Diagnosis and Treatment of Chronic Insomnia: A Review

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Objective: **Insomnia has high prevalence rates and is associated with significant personal and socioeconomic burden, yet it remains largely underrecognized and inadequately treated.** ***Methods:*** **A PubMed search for English-language articles covering randomized controlled trials published between 1970 and 2004 was conducted. Search terms used were "insomnia," "behavioral therapy," and the generic names of agents commonly used to treat insomnia (the Food and Drug Administration–approved benzodiazepines and nonbenzodiazepines, trazodone, and over-the-counter agents).** ***Results:*** **Evidence from epidemiologic studies, physician surveys, and clinical studies suggests that numerous patient and physician factors contribute to the fact that the needs of patients with insomnia remain unmet, including low reporting of insomnia by patients, limited physician training, and office-based time constraints, as well as misconceptions about the seriousness of insomnia, the advantages of treatment, and the risks associated with hypnotic use. Nonpharmacologic therapies produce long-lasting and reliable changes among people with chronic insomnia and have minimal side effects. Pharmacologic therapies have proven effective with improving wake time after sleep onset and sleep maintenance and reducing the number of nighttime awakenings. However, pharmacologic therapy has a greater chance of producing side effects. No conclusive evidence exists to favor either pharmacologic therapy or behavioral therapy.** ***Conclusions:*** **Insomnia is particularly challenging for clinicians because of the lack of guidelines and the small number of studies conducted in patient populations with behavioral and pharmacologic therapies. Current treatment options do not address the needs of difficult-to-treat patients with chronic insomnia, such as the elderly, and those with comorbid medical and psychiatric conditions. More research is necessary to determine the long-term effects of insomnia treatments. (*Psychiatric Services* 56:332–343, 2005)**

It is estimated that 10 to 15 percent of the adult population suffers from chronic insomnia; an additional 25 to 35 percent has transient or occasional insomnia (1). Fifty-seven percent of noninstitutionalized elderly persons experience chronic insomnia (2). Despite these high prevalence rates, evidence suggests that insomnia is underrecognized, underdiagnosed, and undertreated (1).

Mental health care professionals frequently treat patients who have insomnia that co-occurs with a psychiatric disorder. A literature review was undertaken to help clinicians better understand the nature of insomnia and the reasons for its underdiagnosis and undertreatment and to provide them with current information about pharmacologic and nonpharmacologic treatments for insomnia.

Methods

A PubMed search for English-language articles published between 1970 and 2004 that reported randomized controlled trials or active comparator trials was conducted. The search terms "insomnia" and "behavioral therapy" were used to search for articles on nonpharmacologic treatments. For articles on pharmacologic treatments the search terms used were "insomnia" and "flurazepam," "quazepam," "estazolam," "temazepam," "triazolam" (Food and Drug Administration [FDA]–approved benzodiazepines), "zolpidem," and "zaleplon" (FDA-approved nonbenzodiazepines), as well as "trazodone" (commonly used for treating insomnia, although not FDA-approved for this purpose) and "diphenhydramine" (also commonly used for treating insomnia).

For nonpharmacologic treatments, a total of 11 papers were identified that discussed cognitive-behavioral, sleep-restriction, and sleep hygiene therapies. In total, 41 studies were identified for approved benzodiazepines. Of these, most were studies in which an active comparator was used and included patients with primary and secondary insomnia. Eight nonbenzodiazepine studies, all of which included a placebo comparison, were identified. Eighteen studies evaluated trazodone's efficacy on sleep endpoints, and in all except two (3,4) of these the sample was limited to patients with depression- or antidepressant-induced insomnia. Six studies evaluated diphenhydramine.

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Results

Barriers to recognition, diagnosis, and treatment

Several factors hinder the appropriate recognition of insomnia and its adequate and appropriate management. They include lack of physician education about insomnia, time-constrained patient visits, beliefs among patients and physicians that sleep complaints are not important, the belief that treatments are not effective or cause more problems, and the lack of research evidence that treating insomnia improves outcomes of comorbid conditions (listed in the box on this page).

Physician training. Most clinicians are not well trained with respect to sleep and sleep disorders. A survey conducted from 1990 to 1991 indicated that 37 percent of medical schools were still failing to include structured sleep medicine sessions in their curricula. On average, less than two hours of total teaching time was allocated to sleep and sleep disorders, and only 11 percent of medical students participated in the clinical evaluation of patients with sleep disorders (5).

Although research in this area is limited, studies have demonstrated that the lack of training in sleep disorders is reflected in knowledge deficits about sleep medicine among primary care physicians (6). In a study that assessed the sleep knowledge of 580 primary care physicians, none rated their knowledge of sleep disorders as excellent; 10 percent rated their knowledge as good, 60 percent as fair, and 30 percent as poor (6).

Office visits. The advent of a managed-care-based clinical environment appears to have contributed to perceptions among clinicians that time spent with patients is too short and that patient load is excessive; these were the findings from a survey of physician assistants, nurse practitioners, and primary care physicians in a large group model health maintenance organization (7). Despite its prevalence, insomnia is rarely discussed in visits to primary care physicians (8–10), and questions about sleep may be swept aside in an effort to save valuable office time. Physicians may avoid exploring problems such as sleep difficulties in order to avoid having to deal with issues that could take up more than the normal allotted time for a patient.

