CURRENT AND EXPERIMENTAL THERAPEUTICS OF INSOMNIA

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INSOMNIA: DEFINITIONS, IMPACT, AND DIAGNOSIS

Definition of Insomnia Symptoms and Disorders

Insomnia can refer to either a symptom or clinical disorder. The symptom of insomnia is the subjective complaint of difficulty falling or staying asleep, poor quality sleep, or inadequate sleep duration, despite having an adequate opportunity for sleep. Two points in this definition deserve specific attention. First, insomnia is a subjective complaint not currently defined by laboratory test results or a specific duration of sleep or wakefulness. Second, the insomnia symptom occurs despite the individual having adequate opportunity to sleep. This distinguishes insomnia from sleep deprivation, which has different causes, consequences, and clinical presentations. As a disorder, insomnia is a syndrome consisting of the insomnia complaint, together with specific diagnostic features (either clinical or laboratory), significant distress or functional impairment, and the absence of specific exclusionary features.

Prevalence of Insomnia Symptoms and Disorders

Insomnia symptoms and disorders are widely prevalent. A number of recent epidemiologic studies indicate a prevalence of 30% to 45% for insomnia *symptoms* in the prior year (1–3). The specific prevalence depends on the definition of insomnia symptoms used. The prevalence of insomnia *disorders* is obviously much lower, in the range of 10% to

15% (4,5). Epidemiologic studies point to a consistent set of risk factors for insomnia. These include a previous history of insomnia, increasing age, female gender, psychiatric symptoms and disorders, medical symptoms and disorders, impaired activities of daily living, anxiolytic and hypnotic medication use, and low socioeconomic status. The increasing prevalence of insomnia with age may be explained in large part by increasing comorbidity with medical and psychiatric disorders and medication use. The incidence of insomnia also increases with age and is greater in women than men. On the other hand, remission of insomnia decreases with age and is less common in women. Together, prevalence, incidence, and remission data indicate that insomnia is often a chronic condition. Between 50% and 80% of individuals with insomnia at baseline have a persistent complaint after follow-up intervals of 1 to 3.5 years (1,6-8).

Impact of Insomnia

Studies in working populations show that individuals complaining of insomnia have more mood symptoms, gastrointestinal symptoms, headache, and pain (9). In addition, individuals with insomnia have greater self-ratings of role impairment, days of limited activity, days spent in bed, and higher total health costs (10). Health-related quality of life is significantly lower for individuals with insomnia than for those without (11). Individuals with insomnia may also have higher rates of serious accidents or injuries (12) and injurious falls (13). The economic costs of insomnia are also substantial. One recent estimate places the annual direct costs for insomnia-related problems at nearly \$14 billion (including \$11 billion related to nursing home care) (14). Insomnia has been identified as a significant risk factor for institutionalization in the elderly in some studies (15), but not in others (3). Despite these morbidities, insomnia does not appear to be an independent risk factor for mortality (3,16).

Perhaps the greatest morbidity associated with insomnia is an increased risk for psychiatric disorders. Several large,

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Incidence (%) over 3.5 years

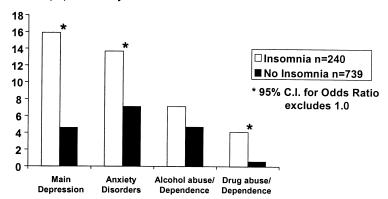


FIGURE 133.1. Insomnia is a risk factor for depression. Odds ratio's for developing new-onset psychiatric disorders among individuals with and without insomnia. Subjects were young adults in a health maintenance organization, interviewed at baseline, and at a 3.5-year follow-up. Baseline insomnia was a significant risk factor for incident depressive, anxiety, and substance use disorders. Data from ref. 19.

carefully controlled studies have found that individuals with insomnia are at significantly increased risk for the development of depression, anxiety, and substance use disorders (4, 17-21). These studies have included subjects from young adults to the elderly, and follow-up intervals from 1 to 35 years. Figure 133.1 shows data from the Breslau and associates study that are representative of these findings. The obvious—and unanswered—question is whether early identification and intervention in insomnia could prevent this costly outcome.

Differential Diagnosis

Insomnia can be the final result of many factors acting singly or in combination (Fig. 133.2). Many of these factors may

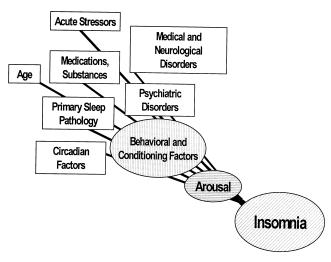


FIGURE 133.2. Causes of insomnia. Insomnia may result from many factors acting simply or in combination. Behavioral and conditioning factors often perpetuate insomnia that originally arises from other causes. Cognitive, affective, and somatic arousal may be the final common pathways leading to insomnia.

lead to behaviors and conditioning that further reinforce the original problem. For instance, an individual who sleeps poorly may spend more time in bed in an effort to "catch up" on sleep. This extended time in bed occurring in an individual with impaired *ability* to sleep can further contribute to impaired sleep continuity and to the bed becoming a conditioned stimulus for wakefulness. Furthermore, most of the factors underlying insomnia contribute to increased physiologic arousal, which may constitute a final common pathway leading to insomnia complaints.

