

Current and New Thinking in the Management of Comorbid Insomnia

David N. Neubauer, MD

Abstract

Insomnia occurs predominantly in conjunction with a medical or psychiatric illness. New thinking regarding the treatment of comorbid insomnia has moved the field away from practices that called for treating the comorbid condition to resolve the coexisting insomnia to one in which the insomnia is treated as a separate condition. Although 10 medications currently are approved by the US Food and Drug Administration for the treatment of insomnia, only 2, eszopiclone and zolpidem, have been evaluated for efficacy in patients with chronic comorbid insomnia. Studies suggest clear benefits in comorbid insomnia. Nonpharmacologic treatments, such as cognitive behavioral therapy, sleep hygiene, and relaxation training, have also been investigated for comorbid insomnia, with studies suggesting these approaches may be effective either alone or in conjunction with medications. While behavioral issues should be optimized, clinicians need to customize treatments for patients with comorbid insomnia based on coexisting medical and psychiatric morbidities, age, medical history, current medications, and lifestyle issues.

(Am J Manag Care. 2009;15:S24-S32)

For author information and disclosures see end of text.

Comorbid insomnia is a relatively new term within the sleep medicine community, arising from the 2005 National Institutes of Health (NIH) State-of-the-Science conference statement on chronic insomnia.¹ The nomenclature change may seem insignificant, but it represents an important shift in the way insomnia is viewed in relation to coexisting morbidities. Rather than being considered “secondary” to medical and psychiatric conditions, with the assumption that it will resolve with the correction of the medical condition itself, insomnia is increasingly being appreciated as a separate morbidity requiring treatment either alone or in conjunction with the comorbid condition.

This shifting paradigm comes none too soon, given the prevalence of comorbid insomnia. As noted in Dr. Thomas Roth’s article in this supplement,² up to 90% of insomnia patients seen in primary care practices have comorbid conditions.^{3,4} The 2002 National Health Interview Survey data suggested that just 4.1% of those reporting insomnia or trouble sleeping were free of other health conditions, with obesity, hypertension, congestive heart failure, and anxiety or depression being the most frequently encountered.⁵

Meanwhile, a recently published study of 8937 community-living adults found a strong association between frequent (3-4 or 5-6 nights/week) nocturnal awakenings and the presence of major depressive disorder (MDD), bipolar disorder, chronic pain, allergies, and anxiety disorders. The study found that 22.5% of patients with 1 disease, 35.0% with 2 diseases, and 43.8% with 3 or more diseases reported nightly nocturnal awakenings compared with 17.8% of the patients with no comorbid conditions (all $P < .001$). The nocturnal awakenings were primarily chronic, with 90% of patients who experienced them reporting occurrences lasting more than 6 months.⁶

Although the epidemiology of comorbid insomnia and its coexisting morbidities is being defined, clinical studies investigating the most appropriate treatments for this form of insomnia are still emerging. This article attempts to delineate the existing literature on current and investigational options for the treatment of chronic, comorbid insomnia, as well as the unique challenges such treatment poses for clinicians.

Considerations in Comorbid Insomnia Treatment

As with primary insomnia, comorbid insomnia may be described as either sleep-onset insomnia (difficulty falling asleep), sleep-main-

tenance insomnia (interrupted sleep characterized by frequent or extended nighttime awakenings), or early-morning awakenings coupled with an inability to return to sleep.⁷ Patients may exhibit 1 or more manifestations. However, it appears that frequent night awakenings are particularly common in patients with comorbid conditions.^{6,8} A meta-analysis of 177 studies identified sleep continuity problems as the most prevalent form of insomnia in patients with a variety of psychiatric and substance abuse comorbidities.⁹ Posttraumatic stress disorder, for example, is associated with sleep continuity disturbances and recurrent nightmares.¹⁰ Patients with cancer are at least twice as likely to experience sleep disturbances, especially those with lung and breast cancer, who tend to suffer from insomnia and fatigue in particular.¹¹ Given that different treatment approaches may best be used for patients with different comorbid conditions, this should be an important consideration when choosing an appropriate treatment.

Other considerations include the role of comorbid disorders and their treatment in precipitating or prolonging the insomnia symptoms, as well as the role of the sleep disturbance on the course of the comorbid condition; interactions between existing medications and insomnia pharmacotherapy; the patient's substance abuse history; adverse effect profile of specific treatments; and age-specific considerations (children or elderly).