Reporting sleep problems or eliciting a sleep history. Deficits in knowledge about sleep medicine and time constraints both contribute to the reticence among physicians to tackle issues related to sleep. In the World Health Organization's international collaborative study on general health care, attendees in 15 primary care settings in several countries found that physicians detected insomnia in less than 50 percent of patients who had insomnia symptoms (8). A survey by Papp and colleagues (6) found that time spent counseling patients on the benefits of sleep was less than that spent discussing diet or exercise.

Neglect of sleep difficulties appears to partially be the result of reluctance on the parts of both patients and physicians to discuss sleep. Ford and Kamerow (10) found that of those in their cohort who described difficulty sleeping only 9 percent reported the problem to a physician. Shochat and colleagues (9) found that only 30 percent of patients with sleep difficulties seen in primary care clinics had ever spoken with their physicians about a sleep problem; those who did so reported that they—and not their physicians—were the first to raise the subject of sleep difficulties. Almost 36 percent of patients in the chronic insomnia group reported that the physician's recommendation for management was not effective.

Perception of treatments. There is also a reticence among clinicians to treat insomnia on the basis of their misperceptions about the lack of efficacy of existing agents, restrictions on prescribing hypnotic medications, and the perceived risks associated with use of these agents. Historically, studies that have evaluated medications in randomized controlled trials of insomnia lasting more than six weeks are rare; a meta-analysis of studies using benzodiazepines and zolpidem published in 1997 demonstrated that median duration of trials was seven days (11). Until recently, little was known, therefore, about efficacy and safety beyond this duration of treatment, despite the fact that many patients may require longer-term treatment. FDA labeling states, "Hypnotics should generally be limited to seven to ten days of use, and reevaluation of the patient is recommended if they are to be taken for more than two to three weeks. [The drug] should not be prescribed in quantities exceeding a one-month supply" (12). These regulations restrict prescription of hypnotics to short-term treatments and make the chronic prescription of sedative-hypnotics difficult.

FDA labeling was initially directed by the National Institute of Mental Health's (NIMH's) clinical guidelines, which have remained unchanged since they were first published in 1984 (13). These early findings were based on data that suggested the risk of abuse and dependence associated with benzodiazepines, as well as risks of tolerance, withdrawal, and rebound insomnia phenomena (14). It is important to note that these guidelines are now considered obsolete by the National Institutes of Health (NIH). In referring to the 1984 guidelines, the NIH Web site now states, "This statement is outdated and is no longer

Barriers to recognition and treatment of insomnia

Inadequate physician training in insomnia
Time-constrained physician office visits
Lack of discussion about sleep problems during patient consultations
Belief among patients and physicians that sleep complaints are not important
Perception by physicians that treatments for insomnia are ineffective or associated with risks
Lack of evidence that treating insomnia improves outcomes of comorbid conditions

viewed by NIH as guidance for medical practice," which highlights the lack of guidance and direction for the physician treating patients with insomnia (15). These concerns about the risks of benzodiazepines have likely persisted and have even been transferred to newer agents.

Physicians may not be aware of behavioral techniques for treating insomnia, are generally not trained to perform them, and may not have sufficient time with patients to provide these treatments. Furthermore, because of the paucity of therapists trained in behavioral treatments for sleep disorders, most physicians cannot easily refer patients for needed therapy.

Lack of evidence that treatment improves outcomes. Although insomnia is associated with substantial personal and societal impact, no prospective studies have been done to demonstrate that treating insomnia significantly improves outcomes of its associated comorbid conditions. Walsh and Ustun (16) estimated total direct annual cost in the United States attributable to insomnia, including prescription and nonprescription medications, outpatient visits to health care professionals, and inpatient or nursing home care, to be approximately $12 billion for health care services and $2 billion for sleep-promoting agents. The impact of treatment of insomnia on this substantial financial burden is unknown, as is the impact of improving insomnia on other negative correlates.

People with insomnia report more days of limited activity, more days in bed due to illness, greater health care costs, and a higher incidence of moderate-to-severe occupational role disability than people without insomnia (17). Insomnia is also associated with greater health care utilization (17).

Evidence also suggests that insomnia may lead to the development of depression (18). Insomnia is also associated with an increased risk of suicide in depression (19) and resistance to cognitive-behavioral therapy (20). Finally, the strongest evidence for a causal relationship between insomnia and subsequent illness is in bipolar disorder, where sleep loss has been demonstrated to precipitate or exacerbate episodes of mania (21).

It is important to note that correlations between insomnia and comorbid illnesses, as well their outcomes, do not necessarily imply causality. The lack of data demonstrating that insomnia has an impact on other illnesses and that treating insomnia improves outcomes in other illnesses is an inherent problem in the field of insomnia research, and more studies need to be conducted in this area. Although some physicians may have observed that treating secondary insomnia benefits patients, there is limited evidence that treating insomnia actually improves outcomes in comorbid illness (22), and this may be another factor in clinicians' reluctance to recognize or treat insomnia.

What is insomnia?

