

A consensus statement on insomnia in adults issued by the National Institutes of Health (NIH) emphasizes a persistence of symptoms in most patients with insomnia; the comorbid disorders that can be associated with insomnia, particularly psychiatric conditions, such as depression; and considerations in the choice of treatment regimens, especially long-term regimens.

The statement, called the NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults, was the culmination of a 3-day conference held June 13-15, 2005 (Sleep. 2005;28:1049-1057).

The consensus statement and recent research in insomnia in support of its concepts are the focus of this supplement. Interviews with specialists in sleep medicine were also conducted to develop this report.

—Wayne Kuznar

High prevalence in primary care

According to the NIH statement, approximately 30% of the general population complains about sleep disruption, with higher prevalence rates found in primary care practices, where about 50% of respondents report symptoms of sleep disruption. A higher prevalence of insomnia has been documented in people ≥ 60 years of age and in women, especially during the menopausal years.

Persistence of symptoms

The NIH report defines insomnia as “complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep.” A person may experience 1 or more of the 3 features of insomnia: (1) difficulty in initiating sleep, (2) difficulty in maintaining sleep, or (3) waking up too early. According to *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, these sleep disruptions must result in perceived impairment of daytime function to be diagnosed as insomnia.

Little is known about the incidence, natural course, and duration of insomnia. Rates of spontaneous remission are low. The NIH report describes a persistence of symptoms in adults with insomnia who are followed over the long term. In most insomniacs, the symptoms are of long duration, and the disorder can last for decades in some patients. According to the NIH

expert panel, insomnia can be considered chronic if symptoms persist for 30 days or more. Similarly, *DSM-IV* defines chronic insomnia as difficulty initiating or maintaining sleep or episodes of nonrestorative sleep, occurring 3 or more times per week for at least 1 month that result in clinically significant distress or impairment in daytime functioning.

Diagnosis: Look to history

Although quantitative indices obtained via polysomnography (ie, sleep onset ≥ 30 minutes, percentage of time asleep vs total time spent in bed $\leq 85\%$) have often been used in research to diagnose insomnia, a patient’s report of inadequate sleep is frequently more important to the diagnosis.

According to the State-of-the-Science Conference Statement, “Diagnosis is based primarily on patient-derived and family or caregiver complaints, as determined by the clinical interview.”

Comorbidities are common

Insomnia often appears in the presence of at least 1 other disorder: common comorbidities include major depression, generalized anxiety, substance abuse, dementia, and a variety of physical problems, including arthritis, heart failure, pulmonary and gastrointestinal disorders, Parkinson’s disease, stroke, and incontinence.

Insomnia coexisting with other conditions has

historically been termed “secondary insomnia,” but the NIH panel prefers the term “comorbid insomnia.” “Primary insomnia” is the term used when no coexisting disorder has been identified.

In a review (*Am J Manag Care*, 2006, in press) by Sonia Ancoli-Israel, PhD, professor of psychiatry, University of California, San Diego, the prevalence of sleep disturbances in patients with rheumatoid arthritis was found to be

greater than 50%, sleep maintenance being a more prevalent problem in these patients than difficulty in sleep onset. Sleep disturbances are also present in more than 75% of patients with fibromyalgia.

Gastroesophageal reflux events are also associated with arousal during sleep, which suggests that these patients experience frequent sleep disruption and loss of restorative sleep. Sleep disturbances are also common in patients with type 1 and type 2 diabetes, coronary artery disease, congestive heart failure, obstructive airway disease, and end-stage renal disease, Dr Ancoli-Israel reported.

The prevalence of psychiatric disorders with chronic insomnia is very high. More than 40% of patients with persistent hypersomnia or persistent insomnia have a psychiatric disorder. “Depression is the most consistent correlate of sleep disruption in community-based studies, and sleep disruption is a diagnostic symptom for depressive and anxiety disorders,” Dr Ancoli-Israel observed.

“The research diagnostic criteria for insomnia recently developed by the American Academy of Sleep Medicine indeed share many of the criteria of major depressive disorder,” the NIH panel noted.