No algorithms exist to guide the clinician in the choice of treatments for comorbid insomnia, and there are little data on primary prescribing patterns for this population. However, one study using data from the National Ambulatory Medical Care Survey from 1996 to 2001 found patients with psychiatric comorbidities (the most common conditions comorbid with insomnia) were 80% more likely to receive a prescription for a medication with high abuse potential (diazepam, lorazepam, oxazepam) than patients without such comorbidities.¹²

Pharmacologic Treatment of Comorbid Insomnia

Despite the availability of 10 US Food and Drug Administration (FDA)-approved sleep medications (Table 1),¹³ a considerable percentage of insomnia patients are still treated with pharmaceuticals not indicated for the treatment of insomnia. In a

■ **Table 1.** US Food and Drug Administration–Approved Insomnia Treatment Medications¹³

Benzodiazepine Receptor Agonists		
	Available Doses, mg	Elimination Half-Life, h
Immediate-Release Benzodiazepines		
Estazolam	1.2	8-24
Flurazepam	15, 30	48-120
Quazepam	7.5, 15	48-120
Temazepam	7.5, 15, 22.5, 30	8-20
Triazolam	0.125, 0.25	2-4
Immediate-Release Nonbenzodiazepines		
Eszopiclone	1, 2, 3	5-7
Zaleplon	5, 10	1
Zolpidem	5, 10	1.5-2.4
Modified-Release Nonbenzodiazepine		
Zolpidem Extended Release	6.25, 12.5	2.8-2.9
Selective Melatonin Receptor Agonist		
Ramelteon	8	1-2.6

frequently cited study, Walsh showed that just 4 of the top 16 medications prescribed for insomnia in 2002 had been approved for that indication.¹⁴ Three of the top 5 were sedating antidepressants (trazodone [27.5%], amitriptyline [7.8%], and mirtazapine [6.7%]), and only 2 were FDA approved for insomnia (zolpidem [20.9%] and temazepam [5.6%]). Since 84% of trazodone prescriptions were for doses subtherapeutic for depression (≤ 100 mg), it is likely that they were prescribed for insomnia.

A meta-analysis of studies on antidepressants used for sleep-related complaints found the most commonly reported adverse events were somnolence, headache, dizziness, and nausea, and concluded that they posed a risk of "harm."¹⁵ Other medications often prescribed for insomnia include sedating antipsychotics such as quetiapine and olanzapine. None of the medications prescribed on an off-label basis for insomnia have any substantial clinical evidence regarding their risk/benefit ratio in the treatment of insomnia.¹

Given the high rate of sedating antidepressants and antianxiety medication use on an off-label

basis for the treatment of insomnia,¹⁴ their use for the treatment of insomnia comorbid to psychiatric conditions may seem appealing from both a cost and adherence perspective. However, clinicians should be cautious about residual daytime sleepiness, as many of these psychotropic medications have relatively long half-lives. Prescribing an antidepressant and insomnia medication rather than a single sedating antidepressant may offer several advantages, including greater selection of possible antidepressants and more reliable and rapid sleep improvement with the sleep medication.

Patients also self-medicate with over-the-counter options that contain the antihistamines diphenhydramine and doxylamine with or without analgesics. These options often result in next-day sedation and may cause significant anticholinergic effects, posing a specific risk to the elderly and to patients taking other anticholinergic medications (antidepressants, antipsychotics).¹³

Approximately 4.5% of those with insomnia (1.6 million Americans) used some form of complementary or alternative medicine to treat their condition in the past 12 months.⁵ The 5 most common dietary supplements used for all conditions were echinacea, ginseng, ginkgo biloba, valerian, and melatonin. However, there is little evidence as to the benefits of valerian, which may have toxic effects.¹ Meanwhile, the NIH panel noted that while melatonin “is thought to be safe” in short-term use, “there is no information about the safety of long-term use.”¹

The only medications endorsed by the NIH State-of-the-Science panel on chronic insomnia were the FDA-approved benzodiazepine receptor agonists (BZRAs) indicated for the treatment of insomnia. (Since then, ramelteon, a selective melatonin receptor agonist, has been approved by the FDA.) The panel did not endorse sedating antidepressants, antipsychotics, or antihistamines because of safety concerns or a lack of evidence of efficacy.¹

