CLINICAL PRACTICE

Chronic 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 author's clinical recommendations.*

A 46-year-old woman has difficulty in falling asleep and staying asleep. The problem started after the birth of her second child 15 years earlier in association with mild postpartum depression. Despite having had no recurrence of depression and no major psychosocial stressors, the patient requires two hours to fall asleep most nights, and on the occasions that she falls asleep rapidly, she wakes at 2 a.m. and cannot reinitiate sleep. Her bedtime is 11 p.m., and she has found that going to bed later does not allow her to fall asleep more easily. She has no symptoms of sleep-disordered breathing or the restless legs syndrome and is otherwise well. How should her case be managed?

THE CLINICAL PROBLEM

Insomnia is defined as difficulty with the initiation, maintenance, duration, or quality of sleep that results in the impairment of daytime functioning, despite adequate opportunity and circumstances for sleep.[1,2] (Difficulty with sleep maintenance implies waking after sleep has been initiated but before a desired wake time.) Most research studies adopt an arbitrary definition of a delay of more than 30 minutes in sleep onset or a sleep efficiency (the ratio of time asleep to time in bed) of less than 85 percent.[1] However, in clinical practice, a patient's subjective judgment of sleep quality and quantity is a more important factor. Transient insomnia lasts less than one week, and short-term insomnia one to four weeks.

Chronic insomnia — insomnia lasting more than one month[3] — has a prevalence of 10 to 15 percent[2,4] and occurs more frequently in women, older adults, and patients with chronic medical and psychiatric disorders.[1] It may follow episodes of acute insomnia in patients who are predisposed to having the condition and may be perpetuated by behavioral and cognitive factors, such as worrying in bed and holding unreasonable expectations of sleep duration.[5] Consequences include fatigue, mood disturbances, problems with interpersonal relationships, occupational difficulties, and a reduced quality of life.

Taking a careful history from the patient and a bed partner, if present, usually allows accurate categorization of the causes of insomnia. Asking the patient to keep a diary documenting times of sleep for one to four weeks may be helpful. Polysomnography is rarely needed unless there is a strong suspicion of sleep-disordered breathing or periodic limb movement disorder or unless insomnia fails to respond to treatment.[6]

Insomnia can be classified as primary or secondary (Table 1).[3] The pathogenesis of primary insomnia is unknown, but available evidence suggests a state of hyperarousal. As compared with controls, patients with insomnia show increased global cerebral glucose metabolism on positron-emission tomography when awake and asleep, increased beta activity and decreased theta and delta activity on electroencephalography during sleep, an increased 24-hour metabolic rate, and higher levels of secretion of adrenocorticotropic hormone and cortisol.[8]

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Insomnia secondary to other causes is more common than primary insomnia (Table 1) and must be excluded or treated before making a diagnosis of primary insomnia. If insomnia persists despite treatment of secondary causes, then therapy for primary insomnia should be instituted. Several causes of the disorder may be present in a single patient. Circadian-rhythm disorders, such as shift-work sleep disorder and delayed-sleep-phase syndrome (a delay in the sleep period of more than two hours relative to conventional times), and voluntary insufficient sleep syndrome should be considered in the differential diagnosis, but these are not considered forms of insomnia.

Table 1. Classification of Adult Insomnia.*

Primary insomnia

Idiopathic insomnia — Insomnia arising in infancy or childhood with a persistent, unremitting course

Psychophysiologic insomnia — Insomnia due to a maladaptive conditioned response in which the patient learns to associate the bed environment with heightened arousal rather than sleep; onset often associated with an event causing acute insomnia, with the sleep disturbance persisting despite resolution of the precipitating factor

Paradoxical insomnia (sleep-state misperception) — Insomnia characterized by a marked mismatch between the patient's description of sleep duration and objective polysomnographic findings

Secondary insomnia

Adjustment insomnia — Insomnia associated with active psychosocial stressors

Inadequate sleep hygiene — Insomnia associated with lifestyle habits that impair sleep

Insomnia due to a psychiatric disorder — Insomnia due to an active psychiatric disorder, such as anxiety or depression

Insomnia due to a medical condition — Insomnia due to a condition such as the restless legs syndrome, chronic pain, nocturnal cough or dyspnea, or hot flashes

Insomnia due to a drug or substance — Insomnia due to consumption or discontinuation of medication, drugs of abuse, alcohol, or caffeine

* Modified from the classification of adult insomnia adopted by the *International Classification of Sleep Disorders*.[7]