“We used to talk about insomnia secondary to a medical disorder, whether it was depression or pain. The concept now has shifted to comorbidities,” said Milton Erman, MD, of Pacific Sleep Services, San Diego. “Depression increases the probability that insomnia will be present, but insomnia also increases the risk that depression is going to be present. It’s not a simple cause and effect.” Persistent insomnia may be an early warning signal of depression, he added.

Chronic pain is also a factor in insomnia in many patients, Dr Erman said, and, like depression, often leads to a vicious circle of each exacerbating the other. “Chronic pain leads to insomnia, but the persistence of insomnia reduces pain threshold and makes people susceptible to having a greater impact from their pain,” he explained.

Table 1. Questions to include in the sleep history

- Describe your sleep problem.
- How long have you had a sleep problem? (days, months, years, forever)
- How often does it bother you? (nightly, several times a week, monthly, etc)
- How does your sleep problem affect you in the daytime?
- What have you done to treat it and what was the result of treatment?
- What is your sleep/wake schedule on workdays and days off? (circadian assessment)
- Has anyone told you that you snore? Has anyone told you that you stop breathing at night? (assessment for possible obstructive sleep apnea)
- Do you ever get a weird, uncomfortable, restless, creeping, crawling feeling in your legs or arms at night associated with a desire to move them? (assessment for possible restless legs syndrome)
- Do you enjoy your daily activities? Do you think of death often? Do you feel depressed? (assessment for mood disorders)
- Do you feel a sense of anxiety most of the time? Have you ever had a panic attack? (assessment for anxiety disorders)
- Have you ever been sexually, physically, or mentally abused? At night? Have you ever been afraid to sleep? (assessment for posttraumatic stress syndrome)
- What medications do you take?
- How much coffee, and alcohol, do you drink? Do you take any over-the-counter medications?
- Have you experienced medical problems that interfere with sleep?

Elements of history

As noted previously, the patient’s history is the

basis of a diagnosis of insomnia. A history may uncover shift work, jet lag, and lifestyle choices that undermine the ability to sleep well, noted David Neubauer, MD, associate director, Johns Hopkins Sleep Disorders Center, Baltimore.

In its practice parameters for the evaluation of chronic insomnia (*Sleep*. 2000;23:237-241), the American Academy of Sleep Medicine recommends the following: “Since the complaint of insomnia is so widespread and since patients may overlook the impact of poor sleep quality on daily functioning, the health care practitioner should screen for a history of sleep difficulty. This evaluation should include a sleep history focused on common sleep disorders to identify primary and secondary insomnias.” Questions to be included in the history are listed in Table 1.

The physician should also ascertain if patients having difficulty sleeping are attempting to sleep at appropriate times, Dr Neubauer advised. “Although a lot of people seem to be driven to sleep from about 10 or 11 at night to 6 or 7 in the morning, certainly there are those who are early birds and can’t stay up past 8 PM and then wake up in the middle of the night, and those who can’t fall asleep until the middle of the night and sleep till noon,” he said. These problems suggest that the patient may have a circadian rhythm sleep disorder (Table 2).

Sleep diaries, such as the one shown in Figure 1, may be helpful in assessing sleep patterns and factors associated with poor sleep. In these diaries, patients typically record time in bed, the approximate time to sleep onset, any awakenings, and wake time.

Polysomnography is the most sensitive tool to differentiate wakefulness and sleep but is expensive and may itself disrupt sleep because of the numerous monitoring electrodes employed. Its use as a diagnostic tool should therefore be reserved for patients in whom other sleep disorders, such as sleep apnea, are suspected.