The nature of insomnia itself probably contributes to the difficulties associated with its treatment. Polysomnographic studies of patients with insomnia generally show abnormalities such as prolonged latency to sleep onset, frequent arousals, and reduced amounts of total sleep. However, objective measures of sleep do not always correlate well with the patient's experience of insomnia (23), which may be partially due to the fact that the function of sleep itself is still unknown, making it difficult to pinpoint which objective sleep abnormalities contribute to the clinical entity of insomnia. There is a tendency to assume that insomnia is a problem of insufficient amount of sleep. Yet epidemiologic studies consistently demonstrate the lowest mortality rates for people who sleep an average of seven hours per night, with increasing risks for individuals who sleep eight or more hours per night (24). Furthermore, sleep deprivation does not mimic the effects of insomnia; together, these data suggest that a decreased quantity of sleep alone does not constitute insomnia (22). From a qualitative standpoint, however, data suggest that people with insomnia show increased levels of arousal, evidenced by markers such as increased, higher-frequency electroencephalographic (EEG) activity during sleep and increased metabolism (25–27), but it is not known whether this hyperarousal leads to nonrestorative sleep.

Therefore, it is not surprising that polysomnographic assessments of drugs used to treat insomnia, although perhaps helpful for determining differences between drugs, may not reflect the patient's subjective experience of those drugs, but the ideal would be demonstrating efficacy by both polysomnography and patient report. It is thus important for the clinician to recognize that insomnia, as defined by the *DSM-IV,* text revision (*DSM-IV-TR*) (28), is a subjective clinical diagnosis, and therefore a patient's subjective report of sleep difficulties should direct management in most cases. Questions about the range of symptoms experienced and how they have altered over time are important. Because insomnia is a patient-reported symptom, rather than a polysomnographically defined disorder, referral to a sleep laboratory for polysomnographic diagnosis should be reserved for cases in which another primary sleep disorder, such as obstructive sleep apnea or periodic movement disorder, is suspected, because these may require greater expertise in sleep medicine.

The *DSM-IV-TR* defines insomnia as "difficulty in initiating or maintaining sleep or . . . nonrestorative sleep" and as "causing clinically significant distress or impairment in social, occupational, or other important areas of functioning" (see the box on the next page) (28). As such, all these elements should be considered when diagnosing and treating insomnia. The definition of sleep maintenance remains fairly controversial, but it essentially describes the patient's capacity to remain asleep throughout the night and reflects an assessment of sleep quality. Arousals can be both objectively measured and subjectively reported. Problems with sleep maintenance may consist of longer periods of arousal, which patients are generally aware of, or sleep fragmentation with brief EEG arousals (29), which patients may not be aware of but that still result in the perception of nonrestorative sleep. Currently used metrics include wake time after sleep onset, wake time during sleep onset, and number of awakenings.

Ideally, treatment of insomnia should address components of sleep onset, sleep maintenance, sleep quality, and improvement in next-day functioning.

Symptom instability

Although symptoms of insomnia have been divided into categories of sleep onset, sleep maintenance, and nonrestorative sleep, symptom-specific classification may not always be useful clinically given that there is evidence of instability of insomnia symptoms over time for individual patients. A study of more than 2,500 general practice clinic attendees demonstrated that over a four-month period the nature of sleep complaints of sufferers of insomnia changed, so that only half of those who initially complained of sleep-onset problems continued to do so. The remaining half developed new sleep symptoms, among them sleep-maintenance problems (30).

Difficult-to-treat patients

As noted, long-term prescription of medications for insomnia lacks an evidence base, has been discouraged by existing guidelines, and is a concern among physicians (13). As shown below, no medications are available that treat sleep maintenance symptoms without the risk of next-day impairment. Chronic insomnia, including sleep maintenance problems, occurs more commonly among the elderly (31), depressed patients (32), and medically ill populations (33,34), including those with chronic pain syndromes (34). These patients are often viewed as difficult to treat yet are among the groups that have the greatest need for treatment.

Psychiatric disorders. Insomnia is a very common feature of psychiatric disorders (33). Prevalence rates of insomnia are greatly increased among persons with psychiatric illnesses. A European epidemiologic sample of 1,536 people found that significant insomnia was present in 71 percent, 69 percent, 61 percent, and 32 percent of those with dementia, depressive disorders, anxiety disorders, and alcoholism, respectively (35). Furthermore, on the basis of epidemiologic studies, up to 40 percent of adults in the general population with insomnia have a diagnosable psychiatric disorder (10). Associations between insomnia and psychiatric disorders, particularly depression, are even higher in clinical samples. Approximately three-quarters of patients with insomnia presenting to sleep clinics or primary medical clinics meet diagnostic criteria for psychiatric disorders (36). Overall, insomnia is more strongly associated with depression than it is with any other medical disorder in the primary care setting (37). Symptoms of anxiety and depression were also strongly associated among children with insomnia in a pediatric clinic sample (38).

Psychiatric patients present multiple and varied sleep symptoms. Sleep EEG studies demonstrate significant decrements in sleep continuity—prolonged sleep latency, decreased sleep efficiency, and decreased total sleep across the night—in most groups of psychiatric patients compared with control patients without psychiatric disorders (32,39) (Table 1).