STRATEGIES AND EVIDENCE

COGNITIVE BEHAVIORAL THERAPIES

Cognitive behavioral therapies (Table 2) comprise a group of techniques that address the factors that help perpetuate chronic insomnia, regardless of the cause. Stimulus-control therapy assumes that insomnia is a maladaptive response to factors such as bedtime and the bedroom environment (for example, regularly reading or watching television in bed rather than sleeping) and requires a learning process to reassociate the bed with sleep.[9] Sleep-restriction therapy is based on the premise that people with insomnia can learn to increase their sleep time by inducing temporary sleep deprivation through voluntarily reducing their time in bed.[10] Relaxation therapies are predicated on the hypothesis that insomnia is associated with hyperarousal.[1] The cognitive component of such therapies involves the education of the patient about sleep needs, the correction of unrealistic expectations, and a discussion of anxiety and catastrophic thinking, such as exaggerating to oneself the consequences of poor sleep. Sleep-hygiene education addresses extrinsic factors that can perpetuate insomnia, such as noise in the bedroom and the use of caffeine.[11]

Many randomized, controlled trials have demonstrated the efficacy of cognitive behavioral therapies in primary insomnia. Two large meta-analyses[4,12] concluded that, as compared with placebo, such therapies result in improvements in initial sleep-onset latency and total sleep time (by about 30 minutes for each measure, on average) and the number and the duration of awakenings. About 50 percent of patients show meaningful clinical improvement.[13]

Treatment generally combines several approaches. Although data support the efficacy of the various individual components of therapy (with the possible exceptions of sleep-hygiene education and cognitive therapy alone),[1] combined therapies are more effective than individual techniques alone.[14] The mean reported duration of follow-up after completion of cognitive behavioral therapy is six months, with sustained benefits noted in most studies. Few studies of longer than one year have been performed.[1]

In most studies, cognitive behavioral therapy has been administered by psychologists, with an average of six sessions (totaling 5.8 hours) per patient.[1] Meta-analysis suggests that individual therapy is somewhat more effective than group therapy.[4] Trainees in the fields of psychology and psychiatry,[15] community health nurses,[13] and primary care counselors[16] have successfully administered this therapy during four to six sessions of 20 to 50 minutes each. Successful results have also been report-

ed when therapy (consisting of 3 to 10 sessions) was delivered by primary care physicians who had received three hours of training from a psychologist experienced in treating insomnia.[17] A study of abbreviated cognitive behavioral therapy, administered by junior clinical psychologists in two sessions of 25 minutes in duration two weeks apart, showed significant benefit sustained for at least three months.[18] Self-help treatment by means of videotapes[19] or written material[20] has also proved beneficial.

Table 2. Types of Cognitive Behavioral Therapy.

Stimulus-control therapy*
Go to bed only when sleepy
Use the bedroom only for sleeping and sex
Go to another room when unable to sleep in 15 to 20 minutes, read or engage in other quiet activities, and return to bed only when sleepy; repeat if necessary
Have a regular wake time regardless of the duration of sleep
Avoid daytime napping
Sleep-restriction therapy†
Reduce time in bed to estimated total sleep time (minimum, 5 hr)
Increase time in bed by 15 minutes every week when estimated sleep efficiency (ratio of time asleep to time in bed) is at least 90 percent
Relaxation therapy‡
Physical component: progressive muscle relaxation, biofeedback
Mental component: imagery training, meditation, hypnosis
Cognitive therapy‡
Education to alter faulty beliefs and attitudes about sleep, such as that a minimum of 8 hours of sleep a night is required for health
Sleep-hygiene education‡
Correct extrinsic factors affecting sleep, such as environmental disruption (pets or snoring bed partner); bedroom temperature; fixation on the bedside clock; use of alcohol, nicotine, or caffeine; lack of exercise or exercise too close to bedtime

* Descriptions are from Bootzin et al.[9]
† Descriptions are from Spielman et al.[10]
‡ Descriptions are from Hauri.[11]

PHARMACOLOGIC THERAPIES

Classes of prescription medications that are used for the treatment of insomnia include benzodiazepines, benzodiazepine-receptor agonists, and sedating antidepressants. Benzodiazepines that are approved by the Food and Drug Administration (FDA) for use in insomnia include drugs of long, intermediate, and short half-life, whereas approved benzodiazepine-receptor agonists include drugs of intermediate, short, or ultrashort half-life (Table 3). Benzodiazepines act through the benzodiazepine–γ-aminobutyric-acid–receptor complex by affecting chloride flux. Benzodiazepine-receptor agonists bind to the same receptor complex but have different affinities for various receptor subclasses.

