CLINICAL PRACTICE

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# Insomnia Disorder

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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 author's clinical recommendations.*

**A 77-year-old overweight woman with hypertension and arthritis reports that she has had trouble sleeping for "as long as I can remember." She has taken hypnotic medications nightly for almost 50 years; her medication was recently switched from lorazepam (1 mg), which had been successful, to trazodone (25 mg) by her primary care physician, who was concerned about her use of the former. She spends 9 hours in bed, from 11 p.m. to 8 a.m. She has only occasional difficulty falling asleep, but she awakens two to three times per night to urinate and lies in bed for over an hour at those times, "just worrying." How should her case be managed?**

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## THE CLINICAL PROBLEM

Dissatisfaction with sleep owing to difficulty falling asleep or staying asleep or to waking up too early is present in roughly one third of adults on a weekly basis.[1] For most, such sleep difficulties are transient or of minor importance. However, prolonged sleeplessness is often associated with substantial distress, impairment in daytime functioning, or both. In such cases, a diagnosis of insomnia disorder is appropriate. Reductions in perceived health[2] and quality of life,[3] increases in workplace injuries and absenteeism,[4] and even fatal injuries[5] are all associated with chronic insomnia. Insomnia symptoms may also be an independent risk factor for suicide attempts and deaths from suicide, independent of depression.[6] Neuropsychological testing reveals deficits in complex cognitive processes, including working memory and attention switching,[7] which are not simply related to impaired alertness.

Older diagnostic systems attempted to distinguish "primary" from "secondary" insomnia on the basis of the inferred original cause of the sleeplessness. However, because causal relationships between different medical and psychiatric disorders and insomnia are often bidirectional, such conclusions are unreliable. In addition, owing to the poor reliability of insomnia subtyping[8] based on phenotype or pathophysiology, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*[9] takes a purely descriptive approach that is based on the frequency and duration of symptoms (Table 1), allowing a diagnosis of insomnia disorder independent of, and in addition to, any coexisting psychiatric or medical disorders. The clinician should monitor whether treatment of such coexisting disorders normalizes sleep, and if not, treat the insomnia disorder independently.

*An audio version of this article is available at NEJM.org*

### COEXISTING CONDITIONS

Insomnia is more common in women than in men, and its prevalence is increased in persons who work irregular shifts and in persons with disabilities.[2] Although

KEY CLINICAL POINTS

**INSOMNIA DISORDER**

- Prolonged insomnia is associated with an increased risk of new-onset major depression and may be an independent risk factor for heart disease, hypertension, and diabetes, especially when combined with sleep times of less than 6 hours per night.
- Evaluation of a patient with insomnia should include a complete medical and psychiatric history and a detailed assessment of sleep-related behaviors and symptoms.
- Cognitive behavioral therapy, which includes setting realistic goals for sleep, limiting time spent in bed, addressing maladaptive beliefs about sleeplessness, and practicing relaxation techniques, is the first-line therapy for insomnia.
- In those with acute insomnia due to a defined precipitant, use of Food and Drug Administration–approved hypnotic medications is indicated.
- Long-term use of benzodiazepine-receptor agonists, low-dose antidepressants, melatonin agonists, or an orexin antagonist should be considered for patients with severe insomnia that is unresponsive to other approaches.

the elderly are more likely than younger people to report insomnia symptoms, actual insomnia diagnoses are not more frequent in the elderly, because the effects of sleeplessness on daytime functioning appear to be less dramatic. Roughly 50% of those with insomnia have a psychiatric disorder,[10] most commonly a mood disorder (e.g., major depressive disorder) or an anxiety disorder (e.g., generalized anxiety disorder or post-traumatic stress disorder). Various medical illnesses are also associated with insomnia, particularly those that cause shortness of breath, pain, nocturia, gastrointestinal disturbance, or limitations in mobility.[11]

Although roughly 80% of those with major depressive disorder have insomnia, in nearly one half of those cases, the insomnia predated the onset of the mood disorder.[12] A meta-analysis of more than 20 studies concluded that persistent insomnia is associated with a doubling of the risk of incident major depression.[13] Associations have also been reported between insomnia and increased risks of acute myocardial infarction and coronary heart disease,[14] heart failure,[15] hypertension,[16] diabetes,[17] and death,[18] particularly when insomnia is accompanied by short total sleep duration (<6 hours per night).[19]