Of the FDA-approved insomnia medications now on the market in the United States, 9 are BZRAs (Schedule IV controlled substances), while the tenth operates on melatonin receptors and has no risk of abuse. The BZRAs promote sleep by enhancing the normal inhibitory action of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA_A receptor complex. All of

the FDA-approved hypnotics are relatively rapidly absorbed and generally facilitate rapid sleep onset. Most of the BZRAs are approved for the short-term treatment of insomnia. Eszopiclone, ramelteon, and zolpidem extended-release (ER) have been approved with no implied limitations on their duration of use. In addition, eszopiclone and zolpidem ER are specifically approved for sleep maintenance insomnia.¹⁶⁻¹⁹

Benzodiazepine hypnotics. With the introduction of the nonbenzodiazepine agonists, the older benzodiazepine agents (estazolam, flurazepam, quazepam, temazepam, and triazolam) have fallen out of favor and are prescribed less often. A meta-analysis of studies on their use found the most commonly reported adverse events were somnolence, headache, dizziness, nausea, and fatigue.¹⁵ There is also evidence that using them at higher-than-recommended doses and/or long-term use may be associated with dependency, impairment in psychomotor functioning and coordination, risk of falls in elderly patients, tolerance or dependency, residual effects on waking, respiratory depression, and withdrawal reactions after prolonged use.¹³

Nonbenzodiazepine hypnotics. The introduction of this class of drugs in the early 1990s advanced the pharmacologic treatment of insomnia, whether viewed as transient or chronic, primary or comorbid. The elimination half-life and dose determine the duration of action in promoting sleep or causing residual sedation.²⁰ Zaleplon has the shortest half-life (about 1 hour) and eszopiclone the longest (5-7 hours), with both immediate and ER zolpidem formulations falling in between.¹⁶⁻¹⁹ A meta-analysis of studies on the benzodiazepine and nonbenzodiazepine hypnotics found no significant difference in terms of their effect on sleep latency, although the nonbenzodiazepines were considered safer than the benzodiazepines.¹⁵

The most commonly reported adverse events for nonbenzodiazepine hypnotics are headache, dizziness, nausea, and somnolence,¹⁵ although they appear to have a much lower risk for dependence.¹ Recently, language was added to the package information of all approved sleep-promoting medications concerning the potential for severe allergic reactions and complex sleep-related behaviors, including sleep-driving.¹⁶⁻¹⁹

Melatonin receptor agonists. Ramelteon is the only approved insomnia treatment medication that is not classified as a controlled substance. It is a non-sedating sleep medication that acts on the suprachiasmatic nucleus to influence the circadian rhythm effects on the sleep/wake cycle. Adverse effects include somnolence, dizziness, and fatigue. Ramelteon is not recommended in patients with moderate-to-severe hepatic impairment or in those also taking fluvoxamine.¹⁸

Pharmacologic Studies in Comorbid Insomnia

Eszopiclone and zolpidem are the only compounds with published studies investigating their use in patients with comorbid insomnia.

Eszopiclone. Pollack et al studied the effects of eszopiclone in patients with comorbid insomnia and generalized anxiety disorder (GAD) during a 10-week study. The GAD patients were all treated with escitalopram 10 mg for the entire 10 weeks and randomized to concomitant use of placebo or eszopiclone 3 mg for 8 weeks followed by a single-blind, 2-week placebo period. Compared with the placebo group, the patients treated with eszopiclone experienced significantly greater improvement in sleep and daytime functioning ($P < .05$), greater improvement in anxiety scores ($P < .05$), and better Clinical Global Impressions (CGI) of Improvement at all time points ($P < .02$). The CGI of Severity of Illness was not statistically different after week 1. At week 8, the eszopiclone-escitalopram-treated patients compared with the placebo group demonstrated better anxiety scores for response (63% vs 49%; $P = .001$) and remission (42% vs 36%; $P = .09$).²¹

Fava et al evaluated eszopiclone in a double-blind, placebo-controlled clinical trial involving 545 patients diagnosed with MDD. Patients were randomized to monotherapy with fluoxetine/placebo or cotherapy with fluoxetine and eszopiclone for 8 weeks. Compared with the control group, eszopiclone cotherapy was associated with greater improvements in nighttime sleep, daytime functioning, and more rapid antidepressant effects (assessed via the 17-item Hamilton Rating Scale for Depression [HAM-D-17]) throughout the 8-week treatment period.²² A 2-week, single-blind, placebo, run-out phase of the study found

that the improvements were maintained after discontinuing eszopiclone (with continued fluoxetine treatment) with no withdrawal-related adverse effects.²³