The best-studied comorbid psychiatric condition of insomnia is depression. Objective measures demonstrate loss of slow-wave (stage 3 and 4) sleep, frequent nocturnal awakenings, and frequent arousals, all of which may lead to the perception of nonrestorative sleep (32,39). Many of these symptoms are consistent with sleep maintenance problems. There is also evidence of disturbed rapid eye movement (REM) sleep architecture in mood disorders, with a reduced latency from sleep onset to REM sleep onset and an increased proportion of REM sleep (39). Also, insomnia associated with psychiatric conditions frequently lasts for the duration of the illness, and, more important, sleep symptoms have been found to persist despite remission of depression (40).

Medical disorders. Individuals with insomnia have higher rates of medical illnesses than those without sleep problems. Mellinger and col-

DSM-IV, Text Revision *criteria for primary insomnia*

Difficulty initiating or maintaining sleep or nonrestorative sleep
Causing clinically significant distress or impairment in social, occupational, or other important areas of functioning
Not occurring exclusively during the course of another sleep disorder
Not occurring exclusively during the course of a mental disorder
Not due to the direct physiological effects of a substance or a general medical condition

Table 1

Sleep characteristics of patients with psychiatric disorders versus control patients[a]

Disorder	Sleep continuity	Percentage of slow-wave sleep	REM[b] latency	Percentage of REM sleep
Affective disorder	Consistently decreased	Consistently decreased	Consistently decreased	Consistently increased
Anxiety	Consistently decreased	No change	No change	No change
Schizophrenia	Consistently decreased	No change	Decreased in some studies	No change
Eating disorder	Decreased in some studies	No change	Decreased in some studies	No change
Alcoholism	Consistently decreased	Consistently decreased	No change	Increased in some studies
Insomnia	Consistently decreased	Consistently decreased	No change	No change

[a] Data from meta-analysis by Benca and associates (39)
[b] Rapid eye movement

leagues (33) determined that 53 percent of adults with serious insomnia had two or more health problems, compared with only 24 percent of those with no sleep difficulties. In addition, Ford and Kamerow's study (10) found that patients with insomnia used general medical services more frequently, and higher rates of insomnia have been documented among primary care patients than in the general population (9). There is also evidence that greater severity of sleep disturbance is correlated with worse outcomes among patients who experience pain (34), that among patients with pain insomnia is correlated with the development of depression (34), and that the presence of both depression and insomnia contributes to highest pain severity (41).

Insomnia is also correlated with worse outcomes in a number of medical illnesses, including an increased risk of mortality among institutionalized elderly people (42), greater disability among stroke patients (43), and increased risk of mortality among patients with cardiovascular disease (44).

Elderly patients. Older patients often complain that their sleep is nonrestorative and that they have difficulty staying asleep (31). Foley and colleagues (2) found that 30 percent of elderly patients complained of awakening during the night, 19 percent complained of waking up too early, and 19 percent said they had trouble falling asleep. Polysomnographic findings have also suggested that the primary change in the sleep of older adults is an inability to sustain sleep through the night (45). These findings also suggest that daytime sleepiness among healthy elderly patients without insomnia does not correlate with total sleep time or any sleep stage but is significantly correlated with measures of sleep fragmentation (46).

Nonpharmacologic management approaches

An American Academy of Sleep Medicine task force reviewed 48 clinical trials and two meta-analyses in an attempt to develop practice guidelines for nondrug alternatives for managing primary chronic insomnia (47). Its findings indicated that nonpharmacologic therapies produce reliable and long-lasting changes in chronic insomnia sufferers for several sleep parameters. Seventy to 80 percent of patients treated with nonpharmacologic interventions were found to benefit from treatment; however, there was significant variability in the magnitude of treatment response. Stimulus control, progressive muscle relaxation, and paradoxical intention all met the American Psychological Association's criteria for empirically supported psychological treatments for insomnia, and sleep restriction, biofeedback, and multifaceted cognitive-behavioral therapy (CBT) were viewed as "probably efficacious" treatments (47).

Evidence for favoring pharmacologic therapy over behavioral therapy or vice versa was inconclusive (48). Comparisons of hypnotic and behavioral therapies suggested that hypnotic drugs produce more rapid improvements in sleep in comparison with behavioral treatments such as relaxation and sleep hygiene education (48) and that treatment effects over longer periods (four to eight weeks) are similar for pharmacologic and nonpharmacologic therapies, as well as the combination of the two (49). On the other hand, longer-term outcome studies, such as those of six to 24 months, have indicated that clinical benefit is not as well maintained over time after discontinuation of pharmacologic treatment as it is after cessation of behavioral therapy (48,49). Patients who have received combined treatments do not appear to have as good a long-term outcome as those who receive behavioral therapy alone (50), although reasons for this finding have not been clearly elucidated (47).

A recent randomized controlled study compared CBT, zolpidem, and the combination of the two therapies among 63 patients with sleep-onset insomnia and impaired daytime functioning (51). Participants received four weeks of active treatment with 10 mg of zolpidem, followed by 5 mg of zolpidem nightly for one week, and then 5 mg of zolpidem every second night for one week. CBT of 30 minutes per each session was offered weekly for three weeks, with the final session two weeks later. CBT was the most effective intervention in this study in reducing both subjective and objective sleep onset latency after termination of treatment, either alone or combined with pharmacotherapy followed by combination therapy, whereas effects of pharmacotherapy persisted only during acute administration. However, subjectively reported total sleep time showed similar increases after termination of treatment in both the CBT and zolpidem groups; the second largest increase was in the combination therapy group. No between-group differences were found for objective measures. Although these data support the superior efficacy of behavioral treatment over pharmacotherapy, interpretation may be limited by the small samples, the absence of sleep maintenance insomnia or comorbid conditions among these patients, and the failure to assess the effects of treatment on daytime function. More research in larger patient populations is needed to clarify the relative efficacies of the different treatments for insomnia.