Insomnia reduces quality of life

The limited studies that have been performed in which the effects of insomnia on everyday functioning have been examined suggest that insomnia reduces quality of life and hinders

Table 2. Circadian rhythm abnormalities

Delayed sleep phase syndrome

- Difficulty falling asleep at desired bedtime (bedtime insomnia) and difficulty awakening at desired wake time (wake time hypersomnia)
- Usually little difficulty sleeping when allowed to go to bed late and sleep late
- Typically seen in teenagers
- Treated with morning light (“to get up earlier, watch the sun rise”)

Advanced sleep phase syndrome

- Difficulty staying awake until desired bedtime (bedtime hypersomnia) and difficulty staying asleep until desired wake time (wake time insomnia)
- Usually little difficulty sleeping when allowed to go to bed early and awaken early
- Typically seen in the elderly
- Treated with evening light (“to go to bed later, watch the sun set”)

Jet lag

- Eastward travel, same as delayed sleep phase syndrome
- Westward travel, same as advanced sleep phase syndrome
- General advice for vacations: Do outdoor sightseeing during first week (bright light during new daytime) and visit museums the second week
- Typically takes 1 day to adjust for every 1 hour of time zone change

Shift work sleep disorder

- Difficulty staying awake during night shift (waking hypersomnia)
- Difficulty sleeping during desired day sleep (sleep insomnia)
- Sleep/wake schedule varies during nonwork days by several hours (outside the limit of human entrainment)
- Treatment often unsatisfactory but may include hypnotics or melatonin during daytime sleep and nap before work; attempt to find daytime job if possible

social functioning. Studies indicate that insomnia is positively correlated with work days missed and impaired work performance, and others suggest a relationship between chronic insomnia and impaired memory and cognitive functioning.

TREATMENTS

Sleep hygiene

Patients with insomnia should be instructed about simple sleep hygiene measures that can

help to normalize sleep patterns. These measures include going to bed only when tired, getting up at the same time each day, reducing or eliminating use of alcohol, caffeine, and nicotine, getting regular exercise but not within 2 to 4 hours of bedtime, and keeping the bedroom cool, quiet, and comfortable.

Cognitive-behavioral therapy

Behavioral methods for treating insomnia include sleep restriction, relaxation training, and

Figure 1. Sample sleep diary

		Example				
Complete in AM	Date	Monday; 4/10				
	Bedtime (of previous night)	10:45 PM				
	Rise time	7:00 AM				
	Estimated time to fall asleep (previous night)	30 minutes				
	Estimated number of awakenings and total time awake (previous night)	5 times 2 hours				
	Estimated amount of sleep obtained (during previous night)	4 hours				
Complete in PM	Naps (time and duration)	3:30 PM 45 minutes				
	Alcoholic drinks (number and time)	1 drink @ 8:00 PM 2 drinks @ 9:00 PM				
	List stresses experienced today	Flat tire; argued w/son				
	Rate how you felt today 1-Very tired/sleepy 2-Somewhat tired/sleepy 3-Fairly alert 4-Wide awake	2				
	Irritability 1=Not at all/5=Very	5 = very				
	Medications					

Source: www.nih.gov.

stimulus control. According to Thomas Roth, PhD, director of the Henry Ford Sleep Disorders Center in Detroit, “Every physician should be able to use stimulus control, sleep restriction, and sleep hygiene measures with no effort at all.” Sleep restriction is a behavioral approach that is too often overlooked, he noted.

Stimulus control is a cornerstone of cognitive-behavioral therapy. It involves associating the bed/bedroom with going to sleep. Its principles are making sure the patient goes to bed only when sleepy, establishing a standard wake-up time, getting out of bed and going to another room if unable to fall asleep, avoiding activities incompatible with sleep while in bed (ie, reading, watching television), and refraining from daytime napping.

Sleep restriction therapy consists of condensing the time in bed to the average time typically asleep to improve sleep efficiency. For example, a person who reports sleeping only 5 hours per night but staying in bed for 8 hours would initially be told to decrease the time in bed to 5 hours. The time allowed in bed is increased in 15- or 30-minute increments as sleep efficiency improves. Typically, altering bedtime rather than wake time is the best approach to maintaining a regular sleep-wake rhythm.