Soares et al evaluated eszopiclone in women with insomnia during perimenopause and the early postmenopausal period.²⁴ The incidence of insomnia increases significantly during this time, due in part to the sleep-disrupting effects of vasomotor symptoms. Some studies have shown a direct correlation between the severity of hot flashes, the severity of insomnia, and a diagnosis of chronic insomnia. Chronic pain, poor health, and sleep apnea may be associated with insomnia in this population.²⁵ The use of eszopiclone 3 mg in 410 women randomly assigned to receive either placebo or the hypnotic for 4 weeks decreased sleep latency ($P < .001$) and wake time after sleep onset (WASO) ($P < .01$) at all weekly time points compared with placebo. Total sleep time (TST) also increased in the eszopiclone group relative to placebo (56.6 vs 33.6 minutes [$P < .001$]). Quality and depth of sleep and daytime functioning also increased in the treatment group ($P < .05$), and several menopause-related measures improved, including mood ($P < .05$).²⁴

Zolpidem. Asnis et al evaluated zolpidem in 190 patients treated with either fluoxetine, sertraline, or paroxetine for a depressive disorder.²⁶ The patients had recovered from their depressed mood, but experienced persistent insomnia. After a 1-week, single-blind placebo period, the patients received either placebo or zolpidem (10 mg) nightly for 4 weeks. The zolpidem-treated cohort showed longer sleep times ($P < .05$), better sleep quality ($P < .01$), and reduced WASO ($P < .05$). All effects except the WASO improvement were for weeks 1 through 4; WASO showed improvement at weeks 1, 2, and 4. There was no evidence of dependence or withdrawal symptoms, although patients showed a transient rebound effect on the first posttreatment night in sleep time and quality.

Dorsey et al evaluated zolpidem 10 mg compared with placebo on sleep in 141 women with perimenopausal and postmenopausal insomnia in a 4-week, randomized, multicenter trial. The zolpidem group reported significantly greater TST ($P < .01$) for each week, reduced WASO, fewer awakenings, and improved daytime functioning (all $P < .05$) compared with placebo.²⁷

One study found that zolpidem ER (12.5 mg) given to patients with comorbid insomnia and MDD, who were also being given an selective serotonin reuptake inhibitor, offered significant improvement in sleep onset, sleep maintenance, and TST over the course of 8 weeks.²⁸

Patients given zolpidem ER slept a total of 101 minutes more compared with 64 minutes more among patients given placebo ($P < .0001$). They also experienced fewer nighttime awakenings and decreased WASO compared with patients given placebo ($P < .0001$), and demonstrated an improvement in sleep-related next-day functioning measures such as morning energy and concentration.

Fava et al presented data on a study in which patients received daily escitalopram (10 mg) and zolpidem ER (12.5) or placebo. The first phase (8 weeks) assessed sleep variables; patients whose depression responded were treated for another 16 weeks. Patients receiving zolpidem ER showed significant improvements in TST, WASO, number of awakenings (NAW), sleep quality, and sleep latency compared with placebo ($P \leq .0003$) at each 2-week assessment during the first phase; and also showed significant improvements in TST, WASO, NAW, and sleep quality from weeks 12 to 24 ($P < .05$). Zolpidem ER did not significantly affect improvements in depression and there was no evidence of rebound insomnia upon discontinuation.²⁹

Future Directions in Pharmacologic Treatment of Insomnia

Another short half-life nonbenzodiazepine hypnotic, indiplon, received an approvable letter from the FDA in late 2007 pending additional clinical and preclinical data.³⁰ Although studies find it is effective in the treatment of chronic primary insomnia in adult and elderly patients, no trials have been published detailing its efficacy in comorbid insomnia.³¹⁻³⁴ A modified-release formulation of indiplon has been shown to be effective in treating subjects with sleep maintenance insomnia.³⁴ However, it is not expected that indiplon will become available in the near future.