The differential diagnosis of insomnia disorders includes insomnia secondary to other medical, psychiatric, or substance use conditions; insomnia occurring during the course of primary sleep disorders; and primary insomnia. Insomnia secondary to psychiatric disorders is the most prevalent insomnia disorder, both in general population samples and clinically referred samples (5,22), accounting for 40% to 75% of all diagnoses. Virtually any psychiatric disorder can be associated with insomnia, although mood disorders (major depression, bipolar mood disorder, dysthymia) and anxiety disorders (generalized anxiety disorder, panic disorder, posttraumatic stress disorder) are the most common. Insomnia also may result from specific medical and neurologic disorders; those associated with pain, impaired mobility, and central nervous system (CNS) dysfunction are the most common. Common examples include arthritis, congestive heart failure, chronic obstructive pulmonary disease, and Parkinson's disease. A wide variety of drugs can also cause or contribute to insomnia, including alcohol, caffeine, decongestants, and other CNS stimulants, corticosteroids, and antidepressant medications, particularly selective serotonin reuptake inhibitors. Medications and substances can cause insomnia not only during the time they are being used, but also during withdrawal.

Insomnia also can be associated with specific sleep disorders. One common example is restless legs syndrome (RLS), which consists of an urge to move one's legs accompanied by uncomfortable dysesthesias, usually described as "creepy crawly" or restless feelings. These sensations regularly increase at night, decrease during the day, and are temporarily relieved by movement. RLS is often associated with significant sleep onset insomnia. In addition, RLS is often accompanied by periodic limb movement disorder (PLMD), which consists of repetitive, short (.5- to 3.0-second) bilateral jerks in the toes, feet, ankles, and legs. These movements can lead to brief arousals and a complaint of nonrestorative sleep. Sleep apnea syndromes do not typically present with a complaint of insomnia. More often, sleep apnea presents within a syndrome of excessive daytime sleepiness, loud snoring, breathing pauses during sleep, and obesity or craniofacial abnormalities; however, a minority of patients, including older individuals, may present with insomnia complaints. Circadian rhythm sleep disorders often include prominent insomnia complaints. For instance, individuals with delayed sleep phase syndrome complain of difficulty falling asleep accompanied by difficulty awakening in the morning. Conversely, individuals with advanced sleep phase syndrome complain of early morning awakening and sleepiness in the evening hours. Jet lag and shift work sleep disorders are further examples of circadian sleep disorders that can present with insomnia problems.

Individuals who do not have other sleep disorders are diagnosed with primary insomnia. According to the DSM-IV, this syndrome is defined by a significant insomnia complaint; evidence of distress or impairment; and the absence of a concurrent psychiatric, medical, or sleep disorder that could explain the problem. Approximately 10% to 20% of individuals with significant insomnia are diagnosed with primary insomnia (5,22). This condition is broadly analogous to the term "psychophysiologic insomnia." The latter term invokes the etiologic factors of physiologic and cognitive arousal in association with the insomnia complaint.

Etiology and Neurobiology of Insomnia

Despite the prevalence and consequences associated with insomnia, relatively little is known regarding its neurobiology. One of the earliest and most enduring conceptualizations of insomnia is that of psychophysiologic arousal. Individuals with insomnia have several indicators of sympathetic and hypothalamic-pituitary-adrenal (HPA) axis activation, together with other peripheral indicators of "arousal." For instance, individuals with insomnia may have elevated temperature and muscle tone at sleep onset (23,24), elevated heart rate and sympathovagal tone in heart rate variability (25), and positive correlations among wake time after sleep onset and urinary norepinephrine, DOPAC, and DHPG (26). Studies of whole body metabolic rate, assessed by oxygen consumption, show elevated rates for individuals with insomnia compared to healthy controls, a difference which persists 24 hours per day (27). The psychologic arousal of insomnia is supported by higher rates of self-reported ruminations and intrusive thoughts among individuals with insomnia. It is less clear whether excess cognitive activity actually causes insomnia or is simply a byproduct of it. The cognitive hyperarousal may be the result of a ruminative, anxious personality style that also has been associated with insomnia.

Unfortunately, most studies identifying hyperarousal in insomnia are based on peripheral or "downstream" measures of arousal, rather than CNS arousal per se. Evidence for this type of arousal comes from electroencephalographic studies. Several investigators have demonstrated that individuals with insomnia have reduced sleep propensity not only at night, but also during the day. Individuals with insomnia also have lower δ EEG power (usually taken as an indicator of homeostatic sleep drive) and elevated amounts of β EEG power (usually interpreted as evidence of EEG activation or cognitive activity) (28). In one recent investigation of depressed patients with insomnia, Nofzinger and colleagues found that β EEG activity correlated positively with glucose metabolic rate in the medial orbitofrontal cortex, a region implicated in both behavioral and electroencephalographic activation (29). Behavioral evidence also supports the concept of increased cortical activity during sleep among individuals with insomnia. For instance, individuals with insomnia have better ability to recall auditory stimuli presented during the early sleep period relative to control subjects (30).

