CLINICAL PRACTICE

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Management of Insomnia

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 50-year-old woman presents with a 6-month history of difficulty falling asleep and staying asleep several nights per week, which affects her work performance. She reports having had mild-to-moderate symptoms of anxiety and depression for the past year. She has hypothyroidism, for which she has received levothyroxine therapy; TSH and thyroid hormone levels were normal when measured the previous month. She has tried over-the-counter sleep aids (valerian and melatonin), which have had limited effect, and occasionally has tried hypnotic sleep aids (lorazepam and eszopiclone). She is worried about drug dependence, but also believes that her sleep problem is getting worse. How would you manage this patient's insomnia?

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CME

THE CLINICAL PROBLEM

Insomnia disorder is characterized by dissatisfaction with sleep quality or duration associated with difficulty falling or staying asleep and substantial distress or daytime impairments. The disorder is a sleep disturbance that occurs 3 nights or more per week, persists for more than 3 months, and is not the result of inadequate opportunities for sleep.[1] It frequently co-occurs with other medical conditions (e.g., pain) and psychiatric disorders (e.g., depression), as well as other sleep disorders (e.g., restless legs syndrome and sleep apnea).

Insomnia is the most prevalent sleep disorder in the general population and among the most frequent issues raised by patients during primary care visits, although it often goes untreated.[2] Approximately 10% of adults meet the criteria for insomnia disorder and another 15 to 20% report occasional insomnia symptoms.[3] Insomnia is more prevalent among women and persons with mental or medical problems, and its incidence increases in middle age and later, as well as during perimenopause and menopause.[3,4] Although the pathophysiological mechanisms of insomnia disorder are still poorly understood, psychological and physiological hyperarousal are recognized as core features.

Insomnia can be situational or episodic, but it follows a persistent course in more than 50% of patients. The first episode typically arises from stressful life situations, health problems, atypical work schedules, or travel across several time zones (jet lag). Although most persons resume normal sleep after adjusting to the precipitating event, chronic insomnia may develop in persons who are vulnerable to the disorder. Psychological, behavioral, or medical factors often perpetuate chronic sleep difficulties. For instance, sleeping late in the morning or napping during the day can initially help persons cope with sleep disturbances; however, those same practices can exacerbate sleep difficulties over time and become treat-

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KEY POINTS

TREATMENT APPROACHES TO INSOMNIA

- Insomnia is common, and it frequently occurs when other medical, psychiatric, and other sleep disorders are present.
- Persistent insomnia is associated with substantial distress, functional impairment, and adverse health outcomes, including increased risks of major depression, hypertension, and work disability.
- Current guidelines recommend cognitive behavioral therapy for insomnia (CBT-I) as a first-line treatment for persistent insomnia. CBT-I includes practical strategies for modifying sleep habits, regulating sleep–wake schedules, reducing arousal from sleep, and reframing unhelpful beliefs about sleep and insomnia.
- Medications with an indication for insomnia (e.g., benzodiazepine receptor agonists, dual orexin receptor antagonists, and doxepin) that are approved by the Food and Drug Administration are recommended as alternative or adjunctive treatments. There is inadequate evidence to support over-the-counter medications, antipsychotics, or alternative agents for insomnia.
- Recommended therapies for insomnia produce clinically meaningful reductions in insomnia symptoms, sleep-onset latency, and time awake after sleep onset. CBT-I alone or with medication can promote rapid and sustained alleviation of insomnia symptoms over time.

ment targets. In perimenopausal women, vasomotor symptoms may serve as both a precipitating and perpetuating factor. Chronic insomnia is associated with increased risks of major depression,[5] hypertension,[6] Alzheimer's disease,[7] and work disability.

The assessment and diagnosis of insomnia rests on a careful history to document symptoms, course, co-occurring conditions, and other contributing factors (Table 1).[8] A 24-hour history of sleep–wake behaviors may identify additional behavioral and environmental targets for intervention (Fig. 1). Patient-reported assessment tools and sleep diaries can provide valuable information about the nature and severity of insomnia symptoms, help screen for other sleep disorders, and monitor treatment progress (Table 2).

Table 1. Key Elements of Assessment.