### PREVALENCE AND NATURAL HISTORY

Insomnia is the most common sleep disorder, with a reported prevalence of 10 to 15%, depending on the diagnostic criteria used.[1,2] Insomnia symptoms commonly wax and wane over time, though roughly 50% of those with more severe symptoms who meet criteria for insomnia disorder have a chronic course.[20] The 1-year incidence of insomnia is approximately 5%. Difficulty maintaining sleep is the most common symptom (affecting 61% of persons with insomnia), followed by early-morning awakening (52%) and difficulty falling asleep (38%); nearly half of those with insomnia have two or more of these symptoms.[11] Manifestations of insomnia often change over time; for example, a person may initially have difficulty falling asleep but subsequently have difficulty staying asleep, or vice versa.

### PATHOPHYSIOLOGY

Insomnia is commonly conceptualized as a disorder of nocturnal and daytime hyperarousal, which is both a consequence and a cause of insomnia and is expressed at cognitive and emotional as well as physiological levels.[21] People with insomnia often describe excessive worry, racing thoughts, and selective attention to arousing stimuli. Hyperarousal is manifested physiologically in those with insomnia as an increased whole-body metabolic rate, elevations in cortisol level, increased whole-brain glucose consumption during both the waking and the sleeping states, and increased blood pressure and high-frequency electroencephalographic activity during sleep.[21]

## STRATEGIES AND EVIDENCE

### EVALUATION

The evaluation of insomnia requires assessment of nocturnal and daytime sleep-related symptoms, their duration, and their temporal association with psychological or physiological stressors. Because there are many pathways to insomnia, a full evaluation includes a complete medical and psychiatric history as well as assessment for the presence

**Table 1. Criteria for the Diagnosis of Insomnia Disorder.***

| |
|---|
| Dissatisfaction with sleep quantity or quality, with one or more of the following symptoms: |
| Difficulty initiating sleep |
| Difficulty maintaining sleep, characterized by frequent awakenings or trouble returning to sleep after awakenings |
| Early-morning awakening with inability to return to sleep |
| The sleep disturbance causes clinically significant distress or impairment in daytime functioning, as evidenced by at least one of the following: |
| Fatigue or low energy |
| Daytime sleepiness |
| Impaired attention, concentration, or memory |
| Mood disturbance |
| Behavioral difficulties |
| Impaired occupational or academic function |
| Impaired interpersonal or social function |
| Negative effect on caregiver or family functioning |
| The sleep difficulty occurs at least 3 nights per week, is present for at least 3 months, and occurs despite adequate opportunity for sleep |

* From the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.[9]

of specific sleep disorders (e.g., sleep apnea or the restless legs syndrome). Questioning the patient regarding thoughts and behaviors in the hours before bedtime, while in bed attempting to sleep, and at any nocturnal awakenings may provide insight into processes interfering with sleep. A daily sleep diary documenting bedtime, any awakenings during the night, and final wake time over a period of 2 to 4 weeks can identify excessive time in bed and irregular, phase-delayed, or phase-advanced sleep patterns.

There is often a mismatch between self-reported and polysomnographically recorded sleep in those with insomnia, in which the self-reported time to fall sleep is overestimated and total sleep time is underestimated.[22] Because polysomnography cannot distinguish those with insomnia from those without it,[23] the diagnosis of insomnia is made clinically. Polysomnography is not indicated in the evaluation of insomnia unless sleep apnea, periodic limb movement disorder, or an injurious parasomnia (e.g., rapid-eye-movement [REM] sleep behavior disorder) is suspected or unless usual treatment approaches fail.

## MANAGEMENT

The choice of treatment of insomnia depends on the specific insomnia symptoms, their severity and expected duration, coexisting disorders, the willingness of the patient to engage in behavioral therapies, and the vulnerability of the patient to the adverse effects of medications. Patients with an acute onset of insomnia of short duration often have an identifiable precipitant (e.g., a medical illness or the loss of a loved one). In such cases, Food and Drug Administration (FDA)–approved pharmacologic agents (discussed below) are recommended for short-term use. In patients with chronic insomnia, appropriate treatment of coexisting medical, psychiatric, and sleep disorders that contribute to insomnia is essential for improving sleep. Nevertheless, insomnia is often persistent even with proper treatment of these coexisting disorders.[24]

Treatment for chronic insomnia includes two complementary approaches: cognitive behavioral therapy and pharmacologic treatments.