With advancing knowledge regarding the regulation of the sleep-wake cycle, investigators are developing new compounds for sleep disorders that work on pathways separate from the GABA system. Agomelatine is a selective melatonin receptor

agonist that interacts with M1/M2 receptors and functions as a 5-HT_{2C} antagonist. It is in late-stage clinical trials for a depression indication, although several studies show efficacy in the treatment of insomnia comorbid with depression.³⁵ A double-blind, randomized study of 332 patients with MDD compared the effects of agomelatine and venlafaxine on subjective assessment of sleep latency and depression.³⁶ After 6 weeks, patients' depression responded equally well to both treatments, but the sleep latency score was significantly better with agomelatine ($P = .001$), with improvement apparent at week 1. Other sleep-related outcomes, including quality, awakenings, and sleep items on the HAMD, were also significantly improved compared with venlafaxine ($P = .021$, $P = .040$, and $P = .044$, respectively).

An open study of agomelatine in 15 patients with depression at 6 weeks showed increased sleep efficiency, reduced time awake after sleep onset, greater slow-wave sleep, and improved sleep quality and continuity.³⁷

Researchers are building on the off-label use of sedating antidepressants such as trazodone and of the over-the-counter use of antihistamines by developing compounds with more selective targets, such as the postsynaptic 5-HT_{2A} and histamine H₁ receptors. Other compounds under investigation for insomnia, although not necessarily comorbid insomnia, are neurosteroids, hypocretin/orexin antagonists, corticotrophin-releasing factor antagonists, and alpha-2-delta calcium channel modulators.³⁸ Also being investigated for the treatment of insomnia are ultra-low-dose doxepin formulations and BZRAs with alternate delivery strategies for middle-of-the-night dosing.³⁸

Nonpharmacologic Treatment for Comorbid Insomnia

Several studies have been published on the use of nonpharmacologic treatments for insomnia comorbid with various medical and psychiatric conditions. Most involve the use of cognitive behavioral therapy (CBT). The goal of the cognitive therapy component in treating insomnia is to challenge the patient's dysfunctional beliefs and misconceptions about sleep and insomnia.³⁹ It is typically provided in conjunction with 1 or more behavioral approaches designed to improve sleep.

They include the following:

Sleep hygiene. The principles of sleep hygiene are listed in [Table 2](#). The goal is to create a mental state designed to reduce the hyperarousal associated with insomnia, coupled with a calm and relaxed environment conducive to sleep.⁴⁰⁻⁴²

Relaxation training. The goal of relaxation training is to reduce physiologic and cognitive arousal at bedtime. Techniques used include progressive muscular relaxation, transcendental meditation, yoga, and biofeedback.⁴⁰

Stimulus control. The goal of stimulus control is to help the patient view the bed and bedroom solely as a place for sleep or sexual activity, and to remove influences that do not support sleep. Patients are instructed to avoid other activities while in bed. They should not watch television, use computers, talk on the phone, or read while in bed.⁴⁰ This helps remove bedtime cues that perpetuate the conditioned hyperarousal that has become associated with attempts to sleep and, instead, trains the patient to associate going to bed with a successful attempt to sleep. Patients are also instructed to remain in the bed awake for no more than 10 minutes when attempting to sleep. If they are unable to sleep after that time, they are to get up and engage in nonstimulating activities until they feel sleepy again and then return to bed. Early in therapy patients may need to repeat this cycle several times during the night. Patients are also instructed to avoid daytime napping and to maintain a regular waking time in the morning.

Sleep restriction. The goal of sleep restriction is to limit patients' time in bed so they sleep most of the time they are in bed. This addresses the excessive time in bed while awake that can perpetuate insomnia.⁴³ For instance, patients who are in the bed for 9 hours but report sleeping for only 5 hours are advised to remain in the bed for 5 hours, perhaps from 2 AM until 7 AM. Patients are instructed to maintain a daily sleep/wake log to monitor their nightly amount of sleep. The sleep restriction schedule has patients getting up at their regular morning time, but limits their time in bed by having them go to bed later. Sleep efficiency is the time asleep divided by the time in bed. Once patients' sleep efficiency over 5 nights reaches 90% or greater, they may go to bed 15 to 30 minutes earlier succeeding nights. A drop below 85% requires

■ **Table 2. Sleep Hygiene Elements**⁴⁰⁻⁴²

A regular sleep/wake cycle
Regular exercise in the morning or afternoon, but not within 3 hours of bedtime
Increased exposure to bright light during the day
Avoiding exposure to bright light during the night
Avoiding heavy meals and/or drinking within 3 hours before bedtime
Avoiding stimulants such as caffeine and nicotine, as well as alcohol
Creating a sleep environment that avoids temperature extremes and disruptive noises (consider a white noise machine)
Avoiding excessive wakeful time in bed
Following a regular, relaxing routine before bed

that patients delay their bedtime. Generally, the time in bed is never restricted below 5 hours for safety purposes.