Relaxation methods may also be helpful in treating insomnia. Progressive muscle relaxation, autogenic training, and biofeedback can be used to reduce somatic arousal (eg, muscle tension). Imagery training and meditation may lower cognitive arousal (eg, intrusive thoughts, racing mind). Abdominal breathing can be used alone or in conjunction with other relaxation techniques.

Cognitive therapy includes cognitive restructuring that targets anxiety-producing beliefs about sleep and sleep loss. Behavioral and cognitive-behavioral therapies have demonstrated efficacy in randomized, controlled trials. Most cognitive-behavioral therapies are delivered by mental health practitioners or physicians with formal sleep medicine training.

“In the best of all possible worlds, cognitive-behavioral therapy would be readily available. But we don’t live in that world,” Dr Erman said. A number of practical issues prevent widespread use of cognitive-behavioral therapy as a primary

treatment for patients with insomnia. First, it takes time to perform. Second, it takes time for the patient to learn and for it to take effect. Furthermore, it’s not well reimbursed.

Behavioral and cognitive-behavioral therapies have demonstrated efficacy in randomized, controlled trials.

“You also have to have patients who are motivated to use this cognitive approach and forego medications, or use medications in combination, so it’s a little bit more complicated and harder to pursue,” Dr Erman explained. “I do think that we want to try to incorporate some of those elements from cognitive-behavioral therapy into any treatment approach that we pursue. I always emphasize sleep hygiene issues...and try to minimize some of the anxiety and concern that patients often have about their sleep that further disturbs their sleep.”

Pharmacotherapy

Only the benzodiazepine receptor agonists and a selective melatonin receptor agonist have been approved by the US Food and Drug Administration (FDA) for the treatment of insomnia. Other prescription drugs, such as antidepressants, atypical antipsychotics, and barbiturates, and nonprescription drugs, such as antihistamines, are also used without FDA approval to treat insomnia. The benzodiazepine receptor agonist class includes the traditional benzodiazepines as well as the more recently approved agents that act at certain subunits of benzodiazepine receptors but have a nonbenzodiazepine structure (Table 3).

Benzodiazepine hypnotics. Five traditional benzodiazepine hypnotics have been approved by the FDA for the treatment of insomnia: estazolam, flurazepam, quazepam, temazepam, and triazolam. In double-blind, placebo-controlled studies typically lasting 4 to 6 weeks, these agents have been effective at initiating and/or maintaining sleep. Tolerance to these agents has been known to develop with longer use. Some benzodiazepines are short-acting with half-lives of 2 to 3 hours, whereas others are long-acting

with half-lives of >20 hours. The long half-lives of some of these benzodiazepine hypnotics contribute to their efficacy in maintaining sleep but also result in next-day impairment (ie, morning sedation, cognitive impairment) in a substantial proportion of users. Triazolam has the shortest half-life of agents in this group, resulting in little residual sedative effect, but is associated with an increased rate of anterograde amnesia.

Nonbenzodiazepine hypnotics. Three nonbenzodiazepine hypnotics—zaleplon, zolpidem, and eszopiclone—have been approved by the FDA for the treatment of insomnia. In general, these medications have shorter half-lives than the benzodiazepine hypnotics, promoting faster sleep onset with lesser next-day impairment. The frequency and severity of adverse effects are much lower for the newer benzodiazepine receptor agonists compared with the older ones, most likely because of their shorter half-lives, according to the NIH report.

Potential for addiction or habituation may also be less with the nonbenzodiazepine hypnotics than with the benzodiazepine hypnotics.

Zolpidem has a rapid onset and short half-life. Controlled clinical trials have shown that zolpidem significantly reduces sleep latency and improves sleep efficiency without adversely affecting next-day psychomotor performance (Roth T, et al. *Sleep*. 1995;18:246-251). Efficacy data with the standard-release form of zolpidem, however, do not extend beyond 1 to 2 months. An extended-release formulation of zolpidem has

now been approved. The terminal half-life is similar to that of standard-release zolpidem. The effect of zolpidem CR on wake time after sleep onset appears to diminish within 2 weeks of initiation of treatment.