### *Cognitive Behavioral Therapy (CBT)*

CBT addresses dysfunctional behaviors and beliefs about sleep that contribute to the perpetuation of insomnia (Table 2), and it is considered the first-line therapy for all patients with insomnia,[25] including those with coexisting conditions.[26] CBT is traditionally delivered in either individual or group settings over six to eight meetings. In a meta-analysis of randomized, controlled trials involving persons with insomnia without coexisting

**Table 2. Components of Cognitive Behavioral Therapy for Insomnia.**

| Component | Intended Effect | Specific Directions for Patients |
|---|---|---|
| Sleep restriction | Increase sleep drive and stabilize circadian rhythm | Reduce time in bed to perceived total sleep time (not less than 5–6 hours), choose specific hours on the basis of personal preference and circadian timing, increase time in bed gradually as sleep efficiency improves |
| Stimulus control | Reduce arousal in sleep environment and promote the association of bed and sleep | Attempt to sleep when sleepy, get out of bed when awake and anxious at night, use the bed only for sleep or sexual activity (e.g., no watching TV in bed) |
| Cognitive therapy | Restructure maladaptive beliefs regarding daytime and health consequences of insomnia | Maintain reasonable expectations about sleep; review previous insomnia experiences, challenging perceived catastrophic consequences |
| Relaxation therapy | Reduce physical and psychological arousal in sleep environment | Practice progressive muscle relaxation, breathing exercises, or meditation |
| Sleep hygiene | Reduce behaviors that interfere with sleep drive or increase arousal | Limit caffeine and alcohol, keep bedroom dark and quiet, avoid daytime or evening napping, increase exercise (not close to bedtime), remove bedroom clock from sight |

conditions, CBT had significant effects on time to sleep onset (mean difference [CBT group minus control group], –19 minutes) and time awake after sleep onset (mean difference, –26 minutes), though benefits with regard to total sleep time were small (mean difference, 8 minutes), a finding consistent with the restrictions on overall time spent in bed.[27] The benefits were generally maintained in studies lasting 6 to 12 months. In short-term, randomized trials comparing behavioral treatments with benzodiazepine-receptor agonists (discussed below) in persons with insomnia without coexisting conditions, CBT had less immediate efficacy, but the intervention groups did not differ significantly in time to sleep onset or total sleep time at 4 to 8 weeks,[28] and CBT was superior when assessed 6 to 12 months after treatment discontinuation.[29] A barrier to the implementation of CBT is the lack of providers with expertise in its delivery. This limitation has begun to be addressed by the use of shorter therapies[30] and Internet-based CBT,[31] which have shown efficacy similar to that of longer and face-to-face delivery of CBT. However, sleep hygiene alone (Table 2), which is commonly recommended as an initial approach for insomnia, is not an effective treatment for insomnia.[32]

Adherence to CBT is less than optimal in clinical practice,[33] probably as a result of the extensive behavioral changes required (e.g., reducing time spent in bed and getting out of bed when awake), the delay in efficacy (during which there are often short-term reductions in total sleep time),[34] and pessimism that such approaches can be effective.

### *Pharmacologic Therapy*

Several medications, with differing mechanisms of action, are used to treat insomnia, reflecting the multiple neural systems that regulate sleep (Table 3). Roughly 20% of U.S. adults use a medication for insomnia in a given month,[35] and many others use alcohol for this purpose. Nearly 60% of medication use is with nonprescription sleep aids, primarily antihistamines. In the few existing placebo-controlled trials, however, diphenhydramine had at best modest benefit for either mild intermittent insomnia[36] or insomnia in the elderly[37] and caused daytime sedation and anticholinergic side effects (e.g., constipation and dry mouth) that are particularly problematic in older persons.

#### Benzodiazepine-Receptor Agonists

Benzodiazepine-receptor agonists include agents with a benzodiazepine chemical structure and "nonbenzodiazepines" without this structure. There is little convincing evidence from comparative trials that these two subtypes differ from each other in clinical efficacy or side effects. Because benzodiazepine-receptor agonists vary predominantly in their half-life, the specific choice of drug from this class is usually based on the insomnia symptom (e.g., difficulty initiating sleep vs. difficulty maintaining sleep). FDA approval of these medications is for bedtime use, with the