Typical sleep schedule: bedtime, rise time, and daytime napping
Nature of sleep concern: frequency, duration, course, triggers, and exacerbating factors
Daytime symptoms and effects: activities that are cancelled or avoided as a result of sleep problems
Symptoms of other sleep disorders that may produce insomnia
Loud snoring, restless sleep, and excessive daytime sleepiness (sleep apnea)
Urge to move the legs or unpleasant leg sensations in the evening (restless legs syndrome)
Unusual or aggressive behaviors during sleep: sleepwalking, rapid-eye movement (REM)–sleep behavior disorder
Medical and psychiatric history: identify contributing medical problems and psychiatric conditions
Environmental factors
Bedroom environment, noise, light level, and temperature
Sleep hygiene: alcohol use; use of tea, coffee, or nicotine; exercise patterns
Previous treatments and outcomes
Prescribed and over-the-counter medications and supplements
Behavioral measures to improve sleep

STRATEGIES AND EVIDENCE

Current treatment options for insomnia include prescribed and over-the-counter medications, psychological and behavioral therapies (also referred to as cognitive behavioral therapy for insomnia [CBT-I]), and complementary and alternative therapies. The usual treatment trajectory involves the use of over-the-counter medications and, when the disorder is brought to the attention of a practitioner, prescription medication. Few patients receive CBT-I, owing in part to the lack of adequately trained therapists.

CBTI-I

CBT-I involves a combination of strategies aimed at changing the behavioral practices and psychological factors (e.g., excessive worries and unhelpful beliefs about sleep) that contribute to insomnia. The core components of CBT-I include behavioral and sleep-scheduling strategies (sleep restriction and stimulus control instructions), relaxation methods, psychological and cognitive interventions (or both) aimed at changing unhelpful beliefs and excessive worrying about insomnia, and sleep hygiene education (Table 3).

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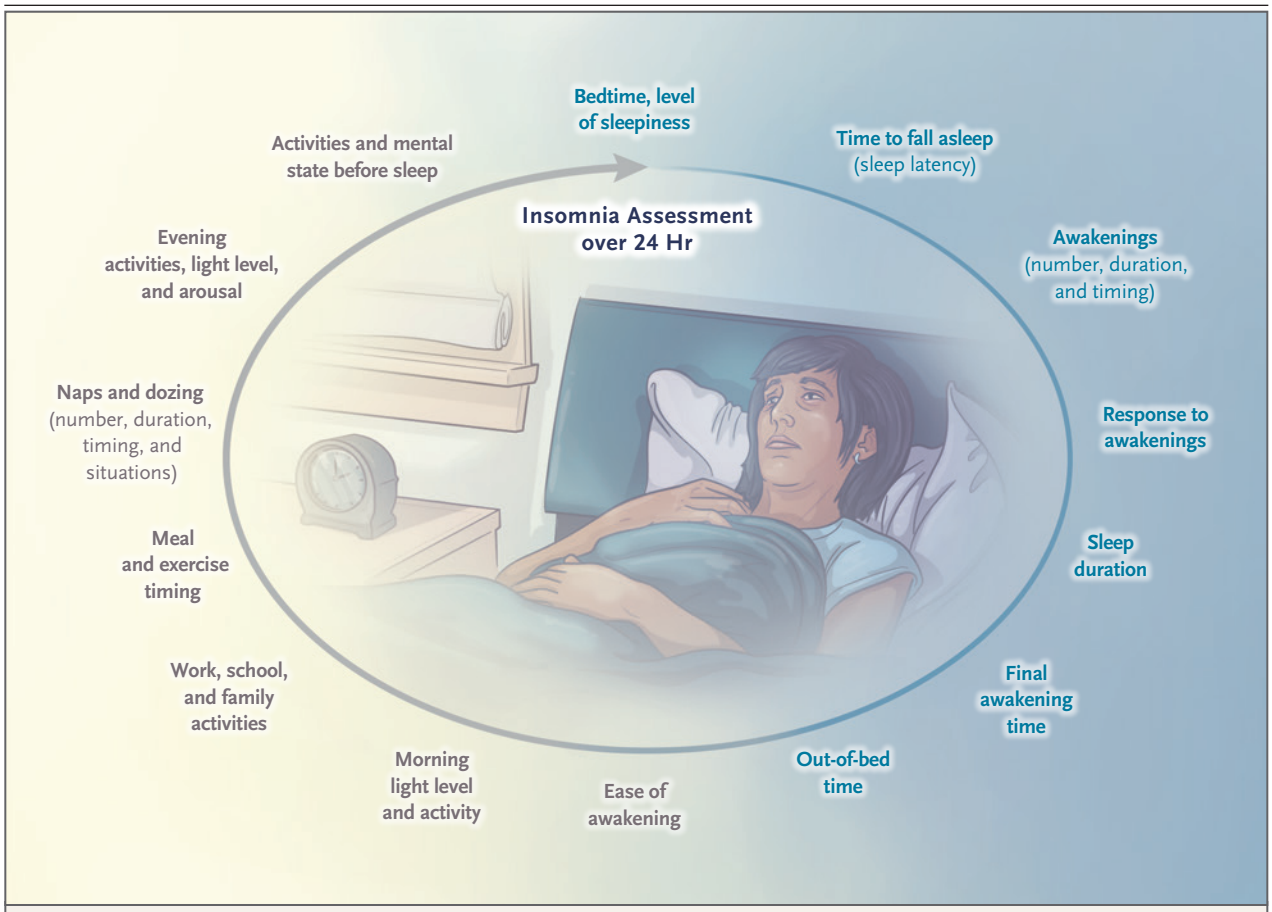