The evidence supporting the use of these approaches in the treatment of primary insomnia is abundant. Smith et al conducted a meta-analysis of 21 studies assessing the benefits of nonbenzodiazepines or behavioral treatments for primary insomnia and found similar outcomes in all sleep measures except sleep latency, which showed a greater benefit with behavioral therapy.⁴⁴ A case-control study of 89 patients found a trial of at least 4 sessions of CBT resulted in a 34% reduction in sleep latency, 13% reduction in the NAW, 56% decrease in WASO, and 29% increase in TST.⁴⁵ These outcomes are similar to those cited in the insomnia treatment CBT and pharmacologic literature.⁴⁴

Most relevant for the purposes of this article is that medical and psychiatric comorbidities do not appear to significantly undermine the outcomes of these nonpharmacologic approaches. An analysis of 12 studies evaluating psychological and behavioral treatments for comorbid insomnia concluded they were effective therapies for medical and, to a lesser extent, psychiatric conditions, with treatment benefits sustained over time.⁴⁶ The studies and the review support the evolving paradigm in the treatment of comorbid insomnia, namely, that insomnia-specific treatment is effective even if the sleep disturbance is related to a comorbid condition.

One study of 60 patients with insomnia associated with chronic pain determined that CBT was

more effective than a control treatment on measures of sleep-onset latency, WASO, and sleep efficiency, but not on the overall NAW or TST.⁴⁷ The researchers did not assess the effect of the insomnia treatment on pain parameters. However, Edinger et al examined pain-related outcomes in their study of 42 patients with fibromyalgia. They found that treating insomnia with CBT significantly improved subjective sleep parameters compared with sleep hygiene or a usual treatment group. They also noted that patients treated with a combination of sleep hygiene and CBT exceeded the researchers' expectations on measures of pain and mental well-being, possibly due, in part, to the exercise instructions included in the intervention.⁴⁸

Insomnia associated with various medical conditions may also be relieved through CBT. Savard et al compared the efficacy of 8 weeks of group CBT with a waiting list control in 57 women with insomnia occurring in the context of breast cancer.⁴⁹ All sleep variables showed significant improvements from pre- to posttreatment, whether measured via sleep diaries or polysomnography ($P = .01$ and $P = .05$, respectively). All benefits were maintained over time, with self-reported improvement on TST and the Insomnia Severity Index showing signs of further improvement. Patients in the treatment group also reported significantly less nightly use of hypnotic agents; exhibited significantly less depression, anxiety, and fatigue ($P < .001$ for each); and had significantly higher scores on the global quality-of-life scale ($P < .0001$).

Combining medical and psychiatric treatments with behavioral insomnia therapies offers another valuable option. Manber et al evaluated the use of escitalopram with CBT in 60 patients with MDD and insomnia.⁵⁰ The control group received escitalopram and a quasi-desensitization procedure. The treatment group exhibited a 61.5% remission from depression compared with 33.3% in the control group. Although this difference was not statistically significant, it was viewed as clinically significant. The treatment group also exhibited a clinically and statistically significant improvement in insomnia (50% vs 7.7%; $P = .05$), with significant improvement in all sleep-related measures except TST.

The use of CBT in patients with such conditions as depression, posttraumatic stress disorder, bipolar disorder, generalized anxiety, and

obsessive-compulsive disorder has been studied and shown to have moderate-to-large treatment effects. These data suggest that CBT may be promising for patients who have medical and psychiatric comorbidities, and may also indirectly improve medical and psychological conditions when successful at improving sleep.⁴⁴

Conclusion

A greater awareness of the incidence of comorbid conditions in patients with insomnia, and the benefit of treating the insomnia as a separate condition not necessarily secondary to the medical or psychiatric morbidity, is changing traditional treatment paradigms of insomnia. Although several BZRA hypnotic and 1 selective melatonin receptor agonist medications are available for the treatment of primary, chronic insomnia, their use in comorbid insomnia is just beginning to be investigated more extensively. Meanwhile, the use of CBT and behavioral therapies in the treatment of comorbid insomnia appears to be effective for a wide range of patients.