**Table 3. Medications Commonly Used for Insomnia.**

| Medication | Dose in Adults | | Half-Life | Most Common Side Effects |
|---|---|---|---|---|
| | <65 yr of age | ≥65 yr of age | | |
| | *mg* | | *hr* | |
| Benzodiazepine-receptor agonists | | | | Daytime sedation, ataxia, anterograde amnesia, complex sleep-related behaviors (e.g., sleepwalking) |
| Temazepam (Restoril)* | 7.5–30 | 7.5–15 | 8–10 | |
| Lorazepam (Ativan) | 0.5–2 | 0.5–1 | 8–12 | |
| Eszopiclone (Lunesta)* | 2–3 | 1–2 | 6–9 | Unpleasant taste† |
| Zolpidem (Ambien)* | 5–10 | 2.5–5 | 2.5 | |
| Triazolam (Halcion)* | 0.125–0.5 | 0.125–0.25 | 2.5 | |
| Zaleplon (Sonata)* | 5–20 | 5–10 | 1 | |
| Antidepressants | | | | |
| Trazodone (Desyrel) | 25–100 | 25–100 | 6–8 | Daytime sedation, orthostasis |
| Mirtazapine (Remeron) | 7.5–30 | 7.5–30 | 20–30 | Daytime sedation, anticholinergic effects, weight gain |
| Doxepin (Sinequan, Silenor)* | 10–50 (3–6 approved) | 10–50 | 12–18 | Daytime sedation, anticholinergic effects, weight gain (not at approved doses) |
| Orexin antagonist: suvorexant (Belsomra)* | 10–20 | 10–20 | 9–13 | Daytime sedation |
| Melatonin agonist: ramelteon (Rozerem)* | 8 | 8 | 1 | Daytime sedation |
| Anticonvulsant: gabapentin (Neurontin) | 100–900 | 100–900 | 5–9 | Daytime sedation, dizziness, weight gain |

* The medication has been approved by the Food and Drug Administration (FDA) for the treatment of insomnia. Since 1984, all FDA-approved hypnotic medications have had no limitations on their duration of use.
† This side effect is in addition to the other side effects of benzodiazepine-receptor agonists.

exception of specifically formulated sublingual zolpidem (1.75 mg for women and 3.5 mg for men). Although not FDA-approved or rigorously studied for middle-of-the-night use, short-acting agents (e.g., zolpidem at a dose of 2.5 mg, and zaleplon at a dose of 5 mg) can also be used effectively to promote a return to sleep as long as 4 hours remain before the user plans to get up in the morning. The use of very-long-acting benzodiazepines (e.g., clonazepam, which has a half-life of 40 hours) for uncomplicated insomnia (i.e., in the absence of a daytime anxiety disorder) is not recommended owing to the risk of daytime side effects.

In a meta-analysis of randomized, controlled polysomnographic trials involving patients with chronic insomnia without coexisting conditions, benzodiazepine-receptor agonists showed significant effects on time to sleep onset (mean difference [group receiving benzodiazepine-receptor agonist minus control group], –22 minutes), time awake after sleep onset (mean difference, –13 minutes), and total sleep time (mean difference, 22 minutes).[38] In placebo-controlled trials, persistent self-reported efficacy for insomnia was shown for nightly use of eszopiclone for 6 months[39] and for intermittent use of extended-release zolpidem over a period of 6 months.[40] A randomized, controlled trial involving patients with chronic insomnia showed that as compared with CBT alone, the combination of CBT and a benzodiazepine-receptor agonist was associated with a larger increase in total sleep time at 6 weeks as well as a higher remission rate at 6 months.[29]

Benzodiazepine-receptor agonists have a number of potential acute adverse effects, including daytime sedation, delirium, ataxia, anterograde memory disturbance, and complex sleep-related behaviors (e.g., sleepwalking and sleep-related eating, which are most common with the short-acting agents). As a result, they have been associated with an increase in motor-vehicle accidents[41] and, in the elderly, falls (albeit inconsistently)[42] and fractures. Recent longitudinal research sug-

gests an association of long-term use of benzodiazepines with Alzheimer's disease,[43] but interpretation of these results is complicated by the possibility of confounding by indication, because anxiety and insomnia may be early manifestations of this disorder. Abuse of these agents is uncommon among persons with insomnia,[44] but they should not be prescribed to persons with a history of substance or alcohol dependence or abuse.