Figure 1. Use of 24-Hour History for Insomnia Assessment.

Insomnia manifests as a sleep problem but affects — and is affected by — daytime behaviors. A thorough insomnia history helps evaluate symptoms and behaviors both at night and during the day. Shown are key parts of an insomnia assessment across a 24-hour day.

Additional psychological interventions, such as Acceptance and Commitment Therapy and Mindfulness-Based Therapy, have been adapted for insomnia, but fewer data support their efficacy, and they take more time to yield benefits (Table 3). CBT-I is prescriptive, focused on sleep, and oriented toward problem solving. It is typically guided by a mental health therapist (e.g., a psychologist) in the context of four to eight consultation visits. There are several variants in the methods for implementing CBT-I, including abbreviated and group formats,[14] the involvement of other providers (e.g., a nurse practitioner),[15] and the use of telehealth or digital platforms.[16]

CBT-I is currently the first-line treatment recommended in the practice guidelines of several professional organizations (labeled as a "strong recommendation" on the basis of the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] method).[17-19] Evidence from clinical trials and meta-analyses indicates that CBT-I produces substantial improvements in patient-reported outcomes, typically measured with the use of a standardized effect-size method (either Cohen's d or Hedges' g). The effect size is a measure of the magnitude of difference between groups, with conventional thresholds for the size of effect as follows: 0.2, small; 0.5. moderate; and 0.8, large. In meta-analyses of these trials, CBT-I showed improvement in insomnia-symptom severity (effect size, 0.98; 95% confidence interval [CI], 0.82 to 1.15), sleep-onset latency (effect size, 0.57; 95% CI, 0.50 to 0.65), and time awake after sleep onset (effect size, 0.63; 95% CI, 0.53 to 0.73). Improved sleep continuity was also associated with a corresponding increase in sleep efficiency (the ratio of time asleep to time spent in bed; effect size, 0.71; 95% CI, 0.61 to 82). Total

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Table 2. Tools for the Clinical Assessment of Insomnia.

Domain and Measure	Description
Sleep–wake characteristics: sleep diary	Completed daily by the patient to collect information about sleep schedule (bedtime, arising time, napping) and estimates of sleep–wake characteristics (sleep latency, number and duration of awakenings, and sleep time). Useful for determining the nature, frequency, and severity of sleep problems and monitoring progress during treatment.[9]
Insomnia symptom severity: Insomnia Severity Index	A 7-item, patient-reported scale for assessing perceived severity of insomnia symptoms and daytime distress and impairments. Scores range from 0 to 28; 0 to 7 indicates no significant insomnia, 8 to 14 indicates subthreshold insomnia, 15 to 21 indicates moderate insomnia, and 22 to 28 indicates severe insomnia. The scale includes guidelines for defining clinical insomnia and response or remission after treatment.[10]
Sleep quality: Pittsburgh Sleep Quality Index	A 19-item patient-reported scale measuring overall sleep quality and a screening tool for other sleep disorders.[11]
Screening for sleep apnea and restless legs syndrome	
STOP–Bang	An 8-item patient-reported questionnaire for evaluating risk of sleep-related breathing disorders.[12]
International Restless Legs Syndrome Rating Scale	A 10-item patient-reported questionnaire assessing frequency, severity, and effect of restless legs syndrome (scores range from 0 to 40, with higher scores indicating more severe symptoms).[13]