An integrative neurobiological model of insomnia should account for evidence of cortical activation during sleep, vulnerability to developing mood disorders, and evidence for sympathetic and HPA axis activation. It should also account for insomnia subjects' complaints of impaired concentration and memory, as well as their reduced propensity for sleep, even during daytime hours. Such a model may involve relative activation of ascending cholinergic and noradrenergic systems with diffuse projections to the cortex through thalamic and basal forebrain systems. The model may also involve reduced efficiency of processing in the frontal cortex, which may explain insomnia patients' complaints of poor concentration and attention. Another component of an integrative neurobiological model of insomnia would involve affective dysregulation. This might include amygdala activation or reduced activity in the subgenual anterior cingulate, similar to that observed in depression (31). Overactivity of ascending arousal systems, together with limbic system dysregulation, could lead to sustained activation of hypothalamic efferent systems, including activation of the sympathetic nervous system and HPA axis.

BEHAVIORAL AND NONPHARMACOLOGIC TREATMENT OF INSOMNIA

Rationale and Efficacy

Most behavioral and cognitive interventions aim to decrease or change factors that interfere with sleep, including maladaptive sleep habits, cognitive or physiologic hyperarousal, and dysfunctional beliefs about sleep and insomnia. The ultimate goal of behavioral treatments for insomnia is to help patients manage their sleep and sleep habits more effectively. In addition to providing a safe alternative to pharmacotherapy, these nondrug treatments offer patients the potential benefit of a greater sense of control over their sleep problems. Most insomnia patients indicate that they would prefer a nonpharmacologic solution to their insomnia (32).

A comprehensive review of the efficacy of nonpharmacologic treatments for chronic primary insomnia, based on two metaanalyses and 48 individual treatment studies, showed reliable improvements in the main outcome measures of latency to sleep- and wake-time after sleep onset (33). Data consistently indicated that approximately 70% to 80% of insomniacs benefited from treatment. The magnitude of improvement was approximately 50%, with sleep latency reduced by about 30 minutes on average, from 60 to 30 minutes, and wake-time after sleep onset reduced from 70 to 38 minutes. Subjective report of sleep quantity and quality improved, based on sleep diary data. Relatively few studies have used PSG or actigraphy to document objective improvement. Improvements with behavioral treatment are well maintained over at least 6 months (34).

Good Sleep Practices (Sleep Hygiene Education)

Sleep hygiene education aims to promote environmental and lifestyle factors that are conducive to sleep, and to minimize those that affect sleep in a negative way, such as latenight caffeine consumption, sleeping with a television or radio on, or engaging in exercise in close proximity to bedtime. Many of these behaviors are not intrinsically problematic, but become detrimental to sleep if they are timed inappropriately. For example, exercise too close to bedtime can cause physiologic arousal that can impair sleep onset, whereas exercise during the late afternoon or earlier evening can have beneficial effects on sleep (35). Lifestyle factors alone are rarely the cause of chronic insomnia, but rather may complicate insomnia arising from other causes. Sleep hygiene modification is seldom considered sufficient treatment for chronic insomnia, and results from intervention studies support its limited efficacy. There is no single standard set of sleep hygiene recommendations; a sample of commonly reported elements is included in Table 133.1.

Stimulus Control Therapy

Stimulus control techniques (36) are based on the premise that insomnia is exacerbated or maintained by a maladaptive conditioned response to the bedroom environment and bedtime routine, which develops as a result of repeated difficulty sleeping. Whatever the initial cause of the insomnia, when

TABLE 133.1. SLEEP HYGIENE RECOMMENDATIONS

Caffeine is a stimulant and should be discontinued 4–6 hours before bedtime.

Nicotine is a stimulant and should be avoided near bedtime and on awakening.

Alcohol is a depressant that can facilitate sleep onset, but can disrupt sleep later in the night. It should be avoided in close proximity to bedtime.

A heavy meal too close to bedtime can interfere with sleep and should be avoided. A light snack is all right.

Regular exercise in the late afternoon or early evening may deepen sleep, whereas exercise too close to bedtime may disrupt sleep.

Minimize light, noise, and excessive temperature during sleep.

Adapted from Morin (1990).

an individual has experienced the frustration of lying in bed being unable to sleep, anxiety develops about the ability to sleep and the potential consequences of lack of sleep. Greater effort is made to lie in bed and consciously try to sleep. This behavior and effort are incompatible with sleep, cause further frustration and alertness, and result in "conditioned" insomnia.

The goal of stimulus control is to recondition cues such as the bedroom and bedtime routine to elicit relaxation and sleep as opposed to anxiety, frustration, and wakefulness. Stimulus control instructions are outlined in Table 133.2. This is a paradoxic approach; the patient must accept the rationale of the treatment and trust the therapist enough to do something that does not make intuitive sense (i.e., get out of bed when he or she wants so desperately to sleep). Stimulus control requires effort and persistence, and often leads to initial resistance and temporary worsening before improvement. Consistency and motivation are important ingredients for a successful response. Quantitative reviews of controlled intervention trials consistently support the efficacy of stimulus control therapy.

TABLE 133.2. STIMULUS CONTROL INSTRUCTIONS

Lie down intending to go to bed only when you are sleepy.
Use the bed and bedroom for sleep and sex only. Do not watch
TV, listen to the radio, eat, or read in bed.

Get out of bed if you cannot fall asleep or go back to sleep within 10–15 minutes; return to bed only when you feel sleepy.

If you still cannot fall asleep, repeat the processing step as often as is necessary during the night.

Set your alarm and maintain a regular arising time in the morning, irrespective of how much sleep you got during the night. Do not nap during the day.

Adapted from refs. 36 and 36a.