Nonprescription products that are marketed for the treatment of insomnia include sedating histamine-1–receptor antagonists (diphenhydramine and doxylamine) and melatonin, but the use of these drugs is not supported by rigorous data. Randomized, controlled trials of the histamine-1–receptor antagonists suggest that they improve sleep subjectively, but conclusions are limited by a small number of subjects, a short duration of drug administration, and a lack of objective measurements; morning sedation is a recognized side effect.[21] Studies of melatonin, which have involved small numbers of subjects treated for short periods with various doses and formulations, have demonstrated conflicting results.[22]

Many randomized trials have shown the efficacy of benzodiazepines and benzodiazepine-receptor agonists in relieving short-term insomnia, but no studies extend beyond six months of use. A meta-analysis of 22 studies of benzodiazepines or the benzodiazepine-receptor agonist zolpidem (Ambien)[23] demonstrated that these medications resulted in significant improvements in sleep latency, total sleep time, number of awakenings, and sleep quality. In a subgroup of nine studies that included relevant data, the average patient receiving medication fell asleep faster than 71 percent of controls, slept longer than 76 percent, woke less often than 74 percent, and reported better-quality sleep than 73 percent. Short-acting agents had the greatest effect on sleep latency, whereas agents with an intermediate or long duration had the greatest effect on total sleep time.

Another meta-analysis of benzodiazepine therapy (including short-, intermediate-, and long-acting agents) confirmed the beneficial effects of this class of drug on total sleep time but did not find a significant effect on sleep latency.[24] Studies of the benzodiazepine-receptor agonist zaleplon (Sonata) have shown a 50 percent reduction of sleep latency as compared with baseline but have had no signifi-

Table 3. Medications for Insomnia Approved by the FDA.

Medication	Duration of Action	Half-Life (hr)†	Dose	Indications	Side Effects	Contraindications or Drug Interactions
Benzodiazepines*						
Temazepam (Restoril)	Intermediate	8–15	7.5–30 mg	Mainly for sleep-maintenance insomnia‡	Drowsiness, dizziness, incoordination	
Estazolam (ProSom)	Intermediate	10–24	0.5–2 mg	Mainly for sleep-maintenance insomnia‡	Drowsiness, dizziness, incoordination	
Triazolam (Halcion)	Short	2–5	0.125–0.25 mg	Mainly for sleep-onset insomnia‡	Amnesia, drowsiness, dizziness, incoordination	Drugs that induce CYP3A4 (including ketoconazole and nefazodone)
Benzodiazepine-receptor agonists*						
Eszopiclone (Lunesta)	Intermediate	5–7	1–3 mg	Mainly for sleep-maintenance insomnia§	Unpleasant taste, dry mouth, drowsiness, dizziness	Drugs that induce CYP3A4 (including ketoconazole and nefazodone)
Zolpidem (Ambien)	Short	3	5–10 mg	Mainly for sleep onset insomnia‡	Drowsiness, dizziness, occasionally amnesia	Possibly drugs that induce CYP3A4¶
Zaleplon (Sonata)	Ultrashort	1	5–20 mg	For sleep-onset or sleep-maintenance insomnia‡‖	Drowsiness	Possibly drugs that induce CYP3A4¶
Melatonin-receptor agonist						
Ramelteon (Rozerem)	Short	2–5	8 mg	Mainly for sleep-onset insomnia	Drowsiness, dizziness, increased prolactin levels	Drugs that induce CYP1A2 (especially fluvoxamine), hepatic failure, pregnancy

* All medications listed here bind to the γ-aminobutyric acid A receptor. All of the agents are contraindicated in pregnancy. They should not be combined with alcohol and should be used only with caution in patients taking other central nervous system depressants. Physicians should consider all factors carefully before prescribing these agents in patients with a history of substance abuse. Flurazepam and quazepam are also approved by the FDA for treatment of insomnia, and clonazepam is sometimes prescribed. However, because of the long half-lives of these drugs, they are generally not recommended. Lower doses should always be used in the elderly, in debilitated patients, and in those with hepatic insufficiency.

† Half-life refers to the drug and its active metabolites.

‡ This drug was approved by the FDA for short-term management of insomnia (generally lasting 7 to 10 days).

§ This drug was approved by the FDA for the treatment of insomnia.

¶ This drug may need to have its dose lowered.