Clearly, efficacy coupled with minimal side effects makes behavioral techniques highly recommended for treating insomnia; however, factors such as cost, lack of availability, and potential problems with patient motivation and compliance may make the use of behavioral techniques difficult. Optimal patient- and treatment-related variables have not been clearly defined (47). A meta-analysis of 59 studies assessing nonpharmacologic treatment of chronic insomnia found that an average of five hours of therapy was provided (52). The results suggested that stimulus control and sleep restriction techniques were most helpful in producing improvements over an average six-month follow-up period, but sleep hygiene treatment alone was not deemed effective.

Most studies have been conducted with highly trained therapists such as psychologists, who may not be available to a primary care physician's office, and evidence indicates that a lower level of training—a trainee therapist, for example—is associated with worse outcomes (47). However, several recent studies have suggested that more limited interventions may be helpful to patients with insomnia. CBT was equally helpful when administered in individual, face-to-face

treatment, in group therapy sessions, or through brief telephone contact (53). In another study, two sessions of CBT led to greater improvement for people with chronic primary insomnia than two sessions of generic sleep hygiene education (54). More research is required to determine the optimal behavioral treatment interventions for insomnia in the primary care setting.

Although sleep hygiene techniques alone do not necessarily lead to consistent improvement in insomnia (55), they are usually a part of most behavioral treatments for insomnia. Sleep hygiene recommendations are listed in the box on this page, and treatments recommended by the American Academy of Sleep Medicine for the nonpharmacological treatment of insomnia are described in Table 2.

Sleep hygiene rules

Wake up at the same time every day, regardless of when you went to sleep.
Maintain a consistent bedtime.
Exercise regularly, preferably in the late afternoon, but not within two to four hours of bedtime.
Perform relaxing activities before bed.
Keep your bedroom quiet and cool (extreme temperatures compromise sleep).
Do not watch the clock at night.
Avoid caffeine and nicotine for at least six hours before bedtime.
Drink alcohol only in moderation and avoid use for at least four hours before bedtime.
Avoid napping; it may interfere with the ability to fall asleep at night.

Pharmacologic treatment approaches

As discussed above, insomnia symptoms tend to change over time. In addition, a survey of a general population sample has shown that a majority of patients with both transient and chronic insomnia have sleep-maintenance problems (56). In recent years attempts have been made to characterize the ideal hypnotic agent (57,58). Attributes proposed for an ideal agent include rapid onset of action and elimination; improved ability to initiate and maintain sleep; improved sleep quality; normal sleep architecture; improved daytime performance and well-being with minimal drug interactions; the absence of hangover effects or unwanted side effects; and no significant potential for tolerance, abuse, dependence, withdrawal, or rebound effects.

Until the advent of the nonbenzodiazepine hypnotics, the most commonly used agents were benzodiazepines. Aside from triazolam, most benzodiazepine hypnotics, which include flurazepam, estazolam, quazepam, and temazepam, have long half-lives, which contribute to their efficacy in maintaining sleep throughout the night but also may result in next-day impairments (59,60). The advent of shorter-acting triazolam and the nonbenzodiazepines zolpidem and zaleplon has resulted in more effective sleep-onset agents with minimal next-day residual effects but possibly with decreased efficacy as sleep-maintaining agents (61–64).

In addition, no currently approved insomnia agents have been evaluated for treating chronic insomnia, as evidenced by the fact that randomized controlled studies of zolpidem, zaleplon, and approved benzodiazepines have not exceeded four weeks for zaleplon (62,64), five weeks for zolpidem (63), or 12 weeks for temazepam (65) of continuous use. Although it is currently unknown what duration of continued efficacy would need to be demonstrated in order to support long-term use of an agent for treating insomnia, there is a clear need to demonstrate efficacy of medications over longer periods.

Benzodiazepines. Currently approved benzodiazepines for the treatment of insomnia are flurazepam, triazolam, quazepam, estazolam, and temazepam. Both subjective and objective studies have generally found improvements in sleep maintenance measures, specifically wake time after sleep onset and number of awakenings, with the longer-acting agents like flurazepam, quazepam, and estazolam (66–70). Their use, however, is also associated with next-day sedation and impaired cognitive and psychomotor function (71). Triazolam's efficacy with regard to measures of sleep maintenance is less evident, probably because of its shorter half-life (72,73).