Choosing the appropriate treatment for patients remains an individual decision based on the patient's medical status, age, existing polypharmacy, type of insomnia, and lifestyle issues. Clinicians have a wide range of options at their disposal, which may be used in the treatment of comorbid insomnia either singly or together. What is most important is that clinicians begin therapy for the insomnia as soon as a clear diagnosis is made, which may minimize later morbidities and potentially improve outcomes for the coexisting morbidity.

Acknowledgment

Thank you to Debra Gordon, medical writer, who assisted in the writing of this article.

Author Affiliation: From the Department of Psychiatry and Behavioral Sciences, Johns Hopkins Sleep Disorders Center, Baltimore, MD.

Funding Source: Financial support for this work was provided by Sepracor.

Author Disclosure: Consultant/advisory board member and lecturer for sanofi-aventis and Takeda Pharmaceuticals North America.

Authorship Information: Concept and design; drafting of the manuscript; critical revision of the manuscript for important intellectual content.

Address correspondence to: David N. Neubauer, MD, Associate Director, Johns Hopkins Sleep Disorders Center, 4940 Eastern Ave, Box 151, Baltimore, MD 21224. E-mail: neubauer@jhmi.edu.

REFERENCES

1. NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. *NIH Consens State Sci Statements*. 2005;22(2):1-30.
2. Roth T. Comorbid insomnia: current directions and future challenges. *Am J Manag Care*. 2009;15:S6-S13.
3. Roth T, Roehrs T. Insomnia: epidemiology, characteristics, and consequences. *Clin Cornerstone*. 2003;5(3):5-15.
4. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *JAMA*. 1989;262(11):1479-1484.
5. Pearson NJ, Johnson LL, Nahin RL. Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 National Health Interview Survey data. *Arch Intern Med*. 2006;166(16):1775-1782.
6. Ohayon MM. Nocturnal awakenings and comorbid disorders in the American general population. *J Psychiatr Res*. 2008;43(1):48-54.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
8. Thase ME. Correlates and consequences of chronic insomnia. *Gen Hosp Psychiatry*. 2005;27(2):100-112.
9. Benca RM, Obermeyer WH, Thisted RA, Gillan JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651-668.
10. Neylan TC. Sleep disturbances associated with post-traumatic stress disorder. *Psychiatric Times*. 2008;25.
11. Liu L, Ancoli-Israel S. Sleep disturbances in cancer. *Psychiatric Annals*. 2008;38:9.
12. Rasu RS, Shenolikar RA, Nahata MC, Balkrishnan R. Physician and patient factors associated with the prescribing of medications for sleep difficulties that are associated with high abuse potential or are expensive: an analysis of data from the National Ambulatory Medical Care Survey for 1996-2001. *Clin Ther*. 2005;27(12):1970-1979.
13. Neubauer DN. The evolution and development of insomnia pharmacotherapies. *J Clin Sleep Med*. 2007;3(5 suppl):S11-S15.
14. Walsh JK. Drugs used to treat insomnia in 2002: regulatory-based rather than evidence-based medicine. *Sleep*. 2004;27(8):1441-1442.
15. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *J Gen Intern Med*. 2007;22(9):1335-1350.
16. Lunesta [package insert]. Marlborough, MA: Sepracor; 2007.
17. Ambien [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2008.
18. Rozerem [package insert]. Deerfield, IL: Takeda Pharmaceuticals; 2006.
19. Sonata [package insert]. Bristol, TN: King Pharmaceuticals; 2007.
20. Fraser AD. Use and abuse of the benzodiazepines. *Ther Drug Monit*. 1998;20(5):481-489.
21. Pollack M, Kinrys G, Krystal A, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psychiatry*. 2008;65(5):551-562.
22. Fava M, McCall WV, Krystal A, et al. Eszopiclone coadministered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry*. 2006;59(11):1052-1060.
23. Krystal A, Fava M, Rubens R, et al. Evaluation of eszopiclone discontinuation after cotherapy with fluoxetine for insomnia with coexisting depression. *J Clin Sleep Med*. 2007;3(1):48-55.
24. Soares CN, Joffe H, Rubens R, Caron J, Roth T, Cohen L. Eszopiclone in patients with insomnia during perimenopause and early postmenopause: a randomized controlled trial. *Obstet Gynecol*. 2006;108(6):1402-1410.
25. Ohayon MM. Severe hot flashes are associated with chronic insomnia. *Arch Intern Med*. 2006;166(12):1262-1268.
26. Asnis GM, Chakraborty A, DuBoff EA, et al. Zolpidem for persistent insomnia in SSRI-treated depressed patients. *J Clin Psychiatry*. 1999;60(10):668-676.
27. Dorsey CM, Lee KA, Scharf MB. Effect of zolpidem on sleep in women with perimenopausal and postmenopausal insomnia: a 4-week, randomized, multicenter, double-blind, placebo-controlled study. *Clin Ther*. 2004;26(10):1578-1586.
28. Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T; ZOLONG Study Group. Long term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep*. 2008;31(1):79-90.
29. Fava M, Asnuis G, Shrivastava R. Zolpidem extended-release, co-administered with escitalopram, improves insomnia in patients with comorbid insomnia and major depressive disorder. Paper presented at: American Psychiatric Association Annual Meeting; 2008; San Francisco, CA.
30. Neurocrine receives approvable letter for indiplon capsules with additional safety and efficacy data required by FDA [press release]. <http://phx.corporate-ir.net/phoenix.zhtml?c=68817&p=irol-newsArticle&ID=1086951&highlight=>. Accessed April 26, 2008.
31. Walsh JK, Moscovitch A, Burke J, Farber R, Roth T. Efficacy and tolerability of indiplon in older adults with primary insomnia. *Sleep Med*. 2007;8(7-8):753-759.
32. Lydiard RB, Lankford DA, Seiden DJ, Landin R, Farber R, Walsh JK. Efficacy and tolerability of modified-release indiplon in elderly patients with chronic insomnia: results of a 2-week double-blind, placebo-controlled trial. *J Clin Sleep Med*. 2006;2(3):309-315.
33. Farber RH, Burke PJ. Post-bedtime dosing with indiplon in adults and the elderly: results from two placebo-controlled, active comparator crossover studies in healthy volunteers. *Curr Med Res Opin*. 2008;24(3):837-846.
34. Roth T, Zammit GK, Scharf MB, Farber R. Efficacy and safety of as-needed, post bedtime dosing with indiplon in insomnia patients with chronic difficulty maintaining sleep. *Sleep*. 2007;30(12):1731-1738.
35. Doghramji K. Melatonin and its receptors: a new class of sleep-promoting agents. *J Clin Sleep Med*. 2007;3(5 suppl):S17-S23.
36. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry*. 2007;68(11):1723-1732.
37. Quera Salva MA, Vanier B, Laredo J, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. *Int J Neuropsychopharmacol*. 2007;10(5):691-696.