Sleep Restriction Therapy

Patients with insomnia often try to compensate for lost sleep by getting into bed early or remaining in bed after awakening in the morning. Many individuals assume that bed rest may be restorative, even if no sleep is achieved. Unfortunately, the excess time in bed results in increased wakefulness in bed, which causes more frustration about difficulty sleeping and leads to even more pronounced insomnia. Increased time awake in bed can thus contribute to conditioned insomnia.

The goal of sleep restriction is to decrease time in bed in order to maximize the sleep efficiency of time spent in bed. Unlike stimulus control, sleep restriction addresses only the amount of time one spends in bed, rather than how the time in or out of bed is spent. This approach involves an initial curtailment of time in bed to the amount of time actually spent sleeping, based on sleep diary entries averaged over at least 1 week's time. Average sleep efficiency, which represents the proportion of time in bed spent asleep, is computed from sleep diaries. After sleep efficiency reaches desired levels (typically 90%), time allowed in bed can be increased by increments of 15 minutes until desired total sleep time at night is reached. If sleep efficiency remains low (<80%), after the initial restriction, time in bed is further curtailed by 15-minute increments until sleep continuity improves sufficiently. Time in bed is not changed if sleep efficiency is between 80% and 90%.

Relaxation and Biofeedback Therapies

Relaxation techniques target the cognitive or physiologic arousal that interferes with sleep, as discussed. A number of relaxation therapies have been used for insomnia, including progressive muscle relaxation and biofeedback to diminish physiologic arousal, and imagery techniques, autogenic training, and meditation to reduce cognitive arousal. Relaxation treatments may be most useful for sleep onset insomnia. In general, the magnitude of improvement seen with relaxation is smaller than for other behavioral approaches (37).

Cognitive and Multimodal Therapies

Insomnia often involves negative, unrealistic, or exaggerated beliefs about sleep and consequences of insomnia. These dysfunctional beliefs can cause emotional arousal and exacerbate the sleep problem (38). Cognitive restructuring has been used to help patients question the validity of automatic, maladaptive thoughts and reformulate them to make them more realistic and adaptive.

Many cognitive and behavioral techniques share common elements, and they are increasingly being used together within multimodal treatment protocols. It makes intuitive

sense for some of the approaches to be combined, such as stimulus control and sleep restriction. The change in behavior advocated and the net result of each are similar, although the rationales are different. An adjustment in thinking, as can be accomplished with cognitive restructuring, can be helpful for successful completion of any behavioral or cognitive treatment. Effective, circumscribed, multicomponent therapies, such as that developed by Morin (39) combine several different treatment approaches within a limited number of treatment sessions to treat insomnia. The treatment protocol potentially can benefit a variety of patients who may respond differently to various aspects of the program. The treatments are integrated in a later session, and relapse prevention is addressed, promoting an overall focus on self-efficacy. From the existing literature, it is not clear that such combined approaches are more effective than the most effective of the individual techniques (e.g., stimulus control) used alone; however, such multifaceted therapies may have the added benefit of treating a broader range of patients without having to individualize treatment.

Other Nonpharmacologic Treatments

Phototherapy

As noted, insomnia associated with circadian rhythm sleep disorders results from problems related to the timing of sleep versus sleep itself. Because light is the most potent zeitgeber, or time cue, for the circadian timing system, phototherapy can be used as part of a treatment regimen to adjust the timing of the sleep/wake cycle and address a corresponding complaint of insomnia and/or sleepiness.

Exposure to bright light shifts circadian phase in a timedependent manner (40). In general, bright light in the early morning hours shifts sleep and circadian rhythms to an earlier time (i.e., causes a phase advance); bright light in the evening hours shifts sleep and circadian rhythms to a later time (i.e., causes phase delays). Phototherapy can be delivered through artificial light, or by exposure to diffuse natural outdoor light. Artificial bright light has been shown to improve sleep maintenance insomnia in older adults (41) and younger adults with chronic insomnia (42); however, it is more typically used to treat circadian rhythm sleep disorders, such as delayed sleep phase syndrome. Practice parameters recently have been developed by the American Academy of Sleep Medicine (AASM) regarding use of phototherapy in the treatment of sleep disorders, including recommendations for light intensity and duration (43).

Exercise

The effects of exercise on sleep have been reviewed elsewhere (35,44). Exercise can increase sleep quality and slow-wave sleep, and reduce sleep latency in some individuals, including older adults (45). Individuals in good physical condition

observe the greatest effects on sleep with exercise in the late afternoon or early evening. Exercise performed in close proximity to bedtime, or by individuals who are unaccustomed to such exercise, can cause arousal. Exercise can be used as part of sleep hygiene recommendations or an overall training program potentially to improve sleep and health in general. Some of the effect of exercise on sleep may be mediated by changes in core body temperature. In particular, a rise in core body temperature with exercise may be followed by an exaggerated temperature decline during early sleep. This temperature decline may promote slow-wave sleep (46).

Passive Body Heating

Elevation of core body temperature by external body heating during the early evening also increases slow-wave sleep in both young and older individuals, and improves sleep continuity in older women with insomnia (47,48). Passive body heating involves immersion in hot water of at least 40°C for at least 30 minutes during afternoon or evening hours prior to bedtime. Although larger trials are needed, this procedure may constitute a relatively noninvasive, nonpharmacologic technique for treating insomnia.

