The person seems to be attempting to get more sleep than needed and may be a “short sleeper”.
   - Advise Sleep Restriction Therapy (see Figure 2)

3) If no, is the primary concern:
   a) Difficulty falling asleep at desired bedtime?
      Pursue history for:
      - Restless legs syndrome (urge to move limbs, at night, worse with rest)
      - Delayed sleep phase syndrome (chronic “night owl”)
      - Anxiety, stress
      - Conditioned insomnia (stays in bed awake trying to sleep, may watch clock) – advise Stimulus Control and Sleep Restriction Therapy (see Figure 2)
      - Use of stimulating medications or substances in evening
   b) Waking frequently but briefly, or having restless sleep?
      Pursue history for:
      - Sleep apnea (gasing or choking at night, witnessed apneas)
      - PLMs (kicking or thrashing during sleep)
      - Use of stimulating medications or substances, especially in PM
      - Menopause (particularly with hot flashes and night sweats)
      - Medical symptoms including pain, dyspnea, GERD
   c) Waking during the night, then difficulty getting back to sleep?
      Pursue history for:
      - Alcohol withdrawal (alcohol use before bed, even without dependence)
      - Anxiety, stress, post-traumatic stress disorder
      - Conditioned insomnia (stays in bed awake trying to sleep, may watch clock) – advise Stimulus Control and Sleep Restriction Therapy (see Figure 2)
   d) Waking up too early, then can’t get back to sleep?
      Pursue history for:
      - Depression
      - Advanced sleep phase syndrome (longstanding “early bird”)
      - Conditioned insomnia (stays in bed awake trying to sleep, may watch clock) – advise Stimulus Control and Sleep Restriction Therapy (see Figure 2)
   e) Chronic insomnia with 1 or more of above patterns, otherwise unexplained:
      - Primary insomnia

Fig. 1. An evaluation approach for chronic insomnia.
shallow, PSG can be helpful in determining whether sleep apnea or periodic limb movements (PLMS, also called nocturnal myoclonus) might be causing frequent brief awakenings.

Insomnia differs from purposeful sleep deprivation in that the person with insomnia not only wants to sleep but is allowing opportunities for sleep to occur. In fact, people suffering from insomnia may try to force sleep, which backfires in contributing further to arousal and alertness.

“Insomnia” has specific definitions in sleep medicine research and practice, in which certain common conditions presenting as the symptom insomnia have been ruled out and certain diagnostic criteria have been met. The distinction between lay use and specialty use of the term is crucial to keep in mind when interpreting medical literature, because interventional studies on “insomnia” typically seek to enroll subjects who have otherwise-unexplained insomnia (“primary insomnia”), sometimes also including people with insomnia related to depression or anxiety.

Research criteria for “insomnia disorder” require not only some pattern of difficulty sleeping but also allowance of adequate opportunity for sleep and any of several daytime symptoms stemming from the sleep problem. Research criteria for “primary insomnia” (chronic otherwise-unexplained insomnia) add that the person is not taking psychoactive substances that would affect sleep, nor that the insomnia can be ascribed primarily to a medical or psychiatric condition or to an underlying sleep disorder such as sleep apnea. On the other hand, the American Psychiatric Association has recategorized “primary insomnia” and other types of insomnia from the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV all into “insomnia disorder” in DSM-5, aiming to focus on the need to address insomnia regardless of whether it is idiopathic or related to a psychiatric or medical disorder.

Conditions for which people experiencing insomnia would be excluded on first screening from a research study on insomnia include several conditions prevalent in the general population and particularly in primary care practices, such as restless legs syndrome (RLS), circadian rhythm disorders, and suspected obstructive sleep apnea (OSA), which are described further later.

**Patterns of Insomnia**

Insomnia is commonly divided into several different categories, by duration and by pattern during the night.

Duration is “acute” (or “transient”) versus “chronic” (or “persistent”). The research definitions of these timeframes do not assist in the primary care evaluation and management of patients seeking help for insomnia. In acute insomnia, the cause may be readily apparent (for example, a stressful situation, new medication, or uncomfortable new medical symptom) and/or the person may be able to anticipate it in advance (for example, travel across multiple time zones). Acute insomnia should be treated with sedative-hypnotic medication and/or the inciting factor promptly addressed, where possible, to reduce daytime impairment from sleepiness, nighttime suffering, and the likelihood of development of chronic insomnia.