Temazepam is the most commonly used benzodiazepine hypnotic (74). Objective sleep laboratory data regarding the ability of temazepam to improve sleep maintenance as defined by number of awakenings during sleep have been equivocal. Two objective studies did not find significant reductions in number of awakenings with doses of 15 mg to 30 mg of temazepam (72,75). Another study (76) of 48 people with insomnia did show a significant improvement compared with placebo for 15 mg and 30 mg of temazepam on number of awakenings, although significant reductions were seen at only one of the two sites used for the study. Temazepam may also be associated with the development of tolerance (77). Although adverse events associated with use of temazepam have not been explored to the same extent as those of other benzodiazepines, benzodiazepine use in general has been associated with daytime drowsiness (71), memory impairment (71), psychomotor impairment (71), and risk of tolerance, abuse, and dependence (72). Temazepam itself has been implicated in causing next-day sedation (78) and impairment in memory and cognition (78) and has demonstrated evidence of rebound insomnia on withdrawal and dependence liability (72). Triazolam has also been implicated in causing rebound insomnia (79).

Currently available nonbenzodiazepine hypnotics. Evidence for the utility of currently available nonbenzodiazepine hypnotics points to their primary efficacy as sleep-onset, rather than as sleep-maintenance,

Table 2

Recommended behavioral therapies for insomnia

Level of recommendation	Therapy	Description
Empirically supported treatments[a]	Stimulus control	The main objective is to reassociate the bed and bedroom with the rapid onset of sleep.
		Instructions: Go to bed only when sleepy; use the bed and bedroom only for sleep; leave bed and go into another room when unable to fall asleep or return to sleep easily; return to bed only when sleepy again; maintain a regular morning rising time regardless of duration of sleep the previous night; avoid daytime naps.
	Progressive muscle relaxation	This method is based on the idea that mental relaxation will be a natural outcome of physical relaxation—it is a deep-relaxation technique.
		Instructions: Tense or tighten one muscle group at a time, then release tension; muscle groups are tightened and relaxed one at a time in a specific order; a greater degree of muscle tension is attempted in subsequent exercises as patient becomes familiar with the technique.
	Paradoxical intention	Based on the concept that performance anxiety contributes to preventing proper sleep: persuade the patient to engage in the most feared behavior (that is, staying awake); as the patient stops trying to fall asleep, the performance anxiety related to attempting to fall asleep is reduced.
Probably efficacious treatments[b]	Sleep restriction	The objective is to reduce time in bed to lower the chance of fragmented and poor-quality sleep.
		Instructions: Reduce amount of time spent in bed to increase the percentage of time spent asleep—improves patient's sleep efficiency (time asleep/time in bed); time allowed in bed per night is increased by 15 to 30 minutes as sleep efficiency improves; adjustments are made over a period of weeks until optimal sleep duration is achieved—best to alter bedtime and maintain constant rising time to maintain a regular sleep-wake rhythm; to minimize daytime sleepiness, time in bed should not be reduced to fewer than five hours per night. Creates a mild state of sleep deprivation, to promote more rapid sleep onset and more efficient sleep.
	Biofeedback	Therapeutic technique that teaches patients how to facilitate increased slow brain wave activity (and thus facilitate falling asleep) by using electroencephalographic (EEG) monitoring. Eventually the patient is able to apply this skill without the use of the EEG.
	Multifaceted cognitive behavioral therapy	The goal is to identify dysfunctional beliefs and attitudes about sleep and replace them with more adaptive substitutes.
		Treatment targets: Unrealistic sleep expectations ("I must get eight hours of sleep per night"); misconceptions regarding causes of insomnia ("My insomnia is due to a chemical imbalance"); amplification of consequences of insomnia ("I can do nothing after a bad night's sleep"); performance anxiety due to excessive attempts at controlling the sleep process.

[a] According to the American Psychiatric Association

[b] Supported by the American Psychiatric Association

agents. Once again, longer-term randomized, double-blind, controlled studies that demonstrate efficacy of these agents have not been performed, but safety over the longer term has been demonstrated in open-label studies (80,81), with minimal evidence of rebound phenomena. By comparison with benzodiazepines, there has been less evidence of subjective and objective next-day residual effects associated with zolpidem (4,63,82) or subjective next-day impairment with zaleplon, even when the latter has been delivered in the middle of the night (83).

Fewer clinically important drug-drug interactions appear to occur with zaleplon and zolpidem than with benzodiazepines (84), which may be related to the differences in CYP metabolism. Whereas triazolam, for example, is biotransformed almost entirely via CYP3A4, the newer agents are biotransformed by CYP3A4 and several other CYP isozymes, which means that CYP3A4 inhibitors and in-

ducers may have less effect on their biotransformation. On the other hand, because these agents are newer, only a few studies have been conducted (84), and further research is needed.

Zolpidem. Zolpidem is an effective sleep-onset agent and has consistently demonstrated reduced time to sleep onset. It was the most commonly prescribed agent for insomnia in 2001 (74) despite the absence of studies of nightly use for longer than five weeks (63). One (63) of the two (63,85) objective studies of zolpidem efficacy in primary insomnia demonstrated significantly improved sleep efficiency; however, neither demonstrated improvement over placebo in reducing wake time after sleep onset or number of awakenings (63,85). Another study, conducted with 15 patients with nonorganic insomnia related to neurotic or stress-related disorders, indicated that, although total sleep time improved significantly with 10 mg of zolpidem versus placebo, there were no statistically significant differences in wake time during the sleep period or number of awakenings (86). These studies (63,86) suggest that zolpidem's efficacy in improving sleep efficiency may be related more to its efficacy as a sleep onset agent rather than a sleep maintenance agent. Subjective studies of zolpidem versus placebo have not consistently demonstrated significant improvement in sleep maintenance parameters, such as wake time after sleep onset and number of awakenings (4,82).