PHARMACOLOGIC TREATMENTS FOR INSOMNIA

Several medication classes are used for the treatment of insomnia, although the strength of evidence regarding their efficacy and tolerability varies considerably. The major classes are benzodiazepine receptor agonists (BzRA), antidepressant drugs (AD), antihistamines, melatonin, and various herbal remedies including valerian root extracts. Of these medications, only BzRAs are formally approved for the indication of insomnia treatment in the United States. Nevertheless, physician-prescribing data show that prescriptions for BzRA hypnotics declined by 150% between 1987 and 1996, at the same time that benzodiazepine nonhypnotic prescriptions for insomnia remained stable, and antidepressant prescriptions increased by 150% (49). In particular, prescriptions for trazodone increased sixfold.

Benzodiazepine Receptor Agonists

Benzodiazepine receptor agonists (BzRAs) include the true benzodiazepines (e.g., triazolam, temazepam, estazolam, and lorazepam) as well as a structurally dissimilar group of nonbenzodiazepine agents, including an imidazopyridine (zolpidem), pyrazolopyrimidine (zaleplon), and cyclopyrolone (zopiclone). BzRAs are the only pharmacologic agents currently approved by the FDA for the treatment of insomnia, and they are labeled for short-term use (i.e., less than 4 weeks).

BzRAs share common pharmacodynamic actions, discussed in Chapter 68. In summary, these agents bind at a specific recognition site in the benzodiazepine-γ aminobutyric acid (GABA)–chloride ion channel macromolecular complex. This binding is responsible for the hypnotic, anxiolytic, myorelaxant, and anticonvulsant actions of BzRAs. There is some evidence that the nonbenzodiazepine BzRAs, specifically zolpidem, may be relatively more specific for hypnotic effects relative to anticonvulsant and anxiolytic effects; this may be related to greater specificity for benzodiazepine type I receptors.

Specific BzRAs differ significantly in pharmacokinetic properties, including the rate of absorption, extent of distribution, and rate of elimination. BzRAs also range widely in elimination half-life, from 1 hour for zaleplon to 120 hours for flurazepam and its metabolites. Finally, these agents differ in terms of active metabolites, which may have longer half-lives than the parent compound. Table 133.3 outlines relevant pharmacokinetic properties for commonly used BzRAs.

BzRAs are efficacious in the short-term treatment of insomnia. Recent metaanalyses examined BzRA effects on sleep latency, sleep duration, number of awakenings, and sleep quality (50,50a). For each of these outcomes, the effect size d ranged between .55 and .75, indicating moderately large effect sizes and substantiating the superiority of these agents over placebo. Other data support a broader range of beneficial outcomes. For instance, treatment with zopiclone for both 14 days and 8 weeks of treatment was associated with greater improvements in quality of life measures, social activities, and professional activities compared to placebo (51). A telephone survey of patients with untreated insomnia and those receiving benzodiazepines showed that the later group reported fewer symptoms of feeling blue, down in the dumps, or depressed, and being easily upset compared to the former group (52).

BzRAs have consistent effects on PSG sleep measures. (See ref. 53 for review.) As expected, BzRAs are associated with reduced sleep latency and wakefulness during the night, and increased sleep duration and sleep quality ratings. Other specific PSG effects depend on the particular agent. For instance, zaleplon, with its very short half-life, has not been demonstrated to consistently affect sleep duration despite its effect on sleep latency. Traditional benzodiazepines reduce REM and stage 3 to 4 NREM sleep, whereas zaleplon and zolpidem are not associated with changes in sleep stages. In addition, BzRAs reduce the number of periodic limb movements and arousals associated with these movements (54). BzRAs can also lead to oxyhemoglobin desaturations during sleep and can theoretically worsen sleep apnea; however, in patients with moderate degrees of sleep apnea, the change in number of apneas and oxyhemoglobin saturation is felt to be clinically insignificant (55).

Although BzRAs have been studied primarily for short-term treatment of insomnia, insomnia is often a chronic

Medication	Usual Adult Therapeutic Dose (mg)	Time to Onset (Minutes)	Terminal Elimination Half-Life (Hrs)	Active Metabolites
Marketed as hypnoti	cs			
Estazolam	0.5-2.0	15–30	8–24	No
Flurazepam	15–30	30–60	2–5 ^a 47–120 ^b	Yes
Quazepam	7.5–30	20–45	15–40 ^a 39–120 ^b	Yes
Temazepam	7.5–30	45-60	8–20	No
Triazolam	0.125-0.25	15–30		No
Zaleplon	5–10	15	1.0	No
Zolpidem	5–10	30	1.5-4.5	No
Not marketed as hyp	notics			
Clonazepam	0.25-2.0	20-60	19–60	No
Lorazepam	0.25–2.0	30–60	8–24	No

TABLE 133.3. PHARMACOKINETIC PROPERTIES OF BENZODIAZEPINE RECEPTOR AGONISTS

condition, and many patients take their hypnotics for longer periods of time. Some patients clearly developed tolerance with continued use of BzRAs, and some polysomnographic studies support this phenomenon (56); however, other PSG studies show continued efficacy over several nights of continued nightly administration. For instance, triazolam, zolpidem, and zaleplon have shown continued efficacy over a period of 4 to 5 weeks in double-blind, placebo-controlled studies (57-60), and single-blind studies have shown continued efficacy by PSG for as long as 6 months (61,62). Studies using self-ratings or observing-ratings have documented efficacy for even longer amounts of time. For instance, double-blind studies have shown continued efficacy for up to 24 weeks with no evidence of tolerance according to mean subject ratings (63,64) and single-blind studies have shown efficacy for up to 1 year of treatment (65,66); however, the role of BzRAs in long-term treatment or maintenance treatment of insomnia remains to be more clearly defined.