Chronic insomnia can develop when acute insomnia occurs and becomes perpetuated, or it may be longstanding without a clear event or time of onset. It may be multifactorial, becoming (or including a component of) psychophysiological (also called “conditioned” or “learned”) insomnia. Chronic insomnia is associated with dysfunctional beliefs about sleep, including hopelessness, helplessness, and fear about the consequences of sleep loss, or, essentially, performance anxiety regarding one’s sleep.
The timing of the difficulty with sleeping during the allotted sleep time is also an important pattern to elucidate:

- Difficulty falling asleep (described medically as “difficulty initiating sleep” and called sleep-onset insomnia)
- Difficulty staying asleep (described medically as “difficulty maintaining sleep” and called sleep-maintenance insomnia)
- Early morning awakening (called terminal insomnia)

Difficulty maintaining sleep can be one or more long awakenings during the night, or poor sleep quality consisting of frequent but brief awakenings or an awareness during the night of being partially awake. This latter pattern may be due to sleep-state misperception (in which states demonstrated on PSG to be “sleep” are experienced as “wake”) or may be due to frequent partial awakenings due to an underlying sleep disorder (most commonly OSA, central sleep apnea [CSA], or PLMS).

The symptom of awakening unrefreshed in the morning is called “unrefreshing sleep” and had been considered in the past to qualify as “insomnia,” but is now recognized to warrant specific evaluation and treatment, typically including PSG.

**Physiology of Sleep and Pathophysiology of Insomnia**

Sleep and wake are different but not mutually exclusive states of the brain, and in fact, “sleep” is itself 2 distinct physiologic states, rapid eye movement (REM) and non-REM (NREM) sleep, during each of which the brain and body behave in specific ways. NREM comprises stages 1 through 4; stages 3 and 4 are deeper and known as “slow-wave” sleep. Sleep disorders in which a person is partially roused from deep sleep or REM sleep to a lighter stage of sleep, or to brief awakening, can present as disrupted sleep (insomnia) or unrefreshing sleep.

Sleep and wake are under circadian and homeostatic control, with contributions from volitional behavior. The circadian biologic rhythm of wake and sleep is governed by the internal clock in the suprachiasmatic nucleus, influenced by genetics as well as by environmental cues (light exposure and daily routines). The homeostatic drive to sleep increases as the time since last sleep increases and declines when sleep of refreshing quality is obtained.

The normal human circadian cycle is closer to 25 hours than 24 hours. There are normal developmental changes to circadian sleep-wake patterns in childhood and adolescence before one’s “chronotype,” the typical daily pattern of alertness and sleepiness for that person, becomes apparent by around age 25. The chronotype is determined by several genes with several polymorphisms, giving an essentially normal distribution of chrono-phenotypes in the adult population, skewed to the right, toward a preference for later sleep times. In people with sleep phase “delay” (those who prefer later sleep and wake times than most of the population), the melatonin peak is delayed. Circadian rhythm disorders manifesting as insomnia due to a mismatch between an individual’s chronotype and expectations of normal sleep-wake times are discussed later.

Humans have a unique and notable ability to stay awake despite the homeostatic drive for sleep and the circadian cycle of sleepiness and wakefulness. A person can purposefully avoid behaviors conducive to sleep and instead pursue those conducive to wakefulness, including upright body position, bright light exposure, engagement in a mentally stimulating activity, and consumption of caffeine or other wake-promoting substances. “Insomnia” requires some attempt to sleep (lying down in a darkened place) but in many cases insomnia can be caused or perpetuated by the persistent influence of wake-conducive factors in the hours before sleep. Ironically, although
humans can force the wake state, attempting to force sleep can backfire and cause arousal. Sleep has to be “allowed” to occur, which can be very difficult for people who are trying desperately to enter that state. People vary in their susceptibility to hyperarousal and to insomnia. Twin studies demonstrate a genetic component to susceptibility, particularly for sleep maintenance insomnia.5 “Primary” insomnia, the sleep medicine diagnosis for otherwise-unexplained chronic insomnia, is not just a sleep problem but is characterized by 24-hour hyperarousal.6

An important early step in the approach to insomnia is clarifying through history whether the problem is a mismatch of the timing of sleep attempted versus achievable for that person, or whether internal and/or external factors cause hyperarousal to defeat attempts to sleep at a time that otherwise should work for the person to sleep.