With a half-life of only about 1 hour, zaleplon affects primarily sleep onset with lesser effect on sleep maintenance (Barbera J, Shapiro C. *Drug Saf*. 2005;28:301-318). Although doses higher than 10 mg may promote sleep maintenance, they may increase the risk for side effects. Long-term safety and efficacy beyond 3 months have not been established for zaleplon.

At 5 to 6 hours, eszopiclone, the most recently approved nonbenzodiazepine hypnotic, has the longest half-life of the nonbenzodiazepines. Studies show that at the doses available, this longer half-life appears adequate to produce effects on sleep maintenance as well as sleep onset while minimizing morning sedation (Rosenberg R, et al. *Sleep Med*. 2005;6:15-22). “With the exception of eszopiclone, the benefits of these agents [benzodiazepine receptor agonists] for long-term use have not been studied using RCTs [randomized controlled trials],” the NIH panel notes. Duration of eszopiclone use is not limited, and recent findings have shown efficacy and safety with minimal tolerance or abuse liability over 12 months of use (Roth T, et al. *Sleep Med*. 2005; 6:487-495).

At the 2005 annual meeting of the American Psychiatric Association (APA) in Atlanta, Erman and colleagues reported on a crossover study of

Table 3. FDA-approved drugs for treatment of insomnia

Agent	Dose range (mg)	Half-life (hr)
Benzodiazepine hypnotics		
Flurazepam	15-30	50-100
Estazolam	1-2	10-20
Quazepam	7.5-15	39
Temazepam	7.5-30	4-18
Triazolam	0.125-0.25	2-3
Nonbenzodiazepine hypnotics		
Zolpidem	5-10	2-3
Zolpidem CR	6.25-12.5	2.8
Zaleplon	5-10	1-2
Eszopiclone	1-3	6
Melatonin receptor agonist		
Ramelteon	8	1.0-2.6

eszopiclone or zolpidem in the treatment of primary insomnia. In the study, 64 adult patients with primary insomnia received 2 nights' treatment with placebo, eszopiclone (1, 2, 2.5, and 3 mg), or zolpidem (10 mg) in a random order.

By polysomnography, all the active treatments reduced latency to persistent sleep and increased sleep efficiency compared with placebo, but only eszopiclone 2.5 mg and 3 mg significantly reduced both wake time after sleep onset and the number of awakenings relative to placebo. All the active treatments improved sleep quality and sleep depth relative to placebo. Morning sleepiness was improved only with the 2.5- and 3-mg doses of eszopiclone. The combined incidence of dizziness and somnolence was 20% with zolpidem compared with 9.4% with eszopiclone 3 mg. Hallucinations were reported only with zolpidem (4.7%).

Two formulations (immediate-release and modified-release) of indiplon, another new non-benzodiazepine hypnotic, are being investigated in clinical trials in patients with chronic and transient insomnia. In a phase 3 study reported at the 2005 annual APA meeting, 200 adults with chronic primary insomnia received 10 or 20 mg of indiplon or placebo nightly for 35 days. Compared with placebo, both doses of indiplon significantly reduced latency to persistent sleep, the primary end point, and improved sleep quality. The effects were sustained throughout the study period, and there was no evidence of next-day residual sedation or withdrawal on discontinuation of treatment.

Melatonin receptor agonist. Ramelteon is the most recent agent approved for the treatment of insomnia and is the only one not scheduled as a controlled substance. As a melatonin receptor agonist, it works by reinforcing natural sleep rhythm. It is indicated for insomnia characterized by difficulty falling asleep. In a clinical trial of 375 healthy adults with transient insomnia, performed by Roth and colleagues, those treated with 16 mg or 64 mg of ramelteon had a significantly shorter latency period to persistent sleep and significantly longer total sleep times compared with placebo recipients (Roth T, et al. *Sleep*. 2005;28:303-307). It should be noted, how-

ever, that the usual recommended dose, 8 mg, was not studied.