BzRAs can have significant adverse effects. The most common of these is a continuation of their desired therapeutic effect, sedation during the daytime. Daytime sleepiness is clearly more severe with longer-acting agents such as flurazepam, which has been documented in PSG studies (57, 67). Similar PSG studies of short-acting hypnotics have not shown an increase in daytime sleepiness. BzRAs are also associated with dose-related anterograde amnesia that may even be partially responsible for their therapeutic affect (68, 69). BzRAs can also impair other aspects of psychomotor performance, including reaction time, recall, and vigilance. Whether or not such deficits improve with this continuation of the drug is more controversial, with some studies noting

improvement following discontinuation (70,71) and other studies failing to show such improvement (72).

BzRAs are significantly related to an increased risk of injurious falls and hip fractures in elderly people. In particular, risk seems to be increased with the use of long-acting agents, high doses, multiple agents, and cognitive impairment in patients (73,74). Data regarding automobile crashes are somewhat mixed. Self-report data have shown an increased rate of motor vehicle accidents in those taking hypnotics (12) but a case-control study in older individuals failed to show an elevated risk associated with benzodiazepines (75). Other studies have shown risk associated with long half-life drugs and recent initiation of treatment, but not with longer-term treatment (76). An analysis of data from over one million subjects in a national cancer database demonstrated an increased risk of all-cause mortality among older individuals using hypnotics, even after controlling for symptoms of insomnia, although the hypnotic drugs examined included barbiturate and other drugs as well as benzodiazepines (77). In fact, examination of two specific benzodiazepine agents in this cohort did not show an elevated mortality risk.

Several discontinuation phenomena have been examined in relation to BzRAs. *Rebound insomnia* refers to an increase in insomnia symptoms beyond their baseline level. Rebound is thought to be associated primarily with short-acting BzRAs, although recent evidence for zolpidem and zaleplon does not show this effect. Patients who demonstrate rebound insomnia tend to have worse baseline sleep and higher medication doses than patients without rebound (78, 79). The behavioral aspect of taking a pill may contribute to rebound insomnia. Individuals who have shown a poor

^aParent compound.

^bActive metabolite.

response to treatment may show the greatest rebound (80). Withdrawal refers to the appearance of new symptoms on discontinuation of the drug. Withdrawal may occur in 40% to 100% of patients treated chronically with benzodiazepines, and can persist for days or weeks following discontinuation (81,82). Withdrawal symptoms can include dizziness, confusion, depression, and feelings of unreality. Cognitive and behavioral treatments can help patients discontinue chronic benzodiazepine use (83). The prevalence of true withdrawal phenomenon in any individuals treated with once-daily hypnotic doses of BzRAs is not well known. Recurrence is another potential discontinuance syndrome that has received little attention in insomnia. Given that insomnia tends to be chronic, it should not be surprising that many patients complained of their original symptom after discontinuation of an affected treatment. The role of recurrence in chronic BzRA treatment also remains to be well defined. Finally, abuse of BzRAs used for insomnia appears to be uncommon. One telephone survey showed no greater use of increased doses for BzRAs compare to antidepressants (84). Although data are difficult to obtain, benzodiazepines may be used by .5% to 3.0% of the population for nonmedical purposes in any 1 year (85). Among those who wish to discontinue chronic use of BzRAs, their pattern of use tends to suggest stability or declining doses over time as well as a tendency to intermittent rather than consistent dosing (86). Thus, among individuals with no prior substance use history, abuse of BzRAs appears to be uncommon.

Antidepressant Drugs

Although use of antidepressant drugs (AD) for insomnia has increased dramatically, evidence to support their efficacy is relatively sparse. The most commonly used ADs for insomnia include trazodone, tertiary tricyclic agents, and mirtazapine. These drugs clearly have diverse effects on neurotransmission, as reviewed in Chapter 79. In general, the sedating properties of antidepressants are related to antagonism of serotonin 5-HT₂, histamine, and α_1 -adrenergic receptors.

The effects of various antidepressant agents on sleep have been described primarily in the context of depression treatment. These effects are summarized in Table 133.4 and several recent reviews (87,88). As the table indicates, antidepressant drugs vary widely in their effects on sleep continuity, EEG delta activity and slow-wave sleep, and REM sleep. Sleep continuity effects are likely to be most important in the treatment of insomnia. Some antidepressant drugs also can cause or exacerbate insomnia problems. Selective serotonin reuptake inhibitors (SSRIs) bupropion, noradrenergic selective tricyclic drugs, and strongly serotonergic tricyclic drugs (e.g., clomipramine) are the most common agents to have such effects. In addition, serotonergic specific antidepressants can lead to anomalous sleep stages characterized

TABLE 133.4. EFFECTS OF ANTIDEPRESSANT DRUGS ON EEG SLEEP

	Sleep Continuity	Slow Wave Sleep	REM Sleep
Tricyclic SSRIs, Venlafaxine Trazodone, Nefazodone Bupropion	↓ to ↑ → to ↓	→ to ↑ → to ↓	↓ to ↓↓↓ ↓ to ↓↓
	\uparrow	\rightarrow to \uparrow	ightarrow to $ ightharpoonup$
	\downarrow	$ ightarrow$ to \downarrow	\uparrow

 $[\]rightarrow$, No change.

by eye movements during NREM sleep and they can also cause or exacerbate restless leg syndrome and periodic limb movements (48). Antidepressants may also be associated with slight improvements in sleep apnea (89).