Epidemiology of Specific Sleep Disorders Presenting as Insomnia

Despite the common process of screening potential research subjects to weed out those with insomnia as a symptom but not a research diagnosis, the distribution of different underlying causes for the symptom of insomnia has not been well described. One study in New Zealand7 using a validated questionnaire found 41% of family practice patients reported insomnia, with multiple overlapping contributing factors: depression in 50%, anxiety in 48%, physical health problems in 43%, primary insomnia in 12%, symptoms of OSA in 9%, and delayed sleep phase “disorder” in 2% (with determination of that disorder requiring substance use and depression in addition to “night owl” phenotype). This study did not comment on the prevalence of delayed sleep phase “syndrome” (the term for someone who is an extreme “night owl”) or RLS.

RLS

RLS is common, with a prevalence of roughly 10% overall (5% to 14% in multiple studies using international research criteria), but the severity and frequency vary.6 It is more common in older patients, occurring in up to 19% of patients greater than the age of 80.9 People with RLS report 2- to 3-fold higher rates of difficulty falling asleep and difficulty staying asleep than the general population, with 28% to 69% having difficulty initiating sleep and 24% to 51% having difficulty maintaining sleep.10

Two to 3% of people qualify as “RLS sufferers,” experiencing RLS of moderate severity or worse at least twice a week.10,11 Among RLS sufferers in the general population, 75.5% report difficulty with sleep: 48% endorsing an inability to fall asleep, 39% endorsing an inability to stay asleep, 61% endorsing disturbed or interrupted sleep, and 40% endorsing insufficient sleep.11 In primary care practices, the rate of RLS is higher, with 11% to 24% meeting diagnostic criteria and 3.4% to 9% suffering at moderate severity or worse twice a week or more.10 Among RLS sufferers followed in primary care practices, 88% reported sleep difficulty, with 69% reporting taking 30 minutes or more to fall asleep and 60% reporting waking 3 or more times per night.12

PLMS can also cause difficulty maintaining sleep. The prevalence seems to be roughly similar to RLS with significant but not universal overlap in the affected populations. However, PLMS can also be associated with other conditions such as OSA, in which identification and treatment of the specific triggering condition are advised.

RLS can be primary (familial or idiopathic) or secondary to another medical condition. Some studies, but not all, find higher prevalence in women and with increasing age. RLS occurs commonly in pregnancy, is also associated with low iron stores (ferritin <50 μg/L), chronic renal failure, and chronic neurologic conditions, and has been increasingly associated with many chronic medical conditions of varied types. It can be triggered by multiple medications including tramadol, neuroleptics, and most antidepressants,13 with the exception of bupropion.14
Circadian rhythm disorders

The hallmark of circadian rhythm disorders is that the person is sleepy at some time of the 24-hour day and overly awake at other times, in a (typically) regular pattern than does not match the social norm. The distribution of preferred sleep times (chronotypes) in the adult population is essentially a normal distribution skewed toward later sleep-wake times. The most common time to be asleep on non-work days, preferred by 15% of people in a large European study, centers around 4 AM (eg, falling asleep at midnight and waking at 8 AM).15 However, 35% report sleep centered around an earlier time and 50% report sleep centered around a later time. The later tail extends far, with 8% of people preferring to fall asleep at 3 AM. On work days, the later skewing is not as pronounced, but people who normally go to sleep late and wake up late can have significant sleep loss on work days15 or school days, and/or be out-of-sync with “normal” sleepers, a phenomenon that has been called “social jet lag.”16

Delayed sleep phase syndrome (DSPS) describes a chronotype, extreme “night owls”, with late bedtime and late wake time compared with the “normal.” DSPS was initially reported in 7% of patients referred for specialty evaluation of unexplained insomnia; those with DSPS were younger on average than the rest of the group.17 Delayed sleep phase is associated with attention-deficit/hyperactivity disorder (ADHD)18 and with higher rates of smoking, alcohol use, caffeine use, and depression, attributed at least in part to the mismatch between social expectations and achievable wake times.16 Having one’s preferred sleep time not occur until hours later than the social norm is a chronic (lifelong) pattern that can have potentially long-term social consequences.

Other chronic circadian rhythm disorders, less common than DSPS, include advanced phase sleep syndrome (ASPS) and non-24-hour circadian rhythm disorder (or free-running disorder).

People with ASPS have a longstanding pattern of going to sleep earlier than the social norm, but also waking early; these are extreme “early birds,” who may enjoy their morning time as productive or may complain of terminal insomnia. Early morning awakening, plus the social isolation that can result from a routine early bedtime, can also be seen in depression. ASPS can occur in an autosomal-dominant inheritance pattern.