In a study of 107 patients with chronic primary insomnia, Erman and associates also found that 4, 8, 16, and 32 mg of ramelteon resulted in statistically significant reductions in latency to persistent sleep and increases in total sleep time compared with placebo, with no next-day residual effects (*Sleep Med*. 2006;7:17-24).

Issues with long-term use

Dr Erman pointed out, however, that none of the drugs acting on the benzodiazepine receptor has ever been associated with abuse in clinical trials, hence the FDA's actions in removing short-term limitations on the use of the 2 most recent approvals in this class, eszopiclone and zolpidem extended-release.

When the NIH statement was issued in August 2005, only eszopiclone, which has been studied in a 6-month double-blind trial with a 6-month open-label extension, had been approved for use without a specified time limit. The other approved drugs at the time had only been studied in short-term trials and their approved use was limited to 35 days. (Ramelteon was subsequently approved without restrictions on the duration of its use.)

According to Dr Erman, the FDA's stance is partly a result of recognizing that these drugs are often used long term, especially in patients with comorbidities. "It's not the model that we might have thought about 20 years ago, where you treat the comorbid issue and give the medication, and 2 weeks later you expect that the patients are back to normal sleep," he said. "Insomnia may be a chronic condition, and we also have increasing data from a lot of studies, including the studies that went into the approval for eszopiclone, which went on for 6 months, and studies of zolpidem looking at 3 months of intermittent use."

These drugs are often used long term, especially in patients with comorbidities.

These data show that tolerance does not develop with continued use, Dr Erman noted. "Based on the safety and efficacy data, and the recognition that these tend to be more chronic problems,

I think the FDA is more understanding of the need for longer term therapy, and therefore about not having restrictions in the labeling that tends to cause physicians to be anxious or uncertain about using these drugs for longer periods.”

Ideally, no patient would take a hypnotic agent long term, says Dr Erman, “but we live in the real world where these problems tend to persist and, as a consequence, we’re being given a slightly more open door to the notion that these can be chronic problems and they require more long-term therapy.”

According to the NIH panel, abuse of the benzodiazepine receptor agonists with short-term use “is not a major problem, but problems with their long-term use requires further study in the general population of insomniacs.” Potential for addiction or habituation is less of a concern with the nonbenzodiazepines than with the benzodiazepine hypnotics.

Long-term efficacy and safety data

A 6-month open-label extension of the first 6-month double-blind trial of eszopiclone in 471 patients with primary insomnia was reported by Wessel and colleagues at the 2005 annual meeting of the American Academy of Neurology (AAN) in Miami Beach. In this trial, the first in which the safety and efficacy of a sleep agent was assessed over a continuous 12-month period, eszopiclone 3 mg nightly produced significant, sustained improvements in patient reports of sleep latency, sleep maintenance, total sleep time, sleep quality, and daytime measures compared with placebo,

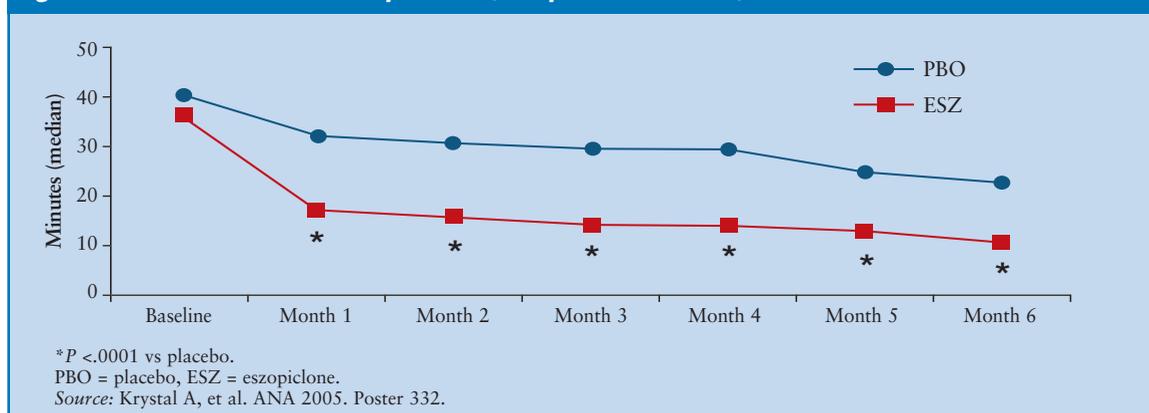
with no evidence of tolerance. Patients who continued to receive eszopiclone in the open-label extension had continued efficacy in all measures of sleep and improvements in daytime functioning. There were no significant withdrawal adverse events on discontinuation of eszopiclone.