sleep time had increased modestly at the end of treatment (effect size, 0.16; 95% CI, 0.08 to 0.24), although additional benefits were often seen several weeks or months after the end of therapy.[17,20,21] Effect sizes are strongest for global insomnia symptom severity. Efficacy does not appear to be moderated by age, insomnia severity, the presence of coexisting conditions, or hypnotic medication use. Smaller improvements have been noted for daytime symptoms (e.g., fatigue and mood) and quality of life,[22,23] which have been attributed in part to the use of generic measurements not specifically developed for insomnia. Overall, approximately 60 to 70% of patients have a clinical response, which is defined as a reduction of 7 points on the Insomnia Severity Index (ISI; scores range from 0 to 28, with higher scores indicating more severe insomnia). A sample ISI form is shown in the Supplementary Appendix, available with the full text of this article at NEJM.org. Approximately 50% of persons with insomnia had remission (total ISI score, <8) after 6 to 8 weeks of treatment, and 40 to 45% had sustained remission for 12 months. Daytime sleepiness is a potential adverse event in the early phase of restricting time in bed, but that effect tends to resolve as the sleep time is increased.[24]

Digital CBT-I (eCBT-I) has gained in popularity over the past decade and could eventually narrow the important gap between demand and access to CBT-I. The SHUTi and Sleepio applications have substantial published evidence supporting their efficacy. A meta-analysis of 11 randomized clinical trials involving 1460 participants that tested Web-based CBT-I found that eCBT-I had a positive effect on several sleep outcomes (i.e., insomnia severity, sleep efficiency, subjective sleep quality, wake after sleep onset, sleep-onset latency, total sleep time, and number of nocturnal awakenings), with effect sizes ranging from 0.21 to 1.09. These effects were similar to those observed in trials of face-to-face CBT-I and were maintained for 4 to 48 weeks after follow-up.[16] Additional digital CBT-I products (e.g., CBT-i Coach, Go! To Sleep, and Sleep Reset) use similar therapeutic principles but have no or limited published efficacy data.

Treating co-occurring conditions such as depression and chronic pain may alleviate insomnia symptoms but generally does not completely resolve them. Conversely, the treatment of insomnia improves sleep in the context of co-occurring conditions but has less consistent effects on the co-occurring conditions themselves. For instance, the treatment of insomnia alleviates depression symptoms and reduces the incidence and recurrence of depression[25] but has only small effects on chronic pain.[26]

Stepped-care approaches may help to address

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Table 3. Psychological and Behavioral Therapies for Patients with Insomnia.

Therapy	Description
Sleep restriction	This intervention limits the amount of time spent in bed (the sleep window) to match as closely as possible the actual sleep time and strengthens the homeostatic sleep drive (the increase in sleep propensity that accumulates with an increased duration of wakefulness). After the initial restriction, the sleep window is gradually adjusted upward or downward on a weekly basis and as a function of sleep efficiency (time asleep ÷ time spent in bed × 100) until an appropriate sleep duration is established.
Stimulus control	Go to bed only when sleepy. Get out of bed when unable to sleep. Use the bed and bedroom for sleep and sex only (no reading, watching television, etc.). Arise at the same time every morning. Avoid napping.
Relaxation training	This method involves the use of clinical procedures (e.g., progressive muscle relaxation and imagery training) aimed at reducing autonomic arousal, muscle tension, and intrusive thoughts that interfere with sleep. Most relaxation procedures begin with some professional guidance and are practiced daily over a period of a few weeks. Relaxation training is not always included in cognitive behavioral therapy for insomnia (CBT-I).
Cognitive therapy	This psychological approach uses Socratic questioning and behavioral experiments to revise common misconceptions about sleep and to reframe unhelpful beliefs about insomnia and its daytime consequences. This method is also intended to reduce excessive worrying about sleep difficulties and their daytime consequences. Additional cognitive strategies may also involve paradoxical intention (willingly trying to stay awake rather than trying to fall asleep) in order to alleviate the performance anxiety triggered by attempting to force sleep.
Sleep hygiene education	The patient receives education regarding general guidelines about health practices (e.g., diet, exercise, and substance use) and environmental factors (e.g., light level, noise, and excessive temperature) that may promote or interfere with sleep. This may also include some basic information about normal sleep and changes in sleep patterns with aging.
Acceptance and commitment therapy (ACT)	ACT is a type of psychotherapy aimed at educating the patient to stay focused on the present moment and accept life experiences, thoughts, and feelings (even negative ones) without trying to change them. ACT involves the use of different methods (e.g., acceptance, defusion, mindfulness, and committed action) and processes in order to increase psychological flexibility.
Mindfulness	This approach is a meditation method that involves observing one's thoughts and feelings and letting go of the need to change or ruminate about things. Originally designed as a method of reducing stress and anxiety, mindfulness has been adapted for the management of insomnia and can be included as one component of ACT.
Brief behavioral treatments for insomnia	This abbreviated version of CBT-I emphasizes behavioral components and is typically implemented in fewer (one to four) sessions. It involves education about sleep regulation and factors that promote or interfere with sleep, along with a tailored behavioral prescription based on stimulus control and sleep-restriction therapy.