Non-24-hour circadian rhythm disorder is seen most commonly in people who lack light perception, thus whose circadian rhythm is not synchronized with the light-dark cycle of daylight.

Shift work sleep disorder results from working during what would normally be one’s sleep time and being off work (and expected to sleep) during what would normally be one’s wake time. It manifests as insomnia during time off work and/or sleepiness at work. Shift work sleep disorder can be acute, subacute, or chronic depending on the person’s schedule at work and on days off.

A short-term mismatch between one’s circadian rhythm and local time, causing insomnia and/or excessive daytime sleepiness, commonly occurs in the following 3 situations:

- Jet lag from travel across multiple time zones
- Adjustment to the clock change when daylight savings time takes effect in springtime (where applicable), heralded by a 23-hour day
- “Sunday night insomnia,” in which staying up later on non-work or non-school days than on work or school days, typically meaning Friday and Saturday nights, allows one’s circadian phase to drift later in relation to clock time, leaving the person not feeling sleepy at the earlier, usual weekday bedtime on Sunday night.
Sleep apnea

OSA can present as insomnia from sleep fragmentation due to frequent brief awakenings. It can also coexist with insomnia of other types, including psychophysiological insomnia; this complicates treatment. Coexisting insomnia with sleep apnea has been well-described in PSG referral populations, where up to 67% of patients referred for sleep apnea evaluation are also found via sleep questionnaires to have insomnia.\(^1\) The distribution of difficulty initiating sleep and difficulty maintaining sleep in this population is similar to that seen in people with insomnia but no sleep apnea.\(^1\)

OSA is common in the general population, and particularly so among primary care patients and those with various chronic conditions including, particularly, hypertension and obesity. OSA is part of the metabolic syndrome. The likelihood that a person has OSA increases with body mass index and with age,\(^2\) but young people and slender people can have OSA. Using the Berlin Questionnaire, one study at 26 primary care sites in the United States found that 36% of patients had a high pretest probability (86% likelihood) of OSA, with the patient endorsing excessive daytime sleepiness the best marker, and reporting either body mass index in the obese range or known hypertension the second best marker for risk.\(^3\) Tonsillar hypertrophy and certain craniofacial features also increase the risk for OSA.

CSA can also present as insomnia with sleep fragmentation, but may be less commonly suspected in the primary care setting. The prevalence of CSA has not been well-described in the general population. It increases with age, after a stroke or with heart failure, with Cheyne-Stokes respiration, and with opioid use. CSA and OSA can coexist in the same patient, and CSA can emerge as a problem after initiation of continuous positive airway pressure (CPAP) therapy for OSA.

Evaluation

History

History is crucial in the evaluation of insomnia. Validated questionnaires exist to probe different history relevant to insomnia including its severity, RLS, OSA risk, and chronotype; these are used in sleep medicine research and practice, but are unwieldy for most primary care practices to keep on hand. This section discusses aspects of history focused on the features of the patient’s insomnia.

Acuity of insomnia should be apparent early on in discussion. For acute insomnia, ask about new stressors, new medications, and new symptoms. If no cause is apparent, consider blood loss (for RLS), nasal congestion (as it causes difficulty breathing), and any new medication or over-the-counter medication or supplement.

For chronic insomnia, probe the pattern (see Fig. 1). If the patient is more focused on his or her frustration with having insomnia, rather than feeling tired or having difficulty functioning during the day, consider sleep restriction therapy (discussed in Treatment below and in Box 1) as a major focus of therapy. Probe further for a description of the pattern—is it difficulty initiating sleep or maintaining sleep? If difficulty initiating sleep, ask particularly about RLS, DSPS, conditioned insomnia, use of stimulating medications or substances, and anxiety or stress. If the patient describes difficulty maintaining sleep, probe whether it is fragmented sleep, long periods of wakefulness during the night, or early morning awakening and pursue further as appropriate (see Fig. 1).

Look for hallmark features, described below.

The diagnostic features of RLS are as follows:

- Compelling urge to move the legs, typically associated with an uncomfortable sensation
### Box 1
**Key components of CBT-I**

Advice for physicians and patients are described here for the 2 most effective elements of CBT-I, Sleep Restriction Therapy and Stimulus Control.

When advising either of these approaches, explicitly acknowledge to the patient that some of these measures will sound counterintuitive and that the insomnia experienced will probably seem worse for the first few days, then should improve.