‖ For sleep-maintenance insomnia, this drug is administered on waking during the night.

cant effect on total sleep time — a result that is consistent with the very short half-life of the drug.[25,26] Zaleplon, administered 3.5 hours after lights out with 4 hours more sleep permitted, did not result in any daytime drowsiness or cognitive impairment.[27] A six-month study of eszopiclone (Lunesta), a benzodiazepine-receptor agonist with an intermediate half-life that was recently approved for use in the United States, showed a 50 percent reduction in sleep latency and 65 percent reduction in wake time after the onset of sleep as compared with baseline.[28] Studies with zolpidem have shown that intermittent use (three to five times a week) can also be effective in chronic insomnia, with sustained benefit on nights the drug is taken and sleep that is no worse than baseline on nights without medication.[29,30]

Withdrawal effects, especially rebound insomnia, are rare after the discontinuation of long-duration benzodiazepines and tend to be mild after the discontinuation of intermediate-acting benzodiazepines.[31-33] However, marked rebound insomnia has been reported after the discontinuation of triazolam, a shorter-acting drug,[34,35] usually lasting one to three nights.[35,36] In contrast, withdrawal studies of zolpidem have shown little or no rebound insomnia,[25,27,31,34,35,37] and no rebound insomnia was noted after withdrawal of zaleplon.[25,27] The rate of withdrawal of benzodiazepines should be individualized, depending on the half-life and dose of the drug, the duration of therapy, and whether the insomnia is acute or chronic.[36]

Several cases of anterograde amnesia the day after the use of triazolam have been reported, but the prevalence of this side effect is unknown.[38] Whereas studies have shown variable deficits in memory

following the use of benzodiazepines of varying half-lives,[39] clinically significant amnesia seems largely limited to the short-acting agents. Amnesia, including that associated with sleep-related eating, has been described with the use of zolpidem,[40,41] but far less frequently than with triazolam. The most prominent side effects of long-acting benzodiazepines are daytime sleepiness, dizziness, and incoordination.[33] These effects may also occur with intermediate-acting agents, but less frequently; they are rare with short-acting agents such as triazolam and generally occur only with high doses.[33] Side effects are more frequent in the elderly, and dose reductions are needed. The use of long-acting benzodiazepines has been associated with an increased risk of falls and hip fractures in older patients.[42]

A problem with most studies of these agents is their limited duration. The mean treatment duration of the 22 studies included in the meta-analysis noted above was 12 days (with a maximum of 35 days).[23] Short-term tolerance, measured by deterioration in sleep measures with time, has not been noted with the use of temazepam for 8 weeks, the use of zolpidem continuously for 4 to 5 weeks[25,31,34,37,43] or intermittently for 12 weeks,[30] or the use of zaleplon for 4 to 5 weeks.[25,27] The longest trial, involving six months of treatment with eszopiclone, showed a sustained beneficial effect without development of tolerance.[28]

Sedating antidepressants have been increasingly prescribed for chronic insomnia,[44] despite a paucity of data from randomized trials to support this practice. Small, randomized trials have demonstrated the efficacy of trazodone in treating insomnia in patients with depression.[45,46] A 14-day trial comparing trazodone, zolpidem, and placebo in patients with primary insomnia showed improvement in sleep latency and duration (as assessed by questionnaire) with trazodone as compared with placebo but less effect than with zolpidem.[47] A four-week study of the tricyclic antidepressant doxepin in the treatment of primary insomnia showed significant improvements in sleep latency (21 percent reduction from baseline), sleep efficiency (13 percent increase from baseline), and total sleep time (13 percent increase from baseline).[48] Side effects of tricyclic antidepressants include dry mouth, postural hypotension, drowsiness, cardiac arrhythmias, and weight gain, whereas trazodone can produce hypotension, constipation, and priapism. Mirtazapine, a tetracyclic antidepressant that has adrenergic and serotoninergic antagonist actions, reduces wake time after the onset of sleep, enhances sleep efficiency, and increases the duration of slow-wave sleep in normal subjects,[49] but data are lacking on its effects in primary insomnia.