resource limitations with traditional psychological and behavioral therapies. One such model recommends education, monitoring, and self-help approaches at the first level, digital or group-based psychological and behavioral treatment at the second level, individual psychological and behavioral treatment at the third level, and pharmacotherapy as a short-term adjunct at each level.[27]

MEDICATIONS

Prescribing patterns for hypnotic medications in the United States have changed substantially over the past 20 years.[28] Prescriptions for benzodiazepine receptor agonists have steadily decreased and prescriptions for trazodone have steadily increased, notwithstanding the absence of a Food and Drug Administration (FDA) indication for the use of trazodone to treat insomnia. In addition, orexin receptor antagonist drugs were introduced in 2014 and are widely used. Hypnotic medications are prescribed at higher rates for women, older adults, and non-Hispanic White patients, which reflects the epidemiologic characteristics of insomnia.[29] The main classes of sleep-promoting medications are summarized in Table 4. Controlled data are sparse regarding the

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Table 4. Medications for the Treatment of Insomnia.

Medication Class and Types	Examples and Approximate Half-Life	Potential Advantages	Potential Disadvantages	Effect Size (95% CI)*
Benzodiazepine receptor agonists†		Consistent evidence of efficacy for sleep onset and sleep maintenance for agents approved by the FDA. Range of half-lives can accommodate different symptom profiles.	Short-term risks: sedation, anterograde amnesia, cognitive and psychomotor impairment, nausea, headaches, complex sleep-related behavior (FDA warning), rebound insomnia Long-term risks: falls, hip fractures, physiological dependence, depression, dementia	Short-acting, 0.83 (0.62 to 1.04); intermediate-acting, 0.67 (0.52 to 0.82); long-acting, 0.58 (0.42 to 0.73); eszopiclone, 0.51 (0.35 to 0.68); zolpidem, 0.45 (0.36 to 0.56); zaleplon, 0.19 (0.00 to 0.37)
Benzodiazepines	Triazolam (4 hr)†, temazepam (10 hr)†, clonazepam (30 hr)†‡			
Nonbenzodiazepines (Z-drugs)	Zolpidem (2.5 hr)†, zaleplon (1 hr)†, eszopiclone (6 hr)†			
Dual orexin receptor antagonists	Suvorexant (12 hr), lemborexant (18 hr), daridorexant (8 hr)	Consistent evidence of efficacy for sleep onset and sleep maintenance. Targeted mechanism of action on wake-promoting orexin system. Lower risk of cognitive and psychomotor impairment than benzodiazepine receptor agonists; low potential for abuse and physiological dependence.	Short-term risks: sedation, cognitive and psychomotor impairment, dizziness, headaches, abnormal dreams, nightmares, sleep paralysis, complex sleep-related behavior, increased depression Contraindicated in patients with narcolepsy	Daridorexant, 0.23 (–0.01 to 0.48); lemborexant, 0.36 (0.08 to 0.63); suvorexant, 0.31 (0.01 to 0.62)
Sedating antidepressants	Doxepin (15 hr), trazodone (9 hr),‡, mirtazapine (30 hr)†‡, amitriptyline (30 hr)†‡	Mechanisms of action involve histamine, serotonin, and adrenergic receptors. Efficacy data for maintenance, variable evidence for sleep onset. Low potential for abuse.	Inconsistent efficacy evidence for insomnia (other than doxepin 3–6 mg) Short-term risks: sedation, cognitive and psychomotor impairment, cardiac conduction delay, anticholinergic effects, nausea, serotonin syndrome, increased suicidality Long-term risks: falls, hip fractures, dementia, physiological dependence (i.e., rebound insomnia); weight gain, metabolic effects (i.e., abnormal glucose metabolism, lipid levels) with mirtazapine	Doxepin, 0.30 (–0.05 to 0.64); trazodone, 0.52 (0.16 to 0.89)