1. **Sleep restriction therapy:** To improve the “sleep efficiency” of time in bed
   - Have the patient estimate actual time spent asleep each night (average times if they span a range)
   - Have the patient choose a time to get up each morning, without fail
   - Have the patient purposefully delay bedtime to only allow the time spent in bed to match his/her estimated time spent asleep plus a 20- to 30-minute cushion (but not less than 5 hours, in case of sleep-state misperception)
   - Counsel the patient to get up at the planned morning time, no matter how tired he/she is
   - Counsel the patient to expect to continue to have insomnia and to feel more tired for the first several days, until increased drive for sleep improves the “efficiency” of sleep during the allowed time in bed
   - After sleep efficiency improves, if daytime tiredness suggests more sleep is needed, the time in bed can be gradually lengthened until efficiency begins to decrease

2. **Stimulus control:** To overcome behavioral conditioning in which the person expects to be awake when attempting sleep.
   - Only go to bed when sleepy.
   - Use the bed only for sleep and sex.
   - Do not watch the clock.
   - Do not lie awake in bed for more than 20 minutes (estimated). If awake in bed, get up, go to a different room, do some quiet nonstimulating activity in low light, then return to bed when sleepy again. Repeat as many times as necessary.
   - Keep a regular daily wake time.
   - Avoid napping.

3. **Cognitive therapy to address dysfunctional, maladaptive beliefs about sleep**

4. **Relaxation exercises**

5. **Sleep education and hygiene,** including advice to avoid caffeine in the afternoon and evening and to get regular exercise

- Occurs in the evening or at night
- Worse with inactivity
- Relieved by movement

The key features of a circadian rhythm disorder are that the person has difficulty being asleep at one end of the day (when sleep is desired) and also has difficulty being awake at another end of the day (when wakefulness is desired). Ask about bedtime and wake time in 3 situations: those that are preferred but do not seem achievable, those that are achieved when aiming for the preferred times, and those achieved when the person can set his or her own schedule (for example, when on vacation). Ask about the circumstances under which a different sleep/wake pattern is required than is readily achievable (for example, work, sleep, child care duties within the family).
For OSA, ask about the following, each associated with increased risk: breathing difficulties during sleep (history of nocturnal gasping or choking, witnessed apneas, and/or disruptive snoring), excessive daytime sleepiness, hypertension, nasal congestion, smoking, and male gender. Nocturia has similar sensitivity as snoring (85% vs 82%) but neither is specific (22% and 43%, respectively).

If sleep is described as shallow or fragmented, but OSA seems low likelihood, ask whether the person is known to move or kick a lot during the night, and whether the sheets are torn off the bed in the morning, suggesting PLMS. A suspicion for OSA or PLMS suggests a polysomnogram may be warranted.

**Physical Examination, Laboratory Work, and Sleep Studies**

Physical examination is of limited utility in evaluating insomnia. Certain features may suggest OSA: obesity, large neck circumference (>40 cm), crowded oropharynx or craniofacial anatomy such as retrognathia.

Laboratory work is of limited utility in evaluating insomnia, except in the evaluation for causes or contributing factors to RLS (particularly ferritin and possibly magnesium level; in initial evaluation also consider renal function and B12 level).

Sleep testing is of limited utility in evaluating insomnia, with the following exceptions:

1. Nocturnal PSG should be obtained when sleep apnea (obstructive or central) or PLMS is suspected and can be useful in evaluating insomnia in which sleep is achieved but is described as restless or unsatisfying. PSG can also be useful in identifying sleep-state misperception but is not routinely performed solely for that purpose.

2. Actigraphy documents physical motion (of an arm) as a proxy for sleep and wakefulness. It is most commonly done when history suggests a circadian rhythm disorder or significant underreporting of sleep time (as in sleep-state misperception), but a proxy suggesting objective sleep time would be useful. For sleep-state misperception, PSG is more specific.

In studies using PSG to quantify sleep, people with chronic insomnia do tend to underestimate the amount of sleep they obtain, whereas people who routinely sleep 6 hours or less but are satisfied with their sleep tend overestimate their sleep duration. When “sleep-state misperception” is severe, the term “paradoxical insomnia” is used.