Although next-day benefits with zolpidem use have not been clearly evaluated or demonstrated (86,87), a study by Saletu-Zyhlarz (86) indicated that there was significant improvement in somatic complaints versus placebo. All other tests of psychomotor function, attention, and memory, as well as subjective reports of well-being, showed no difference compared with placebo. One retrospective case-control study found that use of zolpidem by older people was associated with nearly twice the risk of hip fracture (88), although evidence generally points to the fact that longer-acting agents are more likely to be associated with falls and hip fractures (89). The relationship between hypnotic use and falls is complicated by the fact that sleep problems among elderly people are independently associated with an increased risk of falls (90). Hallucinatory phenomena and other sensory distortions have been reported even with therapeutic doses of zolpidem (91). Possibly because of its limited efficacy for sleep maintenance problems, patients may take higher than recommended doses or take a second dose during the night, which may increase the risk of both acute side effects and next-day residual effects (83).

Zaleplon. Zaleplon is a nonbenzodiazepine of the pyrazolopyrimidine class with a very short elimination half-life of about one hour (62). Several studies have demonstrated that zaleplon is effective in reducing latency-to-sleep-onset insomnia in randomized, controlled, double-blind subjective studies (62,64). It is associated with a minimum of next-day side effects or residual sedation, making it a useful agent for sleep-onset problems (92). However, there are minimal data to support zaleplon's sleep-maintenance efficacy throughout the night when given at sleep onset. In double-blind, placebo-controlled studies, doses of less than 20 mg did not result in significant increases in subjectively assessed total sleep time (62,64). Whereas most clinically significant changes, such as reduced sleep latency and increased sleep duration and sleep quality, were seen at the 20 mg dose in studies by Elie and associates (62) and Fry and colleagues (64), the recommended dose of 10 mg did not result in increased sleep duration. Only in the Fry study (64) did 20 mg of zaleplon improve number of awakenings (wake time after sleep onset was not measured), whereas the 10 mg dose had no effect on number of awakenings, suggesting that higher dosing may be necessary for some patients. At present, however, little is known about side effects associated with use of the 20 mg dose.

Trazodone. Despite limited evidence for its efficacy, questions about its side effect profile, and no FDA approval for use as a hypnotic, trazodone is one of the two most commonly prescribed agents for insomnia (the other being zolpidem) (74). Trazodone's precise mechanisms of action have not been determined; it is believed to be a weak but specific inhibitor of synaptosomal reuptake of serotonin, and its therapeutic effects may also be based on the serotonergic 5-HT_{1a}, 5-HT_{1c}, and 5-H_2 receptors (93). As an antidepressant, trazodone has the advantages of low cost, no restrictions on long-term prescription, and a low abuse potential compared with benzodiazepine receptor agonists (94). However, the risk of side effects associated with trazodone is not trivial and includes orthostatic hypotension and blurred vision (95), which increase the risk of falls, especially among elderly patients. Symptoms such as nausea, dry mouth, constipation, drowsiness, headache, and other central nervous system effects also increase morbidity (95,96). Priapism is a rare side effect of trazodone, not associated with use of benzodiazepine receptor agonists, and its occurrence is considered a urological emergency (97).

Given these drawbacks, it is important to ask how effective trazodone is with respect to insomnia in general and sleep maintenance in particular. Surprisingly, considering the drug's popularity, there is a paucity of data supporting its use for insomnia, especially in primary insomnia populations, because trazodone studies have usually been conducted among depressed patients (98) and have utilized small samples ($N \leq 22$) (98). Objective studies have not exceeded eight weeks (99). Two (3,98) of the three studies (3,98,100) that objectively measured waking time after sleep onset did not show benefit. This finding was also reflected in studies that used subjective measures (101, 102). Although trazodone showed statistically significant subjective improvements from baseline in ease of falling asleep and quality of sleep, it was also associated with negative effects in terms of ease of awakening and feelings at or after wakening, relative to baseline. This finding suggests that the improvements in sleep onset and quality may be counterbal-

anced by negative next-day effects. Studies have also demonstrated evidence of declining efficacy after one to two weeks of treatment, suggesting the possible development of tolerance (3,4). Trazodone has also been associated with rebound insomnia after withdrawal (3).

Over-the-counter medications. Sedating antihistamines are frequently used as sleep aids (103), possibly because of their perceived safety and low cost. A 2002 National Sleep Foundation poll of 1,000 people found that 24 percent of those who reported sleep difficulties used over-the-counter or store-bought sleep aids; 5 percent of those who used over-the-counter drugs reported use every night or a few nights a week (104). Diphenhydramine, the most widely used over-the-counter antihistamine sleep aid, appears to be superior to placebo in several double-blind, placebo-controlled studies (105,106), although neither of these studies used objective polysomnographic measurements. Most studies were of very short duration and involved patients with mild-to-moderate insomnia. No recent controlled studies demonstrate efficacy of diphenhydramine for longer than three weeks for objectively determined measures of sleep maintenance. Diphenhydramine also appears to produce tolerance to its sleep-inducing effects within a few days (107). Moreover, over-the-counter antihistamines have substantial neurocognitive effects, including next-day sedation (105) and impaired psychomotor and cognitive function (108,109).