PHARMACOLOGIC THERAPY VS. COGNITIVE BEHAVIORAL THERAPY

Several randomized, controlled studies have compared cognitive behavioral therapy with pharmacologic therapy and with combined therapy. One study comparing the efficacy of triazolam with cognitive behavioral therapy showed a shorter sleep latency with triazolam at two weeks but equal latencies at four weeks.[50] Another study comparing the efficacy of zolpidem with cognitive behavioral therapy showed that the latter was superior throughout the study.[51] Follow-up at four to six weeks after the discontinuation of medication and the completion of cognitive behavioral therapy showed a sustained benefit only for the cognitive behavioral therapy groups in both studies. A meta-analysis comparing studies of cognitive behavioral therapy with those of hypnotics showed similar short-term outcomes during treatment, except that cognitive behavioral therapy resulted in a greater reduction in sleep latency.[52]

Several studies have compared a combination of cognitive behavioral and drug therapy with cognitive behavioral therapy alone.[43,51,53] All of these reports have shown that at 10 to 24 months of follow-up, improvements are maintained for cognitive behavioral therapy alone but not for combined therapy. The most likely explanation is that patients are less committed to learning and practicing cognitive behavioral therapy techniques if they can control insomnia with medications. In contrast, cognitive behavioral therapy that was instituted while attempting to taper doses of benzodiazepines for patients with long-standing chronic insomnia resulted in a higher percentage of patients who were drug-free, as compared with tapering alone.[54,55]

AREAS OF UNCERTAINTY

Cognitive behavioral therapy has been well established as effective in chronic primary insomnia, but its role in secondary insomnia, especially insomnia as a result of psychiatric disorders, has not been systematically tested. Further studies are needed to demonstrate whether primary care physicians can obtain successful results by teaching behavioral techniques in a small number of sessions compati-

ble with the flow of a busy practice. For patients with chronic primary insomnia who do not benefit adequately from cognitive behavioral therapy, questions remain regarding the role of long-term drug therapy. Although studies of treatment with benzodiazepine-receptor agonists for as long as six months have demonstrated efficacy without evidence of tolerance, it is not known whether these results are sustained over longer periods. Melatonin-receptor agonists have shown benefit in randomized trials.[56,57] Ramelteon (Rozerem) has just received FDA approval, but more published data and clinical experience with the drug will be needed to determine its role in insomnia management.

GUIDELINES FROM PROFESSIONAL SOCIETIES

In 1999, the American Academy of Sleep Medicine published evidence-based practice measures for the nonpharmacologic treatment of chronic insomnia.[58] Stimulus-control therapy, progressive muscle relaxation, biofeedback, sleep-restriction therapy, and multicomponent cognitive behavioral therapy were recommended. Insufficient evidence was available to recommend sleep-hygiene education, imagery training, or cognitive therapy alone as single therapies. A preliminary report of a June 2005 conference on insomnia that was sponsored by the National Institutes of Health (http://consensus.nih.gov/ta/026/InsomniaDraftStatement061505.pdf) notes that both cognitive behavioral therapy and benzodiazepine-receptor agonists are effective in treating insomnia but that the long-term effectiveness of the agonists requires further study.

SUMMARY AND RECOMMENDATIONS

Secondary causes of insomnia must be identified and addressed before a diagnosis of primary insomnia is made. Effective treatment is available for most patients with chronic primary insomnia, such as the patient described in the vignette. Both cognitive behavioral therapy and pharmacologic therapy with benzodiazepines or benzodiazepine-receptor agonists are effective in the short term, but data beyond six months are lacking to support pharmacologic therapies. I would recommend first a course of cognitive behavioral therapy involving stimulus control, relaxation, sleep-hygiene education, or other techniques discussed above. Primary care physicians may refer patients to sleep specialists or psychologists trained in this therapy but may alternatively choose to familiarize themselves with the techniques, given the prevalence of primary insomnia and some data to support that even a few short sessions of therapy delivered by primary physicians can produce significant benefits. Cognitive behavioral therapy should not generally be combined with the use of hypnotic agents, given data suggesting that such an approach reduces the long-term benefit of cognitive behavioral therapy.

Although long-term data are lacking, most sleep specialists recommend long-term use of pharmacologic therapy in a subgroup of patients with chronic primary insomnia who do not respond to cognitive behavioral therapy. Careful monitoring for efficacy, tolerance, and side effects is essential, especially in the elderly. For insomnia that is predominantly associated with the onset of sleep, off-label use of zolpidem or zaleplon should be considered. For insomnia that is predominantly associated with maintenance of sleep, intermediate-acting benzodiazepines such as temazepam can be tried, but these drugs may soon be supplanted by eszopiclone. Zaleplon can also be administered on waking in the latter part of the night. There is little role today for long-acting benzodiazepines in the management of insomnia, unless a coexisting anxiety disorder is present.

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