**Treatment**

Sedating medication and sleep hygiene advice are often assumed to be the 2 approaches to treatment of insomnia. Instead, the first step is to evaluate for an underlying condition, as in identification of a specific condition crucial for identifying further diagnostic measures, specific medication approaches, and/or specific nonpharmacologic approaches. In addition, cognitive behavioral therapy for insomnia (CBT-I) has been shown to have better efficacy than medications at 6 weeks and in the long term for people with chronic insomnia due to primary insomnia (chronic unexplained insomnia), insomnia comorbid with psychiatric and medical disorders, and conditioned insomnia.

Acute insomnia should be treated pharmacologically if the patient desires that approach, with a medication quickly effective for insomnia (benzodiazepine receptor agonist—the “Z” drugs such as zolpidem—or benzodiazepine). The purposes of having a low threshold to treat acute insomnia include prevention of daytime impairment,
reduction of acute suffering, and prevention of perpetuation with development of chronic insomnia.

Chronic insomnia warrants further evaluation as to type, to determine whether a specific approach or treatment may be effective, as above.

In either case, if an underlying cause can be identified, that cause should be addressed and treated.

**Treatment of RLS and periodic limb movements of sleep**

Symptomatic RLS and/or PLMS are treated with dopa agonists (pramipexole, ropinirole, or rotigotine; or, for intermittent use, levodopa) or \( \alpha(2) \beta \) ligands (gabapentin enacarbil, gabapentin, or pregabalin). Clonazepam or opioids are sometimes used in refractory cases. The dopa agonists can cause impulse control behaviors including gambling and impulsive shopping, eating, and sex; patients on these medications should be warned about these possible side effects and should be queried regularly about any such problematic behavior arising during chronic use. The dopa agonists in particular can cause “augmentation,” in which RLS symptoms occur at other times of day and/or in other parts of the body, leading to progressive increase in medication use unless it is recognized, in which case stopping the medication and switching to another class is advised.

A comprehensive approach to the evaluation and management of RLS is outlined in Fig. 2.

**Obstructive and central sleep apnea**

OSA is treated by reducing airway obstruction, either by introducing positive airway pressure to create a “pneumatic splint” or by temporarily or permanently affecting the position of the tongue and other airway structures. The most standard treatment is CPAP (steady) or bilevel positive airway pressure, with that pressure conveyed from the machine to the person’s airway via an interface to the nostrils (or to the nose and mouth). Low-tech single-use nasal valves that give higher resistance to outflow than inflow of air are also available. Supplemental oxygen without positive airway pressure improves oxygenation but does not address, and may even prolong, obstructive events during sleep.

Avoiding the supine position for sleep can reduce apneas and improve sleep quality in more than half of people with OSA, particularly those who are younger and/or not as heavy. Oral appliances worn at night advance the mandible and tongue to reduce obstruction; they are typically not covered by insurance in the United States. Where applicable, weight loss—and even exercise without loss of weight—improves OSA, presumably by reducing adiposity affecting the upper airway. Bariatric surgery for morbid obesity improves OSA in 75% of patients and (after successful weight loss) serves as definitive OSA treatment for some.

In some patients, surgery to remove obstructing tissue, such as large tonsils, can be curative. Multiple different surgeries or ablative approaches can be done to try to improve the anatomy of the airway, from nasal passages to hypopharynx, with reduction of tongue bulk or anterior advancement of the tongue base a common target.

People with OSA should avoid alcohol and other respiratory depressants before bedtime. If sleep medication is considered for a person with OSA, whether to better allow use of CPAP or for coexisting insomnia unrelated to CPAP, a medication that does not suppress respiration should be chosen. Typically, this would be a benzodiazepine receptor agonist such as zolpidem or eszopiclone.

CSA may be treated by treating the underlying cause, with respiratory stimulants if hypoventilation-type, and with CPAP, bilevel positive airway pressure, or adaptive servoventilation.
Circadian rhythm disorders

For the circadian sleep disorders presenting as insomnia, sleep medications are of quite limited benefit. The treatment approach is 4-fold:

a. Expectation management: If expectations can be changed to allow the person to sleep on his or her preferred schedule, this is likely to be the most effective long-term approach. However, responsibilities such as work or family may not allow this tactic.

b. Chronotherapy: The time at which sleep is attempted or allowed is gradually advanced or delayed toward a specific goal. The key is for the person to not

![Diagram of a comprehensive approach to the evaluation and management of RLS. Accelerometry, also called actigraphy, monitors motor activity non-invasively. Its output showing timing of rest and activity may be used as a proxy for sleep/wake cycles or, when placed on a lower extremity, as a measure of limb movements during sleep. DA, dopamine agonist; PRN, pro re nata or as needed. (From Rye DB, Trotti LM. Restless legs syndrome and periodic leg movements of sleep. Neurol Clin 2012;30(4):1137–66.) a FDA-approved for RLS.