Studies with small numbers of subjects and diverse inclusion criteria suggested the beneficial effects of trazodone 150 to 400 mg on sleep continuity measures, as well as a tendency to increase Stage 3 to 4 sleep and improve subjective sleep quality ratings, in insomnia patients (90-92). A more recent 2-week double-blind placebo-controlled study compared the effects of trazodone 50 mg and zolpidem 10 mg to placebo among individuals with primary insomnia (93). This study showed improvements in subjective sleep latency and sleep duration with both active drugs, although there was some evidence for superiority of zolpidem during the second treatment week. Both drugs were well tolerated. Other studies involving primary insomnia have shown beneficial effects of short-term treatment with low-dose doxepin (94) and trimipramine (95) compared to placebo. Finally, a recent open-label trial of paroxetine for primary insomnia in the elderly showed significant improvement in a multivariate measure of sleep quantity based on both diary and polysomnographic sleep measures (96). Small improvements were noted in diary-based measures of sleep quality and PSG measures of sleep efficiency; however, the greatest improvements were noted in daytime symptoms of mood and well being. Thus, it may not simply be the sedating properties of antidepressants that lead to improvements in insomnia.

Indirect evidence for the efficacy of antidepressants, and differential effects among agents, comes from studies in individuals with major depression. For instance, fluvoxamine has a relatively alerting effect relative to desipramine that in turn is more alerting than amitriptyline (97,98). A comparison of trimipramine and imipramine found that both drugs improve sleep quality, although trimipramine was associated with more positive effects on PSG sleep (99). A comparison of fluoxetine with trazodone showed that the later drug was associated with more improvements in in-

 $[\]uparrow$, Increase.

^{↓,} Decrease.

somnia symptoms, but also with a greater percentage of sedating events during the daytime (100). A series of comparisons between fluoxetine and nefazodone has consistently shown that both drugs improve subjective sleep quality among depressed patients, although the change appears to be larger with nefazodone (101,102). Nefazodone also led to improvements in PSG sleep efficiency, whereas fluoxetine was associated with mild decrements.

Antihistamines

Antihistamines such as diphenhydramine and doxylamine are the most widely available over-the-counter preparations for insomnia. The mechanism of action of these drugs involves inhibition of histamine H_1 receptors. Histaminic neurons in the posterior hypothalamus promote wakefulness through interactions with ascending cholinergic nuclei and through projections through the thalamus. Inhibition of H_1 receptors leads to decreased alertness and subjective sedation. The elimination half-life of diphenhydramine ranges from 3 to 5 hours, within increases in elderly persons. In addition to their effects on histamine, these medications can also have antimuscarinic anticholinergic effects.

Despite their widespread use, a large body of well-documented research does not support the efficacy of antihistamines. Diphenhydramine 50 mg, improved subjective ratings of sleep quality, sleep time, sleep latency, and wakefulness after sleep onset in middle-aged subjects with insomnia (103). A more recent study comparing the effects of lorazepam versus a combination of lorazepam plus diphenhydramine showed a slight advantage for the combination preparation in terms of sleep latency and subjective sleep quality (104). On most sleep measures, the two drug preparations were fairly similar. Studies of antihistamines in elderly people demonstrate subjective sedative properties comparable in magnitude to those of benzodiazepines and confirmed by effects such as increased sleep time, decreased awakening, and shorter sleep latency (105,106).

Adverse effects of antihistamines include a range of cognitive and performance impairments (107). The anticholinergic effects of these medications may be of particular concern in elderly subjects. The relative safety and efficacy of antihistamines with more sustained use has not been examined.

Melatonin

Melatonin has been widely used as a "natural" sleep-promoting agent. Data regarding its efficacy and safety have been mixed. The study designs, doses, and outcome measures used in melatonin trials have been quite variable and may contribute to inconsistent findings (108). Melatonin is secreted by the pineal gland during hours of darkness in both diurnal and nocturnal mammals. Melatonin's effect on sleep and wakefulness may result from interaction with

specific receptors in the suprachiasmatic nucleus of the hypothalamus (109). In addition, melatonin shifts circadian rhythms according to a phase response curve (110,111). The half-life of endogenous melatonin is less than 1 hour. Exogenous melatonin is absorbed from the gastrointestinal tract, but a wide variety of preparations are commercially available, ranging from very short-acting to very long-acting agents, with half-lives ranging from several minutes to approximately 8 hours. Doses greater than 1 mg are likely to induce supraphysiologic concentrations. Clinical trials have employed doses ranging from .1 to 80 mg.

During daytime administration, melatonin causes sleepiness in fatigue and healthy subjects (112,113). When administered at night to healthy subjects, melatonin decreases sleep latency (114) and the number of awakenings, and improves sleep efficiency in an experimental insomnia paradigm (115).