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Melatonin, melatonin receptor agonists	Melatonin (1 hr)‡, ramelteon (2 hr) tasimelteon (1–4 hr)‡	Mechanism of action involves melatonin receptors. Efficacy data for sleep onset. Efficacy evidence for insomnia in children with neurodevelopmental disorders. Generally associated with few side effects and low potential for abuse.	Not efficacious for sleep maintenance Short-term risks: sedation, fatigue, dizziness, nausea, abnormal dreams	Melatonin, 0.13 (–0.11 to 0.38); ramelteon, 0.12 (–0.14 to 0.37); tasimelteon
Sedating antihistamines	Diphenhydramine (6 hr)†, doxylamine (10 hr)†, hydroxyzine (20 hr)†‡	Widely available over the counter and by prescription. Mechanism of action involves antagonism of central histamine receptors.	Limited efficacy data for insomnia Short-term risks: sedation, cognitive and psychomotor impairment, anticholinergic effects (e.g., dry mouth) Long-term risk: dementia (anticholinergic effect)	Insufficient data
Sedating antipsychotics	Quetiapine (6 hr)†‡, olanzapine (30 hr)†‡	Sedating in clinical trials of patients with schizophrenia or bipolar disorder. Small studies suggest efficacy on patient-reported and polysomnographic sleep measures in insomnia. Mechanism of action involves multiple receptor types (e.g., serotonin, dopamine, and histamine).	Limited efficacy data for insomnia Short-term risks: sedation, dizziness, cognitive and psychomotor impairment, hypotension, headache, dry mouth Long-term risks: metabolic effects (e.g., glucose metabolism and lipid levels) and weight gain	Insufficient data
Miscellaneous	Gabapentin (7 hr)†‡, pregabalin (6 hr)†‡	Efficacy data for chronic pain (often occurring with insomnia). Subjectively sedating in clinical trials for other conditions. Mechanism of action involves alpha 2–delta receptors. Eliminated by renal excretion.	Efficacy data for insomnia sparse and inconsistent Short-term risks: sedation, dizziness, cognitive and psychomotor impairment, edema, respiratory depression Long-term risks: depression and suicidality, physiological dependence	Insufficient data

* Effect sizes for new (use, <4 weeks) medication treatments on primary outcomes are as defined by any patient-evaluated scales, including the Insomnia Severity Index, Pittsburgh Sleep Quality Index, Leeds Sleep Questionnaire, and sleep diaries.[30] An effect size of 0.2 is considered to be small, 0.5 is considered to be moderate, and 0.8 is considered to be large.
† The Beers Criteria (a list of medications deemed to be relatively inappropriate for patients 65 years of age or older) recommends avoidance of this drug.
‡ This drug is not FDA-approved for the treatment of insomnia. All drugs included in the table are classified by the FDA as Pregnancy category C with the following exceptions: triazolam, temazepam (category X); clonazepam (category D); diphenhydramine and doxylamine (category B).

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long-term efficacy and side-effect profiles of hypnotic medications, despite their frequent long-term use.

Benzodiazepine Receptor Agonist Hypnotics

Benzodiazepine receptor agonist hypnotics include benzodiazepines and nonbenzodiazepines (also known as Z-drugs). These subclasses have different chemical structures, but both are allosteric modulators of a common binding site on γ-aminobutyric acid type A (GABA A) receptors, which accounts for their similar actions and side effects. Some benzodiazepine receptor agonists (e.g., zolpidem) have relative specificity for subpopulations of GABA A receptors that are responsible for sleep promotion relative to anxiolytic, myorelaxant, and anticonvulsant effects. In practice, however, pharmacodynamic differences among benzodiazepine receptor agonists are less salient than differences in pharmacokinetic properties, particularly elimination half-life. Clinical trials and meta-analyses have shown the efficacy of benzodiazepine receptor agonists for reducing sleep-onset latency and wakefulness after sleep onset, with small increases in total sleep time (Table 4).[30,31] Patient-reported side effects of benzodiazepine receptor agonists include anterograde amnesia (in <5%), next-day sedation (in 5 to 10%), and complex behaviors during sleep, such as sleepwalking, eating, or driving (in 3 to 5%), a side effect that is responsible for black-box warnings for zolpidem, zaleplon, and eszopiclone. These side effects are more likely to occur with higher doses, coprescription with other sedating medications, and (in the case of amnesia and sedation) longer-duration agents. The development of drug tolerance and physiological dependence marked by rebound insomnia and withdrawal syndromes occurs with repeated nightly use in 20 to 50% of patients.[32] Although misuse of benzodiazepine receptor agonists (i.e., use without a prescription or at larger doses or longer duration than prescribed) is relatively common, substance use disorder involving benzodiazepine receptor agonists is uncommon.[33] Epidemiologic data show dose-dependent and duration-dependent increases in the risks of hip fractures[34] and dementia with long-term use of benzodiazepine receptor agonists, but confounding by indication may contribute to these observed risks.