Circadian rhythm disorders

For the circadian sleep disorders presenting as insomnia, sleep medications are of quite limited benefit. The treatment approach is 4-fold:

a. Expectation management: If expectations can be changed to allow the person to sleep on his or her preferred schedule, this is likely to be the most effective long-term approach. However, responsibilities such as work or family may not allow this tactic.

b. Chronotherapy: The time at which sleep is attempted or allowed is gradually advanced or delayed toward a specific goal. The key is for the person to not
only achieve \textit{but also maintain} that “goal” sleep-wake schedule—including on days off and vacations—without letting it return to the problematic but more normal-feeling one. Long-term maintenance of a sleep-wake schedule that does not feel natural can be difficult.

c. Phototherapy: The person purposefully gets exposure to bright light at the time of day when he or she is sleepy but would like to be awake. For DSPS, that is light exposure right after awakening; for ASPS, it is light exposure in the evening. Sunlight (and artificial sources of the same range of wavelengths) is effective. Blue light with wavelengths around 450 to 470 nm is the most potent at suppressing melatonin.

d. Melatonin: Ingestion of melatonin 0.3 to 3 mg can be useful in shifting the sleep-wake time, whether due to jet lag or a chronic circadian disorder. A rule of thumb is that it is taken when it is dark out and other people are sleepy but the affected person is not, except that for DSPS it has been shown to be more effective when taken about 6 hours before the desired bed time rather than closer to bed time.\textsuperscript{33} The melatonin serves as a signal that it is dark out and the brain and body should get ready for sleep. It helps keep the circadian clock on a desired schedule rather than reverting to the innate one.

\textbf{Pharmacotherapy for insomnia}

The pharmacotherapy of insomnia (Table 2) relies on 2 general approaches: stimulate a sleep-promoting system (via GABA\textsubscript{A} or melatonin receptors) or suppress one or more wake-promoting systems (particularly via histamine, acetylcholine, and/or serotonin receptors). All sedative-hypnotics have a mild to at-best moderate effect. All should be assumed to increase the risk of falls and to potentially impair functioning the next morning. The oldest of the US Food and Drug Administration (FDA)-approved, particularly the barbiturates, are global central nervous system depressants and therefore risky; they should not be used for the treatment of insomnia. Sedating medications (particularly antidepressants and antipsychotics) are commonly used off-label for the treatment of insomnia, but their use is most appropriate when warranted by another diagnosis. Otherwise, one of the newer nonbenzodiazepine sleep medications is preferred when pharmacologic treatment of insomnia is desired.

\textbf{Melatonin receptor agonists}

Melatonin, as a dietary supplement, is commonly taken for undifferentiated insomnia. It can have mildly beneficial effects in shortening the time to fall asleep and the total sleep time.\textsuperscript{34} A melatonin-receptor agonist, ramelteon, is FDA-approved for the treatment of insomnia with difficulty falling asleep, for which it is modestly effective. No head-to-head trial has been published comparing it with melatonin. The manufacturer claims that ramelteon’s preferential binding to MT1 and MT2 receptors over MT3 receptors may provide a safety benefit, but this claim has not been proven.

\textbf{GABA\textsubscript{A} agonists}

Benzodiazepines (BDZs) bind nonspecifically to GABA receptors, whereas the non-BDZ medications zaleplon, zolpidem, and eszopiclone (called “Z-drugs” or BDZ receptor agonists) bind specifically to GABA\textsubscript{A} and thus more specifically promote sleep without the anxiolytic, amnestic, and respiratory depressant effects of BDZs.

BDZs can provide a satisfying experience of sleep; however, the sleep achieved on them is objectively shallower (more time in stages 1 and 2, less in stages 3 and 4) than “normal” sleep and than sleep achieved on BDZ agonists.\textsuperscript{35} BDZs may be used for acute insomnia in people without OSA and with normal respiratory function and are used chronically for some specific sleep disorders (eg, clonazepam used off-label for REM behavior disorder), but are not advised in the treatment of chronic insomnia.
For pharmacologic management of acute insomnia and chronic unexplained or co- 
morbid insomnia, the Z-drugs are preferred. These medications improve subjective 
and objective measures of sleep\textsuperscript{36} and lead to minimal if any rebound insomnia on 
discontinuation.\textsuperscript{37} Zolpidem in particular has been reported to cause complex 
sleep-related behaviors (including driving while asleep) in some cases; the plethora 
of reports regarding that medication may be due to its widespread use. This complex 
sleep-related behavior may be more likely to occur in situations of a higher blood level 
of zolpidem: in women, at higher doses, in hypoalbuminemia, and/or in conjunction 
with medications that increase zolpidem levels,\textsuperscript{38} such as antifungals. Patients should 
be asked about a history of somnambulism (sleepwalking) before prescription, 
because the risk of these behaviors is higher in that situation.