Studies in insomnia patients have also yielded inconsistent findings. Single-night administration seems to produce very little effect (116). Subjective sleep ratings showed no effect in another trial of 5 mg for 1 week (117), whereas a 14-day trial of 75 mg resulted in increased subjective sleep time (118). Trials of melatonin in elderly people have ranged from 1 to 21 days. The most consistent effect is reduced sleep latency with some evidence as well for reduced nighttime wakefulness using sustained-released preparations (119–122). In a carefully designed 14-day crossover trial, immediate- and sustained-release melatonin were associated with shortened sleep latency, but no change in sleep time, sleep efficiency, wakefulness, or subjective sleep measures (123).

Adverse effects associated with melatonin have not been carefully evaluated. Melatonin has effects on reproductive cycles in several mammalian species, and reports have indicated the potential for worsening of sleep apnea and impaired cognitive and psychomotor performance during daytime administration. There are also some concerns regarding vasoconstriction as a potential side effect.

Valerian Extract

Valerian extract is one of the most widely used herbal remedies for insomnia. These extracts are derived from roots of the genus Valeriana, most often of the species *V. officinelis*. They contain a number of potentially active compounds, including sesquiterpenes and valepotriates. Valerian extracts show affinity for GABA_A receptors, which may be related to the high amount of GABA itself that is often contained in these preparations (124,125). However, GABA does not cross the blood–brain barrier, so this is an unlikely mechanism of action. Other potential actions include affinity for serotonin and adenosine receptors.

Clinical studies with valerian extracts show mild sedative and anxiolytic effects. In particular, four double-blind placebo-controlled studies have examined doses of 400 to 900 mg of valerian extract over periods of time from 1 to 8 days, and in diverse subject populations ranging from healthy young adults to elderly insomniacs (126-129). Subjective effects include decreased sleep latency and improved sleep quality (126,127,129). One study also reported decreased subjectively rated awakenings (126). Polysomnographic studies have shown an increase in stage 3 to 4 NREM sleep and reduced stage 1 sleep (128), with no change in sleep onset time, awake time after sleep onset, or other measures of sleep continuity (128,129). Likewise, valerian was found not to influence the EEG power spectrum during sleep (129). Findings from these studies are hampered by small numbers of subjects, different inclusion criteria, and inconsistent findings. These studies do not demonstrate the efficacy of valerian extract in most groups of individuals with primary insomnia.

Clinical studies have suggested a generally favorable side effect profile for valerian extract; however, the sedative effects of valerian may potentiate the effects of other CNS antidepressants (125).

FUTURE DIRECTIONS

Although considerable progress has been made with regard to the epidemiology of insomnia, further work needs to be done regarding its consequences for health and role functioning. Individuals with insomnia complain not only of sleep disturbance, but daytime consequences as well. In addition, investigations into the neurobiology of insomnia are clearly needed. This will help to define the underlying pathophysiology of insomnia in the general sense, but also help to define the boundaries of specific insomnia disorders. Techniques from cognitive and affective neuroscience, as well as electrophysiology and psychophysiology, will lead to an improved understanding of this condition. Functional neuroimaging experiments will also contribute to our understanding of the circuitry involved in insomnia, and its boundaries with mood and anxiety disorders. To date, no animal model exists for insomnia that would also help to promote research in humans. Finally, genetic studies have been very useful for identifying abnormalities associated with narcolepsy and circadian rhythm sleep disorders. Similar genetic and genetic epidemiology strategies remain to be applied to a study of insomnia.

Several issues also remain with regard to treatment aspects of insomnia. First, the relative benefits and risks of treatment in terms of symptomatic relief, health-related quality of life, and morbidity remain to be defined. These issues are of considerable importance, given the potential for some insomnia treatments to cause significant adverse effects, such as cognitive impairment and injurious falls. The optimal duration of treatment and the conceptualization of potential "maintenance" treatments for insomnia is also an area open for further investigation.

With regard to behavioral treatments, one of the major challenges is designing well manualized and "exportable" treatments that can be applied more readily in a variety of treatment settings, including primary care settings. Several studies have begun to examine the optimal combination of behavioral and medication-treatment approaches. Some of the evidence suggests better durability of treatment effects with behavioral treatment alone (33); however, sequential treatments as well as concurrent treatments need to be investigated. In addition, treatment strategies for nonresponders to either behavioral or pharmacologic interventions must be developed.

Advances in the neurobiology of insomnia may come from basic neuroscience sources. For instance, recent evidence has accumulated regarding the role of adenosine as a modulator of sleep/wake states (130). Relative underactivity of adenosinergic neurotransmission could potentially result in reduced sleep drive. Another focus for dysregulation in insomnia may involve the ventrolateral preoptic area (VLPO) and its interactions with the tuberomamillary nucleus in the posterior hypothalamus (131,132). The GABAergic VLPO has been identified as one of the few "sleep active" areas of the brain; dysregulation in this nucleus and its efferent projections to histaminergic, cholinergic, and noradrenergic nuclei could conceivably shift the sleep/wake balance in the direction of wakefulness. Finally, recent findings regarding the role of orexin in sleep/wake regulation could have direct implications for the neurobiology and pharmacologic treatment of insomnia (133,134). Neuroscience and clinical studies can both inform the optimal management of insomnia disorders.

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