Regular reassessment of the benefits and risks of benzodiazepine-receptor agonists is recommended. If discontinuation is indicated, gradual, supervised tapering (e.g., by 25% of the original dose every 2 weeks), in combination with CBT for insomnia, is strongly recommended for chronic users. Roughly one third of patients who used these discontinuation methods had resumed benzodiazepine use by 2 years of follow-up.[45]

### Sedating Antidepressants

The use of sedating antidepressants to treat insomnia takes advantage of the antihistaminergic, anticholinergic, and serotonergic and adrenergic antagonistic activity of these agents. At the low doses commonly used for insomnia, most have little antidepressant or anxiolytic effect. Although data from controlled trials to support its use in insomnia are limited, trazodone is used as a hypnotic agent by roughly 1% of U.S. adults,[35] generally at doses of 25 to 100 mg. Its side effects include morning sedation, orthostatic hypotension (at higher doses), and (in rare cases) priapism. Doxepin, a tricyclic antidepressant, is FDA-approved for the treatment of insomnia at doses of 3 to 6 mg. It has shown significant effects on sleep maintenance (time awake after sleep onset and total sleep time) but no significant benefit for sleep-onset latency beyond 2 days of treatment.[46] Few side effects were observed at these doses. Mirtazapine has antidepressant and anxiolytic efficacy at doses used for insomnia and is a reasonable first option if patients have insomnia coexisting with those disorders, but it may cause substantial weight gain.

### Other Agents

The orexin antagonist suvorexant, which was approved by the FDA in 2014 for the treatment of insomnia, showed decreased time to sleep onset, decreased time awake after sleep onset, and increased total sleep time in short-term randomized trials.[47] At higher doses (30 to 40 mg, which were not approved by the FDA owing to a 10% rate of daytime sedation), suvorexant showed persistent efficacy for these measures after 1 year of nightly use[48]; lower doses have not been studied for more than 12 weeks. Its major side effect at lower doses is morning sleepiness (5% of patients).

Ramelteon is a melatonin-receptor agonist that is FDA-approved for the treatment of insomnia. Short-term studies as well as a controlled 6-month trial showed small-to-moderate benefits for time to sleep onset but no significant improvement in total sleep time or time awake after sleep onset.[49] Side effects were limited to rare next-day sedation. A meta-analysis of trials of melatonin for insomnia (at a wide range of doses and in immediate-release and controlled-release forms) showed small benefits for time to sleep onset and total sleep time.[50] However, the quality control of over-the-counter melatonin products is unclear.

Although controlled clinical trials to support its use are lacking, gabapentin is occasionally used for insomnia, predominantly in patients who have had an inadequate response to other agents, who have a contraindication to benzodiazepine-receptor agonists (e.g., a history of drug or alcohol abuse), or who have neuropathic pain or the restless legs syndrome. Potential side effects include daytime sedation, weight gain, and dizziness.

## AREAS OF UNCERTAINTY

Insomnia is an independent risk factor for depression, cardiovascular disease, and diabetes. Controlled studies are needed to determine whether long-term treatment of insomnia with CBT or medications (or both) can reduce the risk of these disorders.

Both sleeplessness and the pharmacologic therapies used to treat insomnia are associated with complications. In those who do not choose CBT or do not have a response to it, long-term randomized trials comparing benzodiazepine-receptor agonists, sedating antidepressants, and the orexin antagonist suvorexant to inform the choice of medications are lacking.

## GUIDELINES

The American Academy of Sleep Medicine[25] and the National Institutes of Health[51] have published guidelines for the diagnosis and management of insomnia. The recommendations in this

article are generally consistent with those guidelines.

## CONCLUSIONS AND RECOMMENDATIONS

The woman in the vignette has a long history of insomnia, now complicated by nocturia and pain. Recently, owing to her physician's concerns about her benzodiazepine use, she was switched to a low dose of trazodone, but she reports frequent and prolonged awakenings. Attempting to discontinue lorazepam and replacing it with trazodone were reasonable, given the amnestic and psychomotor side effects of benzodiazepines, although data from studies that directly compare these agents are limited. I would strongly recommend a trial of CBT, including (but not limited to) educating her that 7 hours is an adequate amount of sleep, reducing the time from bedtime to final awakening to that amount, and advising her to get in bed only when sleepy and to get out of bed when not sleeping. Over time, these approaches should reduce the duration of nocturnal awakenings, although she should be cautioned initially about an increase in daytime sleepiness. Attention to her nocturia and nocturnal pain will further minimize her nocturnal awakenings and their duration. If these approaches are ineffective, I would consider an increase in the trazodone dose (if this does not cause unacceptable side effects) or a return to lorazepam, informing her of (and regularly reassessing) benefits and potential risks.

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

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