\textbf{Nonpharmacologic treatments}
Improving satisfaction with the nighttime experience is the key in treating insomnia, and 
sometimes the person’s attempts to achieve sleep are part of the problem. As with 
chronic pain, acceptance of some degree of symptoms can be helpful for sufferers.

\begin{table}
\centering
\caption{Medications used for nonspecific insomnia}
\begin{tabular}{|l|c|c|c|}
\hline
 & FDA-Approved as & FDA Approved for & Supplement (No 
 & Sedative-Hypnotic & Other Indications & FDA Oversight) \\
\hline
Benzodiazepine & Zolpidem & — & — 
receptor agonist & Zaleplon & — & — 
Eszopiclone\textsuperscript{a} & — & — 
Benzodiazepine & Estazolam & Clonazepam & — 
Flurazepam & Lorazepam (All other 
Quazepam & approved BDZ not 
Temazepam & listed at left) & — & — 
Triazolam & — & — & — 
Melatonin receptor & Ramelteon\textsuperscript{b} & — & — 
agonist & — & Melatonin & — 
Histamine antagonist & Diphenhydramine\textsuperscript{b} & — & — 
Doxylamine\textsuperscript{b} & — & — & — 
Histamine, adrenergic, & Doxepin (one 
and/or serotonin & formulation) & Amitriptiline & — & — 
antagonist & — & Doxepin (most 
(as presumed & formulations) & Mirtazapine & — & — 
mechanism for 
sedation) & — & Quetiapine & — & — 
& — & Trazodone & — & — 
Global central nervous & Chloral hydrate 
system depressant & Sodium oxybate\textsuperscript{c} & — & — 
(use not advised) & (discontinued) & — & — 
Ethchlorvynol & — & — & — 
(discontinued) & Butobarbital & — & — 
Butabarbital & — & — & — 
Pentobarbital/
& — & — & — 
carbromal & — & — & — 
Secobarbital & — & — & — 
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Approved for chronic use for insomnia.
\textsuperscript{b} Approved for over-the-counter use.
\textsuperscript{c} Sodium oxybate (xyrem) is FDA-approved for treatment of cataplexy and excessive daytime 
sleepiness in narcolepsy but used off-label by some sleep specialists for severe insomnia. The medi-
cation can be dangerous and can be used for illicit purposes; its prescription and dispensing are 
tightly controlled.
Sleep hygiene advice encourages sleep-conducive behaviors and situations; some people with insomnia may benefit from this advice, but many people with insomnia are already following this advice—or not following some of it may make more sense to them. Sleep hygiene advice has been used for decades as the control intervention in studies on CBT-I and shown, at least for people enrolling in clinical trials on insomnia, not to be effective when used alone.39,40 Although little known to primary care physicians, CBT-I is effective in primary insomnia, conditioned insomnia, and insomnia comorbid with psychological and medical conditions; it should be considered first-line therapy for chronic insomnia.41 CBT-I consists of several different approaches, among which sleep restriction therapy and stimulus control are the most effective components (Box 1).

CBT-I has been shown in double-blind randomized controlled trials to be more effective than relaxation therapy and to have persistent benefit for 6 months after a 6-week intervention.42 CBT-I has been shown to be more effective than sleep medications beyond 6 weeks, although use of zolpidem during the initial CBT-I intervention improved the insomnia remission rate at 6 months more than CBT-I plus subsequent as-needed use of medication did, and more than CBT-I without initial use of medication did.43

Initial studies on CBT-I used 6 face-to-face individual or group sessions with a trained psychologist, but efficacy has been demonstrated when the intervention is shorter — 2 sessions with a therapist followed by 2 phone calls44 — or via other formats: by phone,45 self-help booklet,40,46 and Internet.47 CBT-I will likely become more accessible to patients in primary care practices in coming years.

REFERENCES
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