To further support the long-term use of eszopiclone, the efficacy and safety of this agent over 6 months of treatment was again demonstrated in a second double-blind, placebo-controlled, multicenter trial of 830 patients with long-term primary insomnia. These data were presented in San Diego at the 2005 meeting of the American Neurological Association by Krystal and colleagues. Compared with placebo, 6 months of eszopiclone 3 mg nightly was associated with significant improvements in sleep latency, wake time after sleep onset (Figure 2), total sleep time, number of awakenings, and total severity score. There was no evidence of tolerance or rebound insomnia in those receiving eszopiclone.

Sleep quality and daytime function measures, such as daytime awareness, ability to concentrate, sense of physical well-being, and ability to function, were also significantly better with eszopiclone over the 6 months compared with placebo. Central nervous system–related adverse events occurred in a similar percentage of patients randomized to placebo or eszopiclone.

According to the authors, the results from this second study were consistent with the previous 12-month study and indicate that “nightly use produced consistent and sustained improvements across all sleep and daytime function parameters

Figure 2. Wake time after sleep onset (sleep maintenance)



and was well tolerated with no pharmacologic tolerance, withdrawal, or rebound insomnia.”

A post-hoc analysis of the first 6-month study of 788 patients (Rubens et al, AAN) with sleep maintenance insomnia (sleeping ≤ 6 hours per night) showed that eszopiclone (3 mg nightly) treatment resulted in significantly less wake time after sleep onset compared with placebo. Furthermore, when patients were stratified by the degree of sleep maintenance impairment, the improvement compared with placebo was greatest in patients with longer wake times after sleep onset at baseline, indicating that eszopiclone maintained sleep irrespective of the degree of baseline sleep impairment.

Treatment in patients with comorbidities

The effect of eszopiclone 3 mg nightly in patients with rheumatoid arthritis and coexisting insomnia was reported at the 2005 annual meeting of the American College of Rheumatology in San Diego by Schnitzer and colleagues.

In this study, up to 4 weeks of nightly double-blind eszopiclone or placebo were compared in 153 adults with rheumatoid arthritis who reported insomnia with wake time after sleep onset of ≥ 45 minutes and total sleep time ≤ 6.5 hours. Again, eszopiclone significantly reduced sleep latency, wake time after sleep onset, and nocturnal awakenings compared with placebo, and significantly increased total sleep time, sleep depth, and sleep quality. Daytime alertness, ability to function, and ability to concentrate were all significantly improved with eszopiclone compared with placebo. Total scores on the Insomnia Severity Index, as well as scores on several of its individual components, were also significantly better with eszopiclone compared with placebo. There were significant eszopiclone-related improvements in most rheumatoid arthritis pain scales, including the number of tender joints, and ability to function relative to placebo.

Eszopiclone and fluoxetine coadministration in depressed patients with comorbid insomnia was investigated by McCall and colleagues and presented at the 2005 APA annual meeting. In the study, 545 patients who met *DSM-IV* criteria for major depression received fluoxetine, 20 mg every

morning, plus either eszopiclone 3 mg or placebo nightly for 8 weeks. In addition to improved sleep, patients randomized to eszopiclone had significantly greater improvement in the Hamilton Rating Scale for Depression (HAM-D17) scores at week 4, with progressive improvement at week 8, than those randomized to placebo. At week 8, more eszopiclone than placebo recipients were classified as responders (50% decrease from baseline HAM-D17) (74% vs 61%) and remitters (HAM-D17 ≤ 7) (54% vs 41%). Improvements in HAM-D17 scores with eszopiclone were greater in patients with more severe depression. Furthermore, the Clinical Global Impression Improvement and Clinical Global Impression Severity scores were significantly improved with eszopiclone compared with placebo. Fluoxetine dose increases were more common in the placebo group than in the eszopiclone group.