Sedating Heterocyclic Drugs

Sedating antidepressant drugs, including tricyclic drugs (e.g., amitriptyline, nortriptyline, and doxepin) and heterocyclic drugs (e.g., mirtazapine and trazodone), are commonly prescribed to treat insomnia. Of these, only doxepin (at a dose of 3 to 6 mg daily, taken at night) is FDA-approved for insomnia. The lower doses used in insomnia than in depression and the more rapid onset of action in insomnia than in depression suggest distinct mechanisms of action for these indications. Despite their widespread use, the efficacy of the sedating antidepressants in the treatment of insomnia is not well supported by controlled trials, except in the case of doxepin. Meta-analyses of trazodone trials have shown inconsistent effects on sleep-onset latency, wake after sleep onset, and total sleep time.[35,36] Given these limitations, current evidence suggests that sedating antidepressants in aggregate increase sleep quality, sleep efficiency, and total sleep time, with little effect on sleep latency.[35] Clinicians and patients often prefer these medications, despite their lack of specific FDA indication for insomnia, because of their mild side effects at low doses and clinical experience of efficacy. Side effects can include sedation, dry mouth, cardiac conduction delay, hypotension, and hypertension. Sedating heterocyclic drugs approved for the treatment of schizophrenia and bipolar disorder, such as quetiapine and olanzapine, are sometimes used to treat insomnia. However, the cardiovascular, metabolic, and neurologic risks of these drugs weigh against their use except in persons with co-occurring psychiatric disorders.

Orexin Receptor Antagonists

Orexin (hypocretin)–containing neurons in the lateral hypothalamus stimulate wake-promoting nuclei in the brainstem and hypothalamus and inhibit sleep-promoting nuclei in the ventrolateral and median preoptic areas.[37] Conversely, inhibiting orexinergic neurotransmission inhibits wakefulness and promotes sleep. Three dual orexin receptor antagonists — suvorexant, lemborexant, and daridorexant — are FDA-approved for insomnia. Clinical trials support their efficacy for sleep-onset and sleep-maintenance symptoms.[30,38,39] Side effects include sedation, fatigue, and abnormal dreaming, but they produce less

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cognitive impairment than benzodiazepine receptor agonists.[40] Because a deficiency in endogenous orexin causes narcolepsy with cataplexy, orexin antagonists are contraindicated in patients with this condition.

Melatonin and Melatonin Receptor Agonists

Melatonin is a pineal hormone that is endogenously secreted during darkness at night. Exogenous melatonin produces supraphysiologic blood levels for varying durations depending on the specific dose and formulation. The appropriate dose of melatonin for treating insomnia is not defined. Controlled trials involving adults have shown a small effect on sleep onset, with little effect on wakefulness during sleep or on total sleep time.[41,42] Melatonin is increasingly used to treat sleep problems in children, although its efficacy and safety are not well established except in children with neurodevelopmental disorders.[43]

Drugs that bind to melatonin MT1 and MT2 receptors are approved for the treatment of sleep-onset insomnia (ramelteon) and circadian-rhythm sleep–wake disorder (tasimelteon). Like melatonin, these drugs have little effect on wakefulness after sleep onset or on total sleep time.[42] Somnolence and fatigue are the most common side effects.

Other Medications

Antihistamine medications obtained over the counter (diphenhydramine and doxylamine) and by prescription (hydroxyzine) are among the most commonly used medications for the treatment of insomnia. Data supporting their efficacy are weak,[41] but their availability and perceived safety as compared with benzodiazepine receptor agonists probably contribute to their popularity. Sedating antihistamines can cause excessive sedation, anticholinergic side effects, and an increased risk of dementia. Gabapentinoids, such as gabapentin and pregabalin, are commonly used for the treatment of chronic pain and are also first-line agents for the treatment of restless legs syndrome.[44] These drugs produce sedation and increase slow-wave sleep, and are prescribed off-label for insomnia, particularly when accompanied by pain. Fatigue, somnolence, dizziness, and ataxia are the most common side effects.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

Alternative treatments are widely used among persons with insomnia.[45] Cannabis, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (THC) preparations are also widely used to treat sleep problems, but are associated with mixed findings. The overall quality of evidence supporting the efficacy of cannabinoids for insomnia is low, owing to the absence of large, well-controlled clinical trials and the apparent development of tolerance to hypnotic effects that can result from chronic administration. Variation in cannabis-derived preparations is also relevant. For instance, CBD is stimulating at low doses and sedating at high doses, and THC has the opposite effects.