38. Neubauer DN. New directions in the pharmacologic treatment of insomnia. *Primary Psychiatry*. 2006;13:51-57.
39. Bootzin RR, Perlis ML. Nonpharmacologic treatments of insomnia. *J Clin Psychiatry*. 1992;53(suppl):37-41.
40. National Heart, Lung, and Blood Institute (NHLBI) Working Group on Insomnia. Insomnia: Assessment and Management in Primary Care. NIH Publication 98-4088; 1998.
41. Kupfer DJ, Reynolds CF 3rd. Management of insomnia. *N Engl J Med*. 1997;336(5):341-346.
42. Lippmann S, Mazour I, Shahab H. Insomnia: therapeutic approach. *South Med J*. 2001;94(9):866-873.
43. Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. *Sleep*. 1987;10(1):45-56.
44. Smith MT, Perlis ML, Park A, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry*. 2002;159(1):5-11.
45. Perlis ML, Sharpe M, Smith MT, Greenblatt D, Giles D. Behavioral treatment of insomnia: treatment outcome and the relevance of medical and psychiatric morbidity. *J Behav Med*. 2001;24(3):281-296.
46. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). *Sleep*. 2006;29(11):1398-1414.
47. Currie SR, Wilson KG, Pontefract AJ, deLaplante L. Cognitive-behavioral treatment of insomnia secondary to chronic pain. *J Consult Clin Psychol*. 2000;68(3):407-416.
48. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. *Arch Intern Med*. 2005;165(21):2527-2535.
49. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol*. 2005;23(25):6083-6096.
50. Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep*. 2008;31(4):489-495.