Buysse and colleagues reported on the sleep effects of eszopiclone with fluoxetine in this same cohort of 545 patients. Compared with placebo, eszopiclone was associated with significantly shorter sleep latency and greater total sleep time at each treatment week; significantly lower wake time after sleep onset at weeks 1, 3 to 5, and 7 to 8; and higher ratings across the treatment period in sleep quality and depth. Those assigned to eszopiclone also had higher ratings for daytime alertness, ability to concentrate, and well-being. “The rapid sleep improvement with adjunctive eszopiclone may be important, given the relatively slower onset of antidepressant effects with selective serotonin reuptake inhibitors [SSRIs],” the authors concluded.

As these studies imply, cotreatment of insomnia and its comorbidity offers the best chance to improve both conditions, said Dr Roth. “Don’t just treat one and hope the other one gets better, because it won’t,” he warned. “If you have insomnia and depression, or insomnia and pain, treat them both.”

Dr Erman agreed and added, “you get these vicious circles. The factors are more complex with comorbidities, and you want to be sensitive without ignoring either.”

In patients with chronic pain, for instance, “you want to treat the pain so they can sleep bet-

ter and then prepare to attend to the sleep issue so that the pain complaints may be less in the daytime,” said Dr Erman. “If you have pain that disrupts, not only do you sleep worse, but the pain is worse the next day.”

The same holds true for depression, he noted. “The medications used most often these days—the SSRIs—don’t do a very good job of treating the insomnia complaint. You have 60% or more of patients who have sleep problems related to their depression...you probably want to think about treating the sleep complaint as well because of the data generated with eszopiclone that shows that the outcomes are better when you treat both components.”

Conclusions

“Although we’d love to have people off sleep medications, we have to look at how they are feeling and how they are functioning, and ask whether their life, relative to what we perceive to be the cost in terms of risk, side effects, and adverse events is better when they are on the medicine than when they are not,” Dr Erman explained. As with the treatment of depression, the notion of long-term therapy is accepted if it helps patients remain stable, he added.

Invariably, studies of treatments for insomnia must go beyond 1 year, given the chronic nature of insomnia, the NIH panel concluded. For those treatments that have been systematically evaluated, “the panel is concerned about the mismatch between the potential lifelong nature of this illness and the longest clinical trials, which have lasted 1 year or less.”

Large-scale, multisite studies are needed, the panel said, to compare different insomnia treatments and to evaluate their effects over longer

time frames. These studies should use objective and subjective measures of daytime function and quality of life in addition to traditional sleep parameters and should evaluate costs and cost-effectiveness of treatment.

Key points

- Approximately 30% of the general population and 50% of primary care patients report sleep disturbances.
- Insomnia is characterized by difficulty in initiating or maintaining sleep or waking up too early.
- Insomnia is considered chronic if symptoms persist ≥ 30 days.
- Patients with insomnia typically have 1 or more psychiatric and medical comorbidities.
- The diagnosis of insomnia is based primarily on the patient’s history.
- Cognitive-behavioral approaches, such as stimulus control and sleep restriction, have demonstrated efficacy in treating insomnia, but practical issues prevent widespread use of these techniques as primary treatment.
- Only 2 classes of drugs have been FDA-approved for the treatment of insomnia: benzodiazepine receptor agonists and a selective melatonin receptor agonist.
- The newer benzodiazepine receptor agonists have fewer and less severe adverse effects than the traditional agents in this class.
- The need for long-term therapy of chronic insomnia is gaining acceptance and 3 of the newer sleep agents—eszopiclone, ramelteon, and zolpidem extended-release—are approved without time limitations on their use.

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