SELECTION OF HYPNOTIC MEDICATION

When medication is the selected treatment, a short-acting benzodiazepine receptor agonist, orexin antagonist, or low-dose heterocyclic drug is a reasonable first choice in most clinical scenarios. Benzodiazepine receptor agonists may be preferred in the treatment of patients with insomnia with predominantly sleep-onset symptoms, in younger adults, and when short-term use is likely (e.g., in response to acute or periodic stressors). Low-dose heterocyclic drugs or orexin antagonists may be preferred in treating patients with symptoms that are predominantly related to sleep maintenance or early awakening, older adults, and patients with substance use disorders or sleep apnea. The Beers Criteria list of medications deemed to be relatively inappropriate for patients 65 years of age or older includes benzodiazepine receptor agonists and heterocyclic drugs, but does not include doxepin, trazodone, or orexin antagonists. Initial medication treatment often includes nightly use for 2 to 4 weeks followed by reevaluation of effects and side effects. Intermittent administration (2 to 4 times per week) is encouraged if long-term use is appropriate. Patients should be instructed to take medications 15 to 30 minutes before bedtime. With prolonged medication use, drug dependence develops in some patients, particularly with the use of benzodiazepine receptor agonists. A systematic tapering schedule (e.g., by 25% per week) can help to reduce or discontinue the use of hypnotics after long-term use.[46,47]

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COMBINATION THERAPY OR SINGLE THERAPY

Evidence from the few head-to-head comparative studies available indicates that both CBT-I and hypnotic medications (mostly Z-drugs) produce equivalent improvements in sleep continuity in the short term (4 to 8 weeks),[48-51] although medication has been shown to increase total sleep time more than CBT-I. Combined therapy produces improvement in sleep more quickly than CBT-I alone, but this advantage decreases by the fourth or fifth week of treatment,[52] and CBT-I used alone produces more sustained benefits over time than medication or combined therapy. Some patients may have less adherence to behavioral recommendations when the easier alternative of taking a sleep medication is also available.

GUIDELINES

Current guidelines that have been endorsed by health care and professional organizations recommend CBT-I as the first-line treatment for insomnia and medications as alternative or adjunctive treatment, within the context of shared decision making.[17-19,53,54] Guidelines recommend CBT-I with a strong level of support, and subcomponents such as brief behavioral treatment, sleep restriction, and stimulus control are recommended with lower levels of support. Among medications, guidelines make weak recommendations with moderate-quality evidence for the use of FDA-approved hypnotic medications (e.g., benzodiazepine receptor agonists, doxepin, and orexin antagonists) and weak evidence against the use of other agents, including heterocyclic drugs such as trazodone and antipsychotic agents. Recommendations in this article are generally consistent with these guidelines.

AREAS OF UNCERTAINTY

Evidence is lacking regarding the long-term efficacy of medications and the development of tolerance to medications for insomnia. The role of intermittent medication and the appropriate schedule for administration are still unclear. Although network meta-analyses address the relative efficacy and side effects of different medication classes, few large trials have directly compared different active medications. Telehealth and digital CBT platforms offer potential solutions for some patients, although more information is needed to identify the patients who benefit most. Additional work is needed to identify reliable insomnia phenotypes[55] and test whether persons with those phenotypes have different responses to more personalized therapeutic approaches.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette spends long periods of time in bed with considerable variability in the time taken to fall asleep and the time sleeping. She described anxiously worrying about falling asleep and staying asleep. We would initiate CBT-I with a focus on reducing overall time in bed to improve sleep consolidation, maintaining regular sleep–wake times to strengthen circadian sleep regulation, and performing cognitive exercises to reduce sleep-focused rumination. If insomnia recurred in the setting of stressful life events, we would prescribe doxepin for intermittent use on those occasions.

The content of this article is solely the responsibility of the authors and does not necessarily represent the views of the Patient-Centered Outcomes Research Institute or its Board of Governors or Methodology Committee.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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