The potential for diphenhydramine-related toxicity and drug-drug interactions is substantial (110). Side effects include urinary retention and blurred vision (111); orthostatic hypotension, dizziness, and palpitations (105,111); increased liver enzymes (105,106); and drowsiness, dizziness, grogginess, and tiredness (105). The available evidence suggests that diphenhydramine and related over-the-counter antihistamines do not represent a viable treatment strategy for long-term sleep maintenance in chronic insomnia.

Evidence-based research and the difficult-to-treat patient

Little work has been done to evaluate the use of hypnotic agents for patients with comorbid psychiatric or medical conditions, although one study demonstrated improvement in total sleep time, daytime sleepiness, and morning stiffness among patients with rheumatoid arthritis who were treated with triazolam (112).

Only one study has evaluated adjunctive hypnotic therapy for patients successfully treated for depression who had residual insomnia. Zolpidem as an adjunct to a selective serotonin reuptake inhibitor was associated with longer sleep times, greater sleep quality, and reduced number of awakenings than was a selective serotonin reuptake inhibitor and placebo over four weeks (113). As noted, trazodone has been investigated as an adjunctive therapy in antidepressant-induced insomnia and was shown to decrease the number of nocturnal awakenings in a one-week study (114); it improved overall sleep better than placebo in another small study (115). There is also evidence that among patients with bipolar disorder, manic episodes resolve more quickly for patients who sleep more (116), although randomized, controlled trials assessing hypnotic therapy are yet to be conducted. Evidence shows that behavioral therapy is as effective for patients with secondary insomnia as it is for those with primary insomnia (117–119).

Discussion

Recent developments in pharmacologic therapy have yielded promising new agents that may be effective for sleep maintenance, as evidenced in clinical trials of patients with insomnia. Eszopiclone is a novel nonbenzodiazepine (cyclopyrrolone) agent with a half-life of five to six hours (120). A recently published study demonstrated that 3 mg of eszopiclone was effective in improving patient-reported sleep and next-day function in patients with chronic insomnia (121). The study was a randomized, double-blind, placebo-controlled design evaluating nightly treatment for six months among 788 patients with chronic insomnia. In this study, after the first week and at the end of six months of treatment, 3 mg of eszopiclone significantly reduced time to sleep onset and improved measures of sleep maintenance, including wake time after sleep onset and number of awakenings. Sleep quality was also improved. Furthermore, patients reported significant subjective improvements in daytime alertness, sense of well-being, and daytime ability to function. No evidence was found of clinically significant tolerance or residual, next-day effects. This study is the first long-term, placebo-controlled evaluation that was conducted with any hypnotic that evaluated the effect of treatment on both sleep and next-day functioning, and it is notable that the findings demonstrated significant improvements in all four components of the *DSM-IV-TR* definition of primary insomnia. Polysomnographic data were not obtained, however, and longer-term conclusions about drug-seeking behavior and discontinuation effects could not be drawn from this study (121). The six-month findings were replicated in another six-week, double-blind, randomized, placebo-controlled, polysomnographic study, in which efficacy was demonstrated by using both subjective and objective sleep measures, which were well correlated (122). Eszopiclone received FDA approval for sleep onset and sleep maintenance insomnia in late 2004.

Another new agent is indiplon, a nonbenzodiazepine GABAA modulator. In a-yet-to-be-published study of elderly patients (123), modified-release indiplon, at doses of 20 mg, 30 mg, and 35 mg, was reported to significantly improve objective polysomnographic measures of sleep maintenance (wake time after sleep onset and number of awakenings) and sleep-onset latency compared with placebo over two nights of active treatment in a group of patients selected for their sleep maintenance difficulties (elevated amount of waking time after sleep onset). Subjective measures of sleep were also significantly improved. Because the second eszopiclone and indiplon studies have been reported only in

abstract form and have not yet been published, it is difficult to assess these studies fully.

Conclusions

There are numerous barriers to the appropriate recognition, diagnosis, and treatment of insomnia, despite the fact that it is highly prevalent and associated with a number of adverse personal and socioeconomic consequences.

Behavioral therapies, which are at least as effective as pharmacologic therapies and appear to have longer-lasting efficacy after cessation, should always be offered to patients complaining of insomnia, either alone or in combination with pharmacologic therapy.

Commonly prescribed newer hypnotic medications demonstrate sleep-onset efficacy but limited sleep-maintenance efficacy, and older agents, although effective at maintaining sleep, may produce substantial next-day residual effects. In addition, data for efficacy and safety of any agents in long-term use are limited. Trazodone is also commonly prescribed as a sleep agent; however, evidence for its efficacy is limited, and its next-day effects and side effects are significant.

Patients who suffer from longer-term insomnia and have predominantly sleep-maintenance problems, such as those with psychiatric or medical illnesses, are particularly challenging for clinicians, because little research has been conducted in these patient populations with either behavioral therapy or pharmacotherapy, and guidelines are lacking. Although a recently completed six-month study has demonstrated that newer hypnotic agents can have long-term efficacy and a positive impact on subjective next-day functioning, more research is needed to improve the therapeutic armamentarium for difficult-to-treat patients as well as to determine the long-term benefits of treating insomnia. ♦

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