SUPPLEMENT

New Paradigms in Comorbid Insomnia

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THE AMERICAN JOURNAL OF MANAGED CARE

New Paradigms in Comorbid Insomnia

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New Paradigms in Comorbid Insomnia

This supplement to *The American Journal of Managed Care* reviews the current evidence regarding comorbid insomnia in various populations.

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New Paradigms in Comorbid Insomnia

*I*nsomnia is a highly prevalent sleep disorder throughout the world.[1] It is defined as difficulty in initiating and maintaining sleep, or nonrestorative sleep associated with some type of daytime impairment or distress. It can occur as an independent disorder (ie, primary insomnia) or, more commonly, with 1 or more medical, psychiatric, or primary sleep disorders (comorbid insomnia). Insomnia is a chronic disorder and typically does not remit spontaneously. It is important to differentiate insomnia from sleep deprivation. Sleep deprivation refers to the loss of sleep associated with inadequate opportunity or circumstance for sleep. In contrast, insomnia refers to the loss of sleep despite adequate circumstance and opportunity to sleep but an inability to do so.[2]

The medical view of chronic insomnia and its impact in the medical, social, economic, and workplace spheres received renewed attention after an independent panel of sleep experts issued a State-of-the-Science Conference Statement on the condition in 2005, the first since 1983. The conference, sponsored by the National Institutes of Health, confirmed the significant prevalence of insomnia in conjunction with other medical and psychiatric conditions. More important, however, it gave credence to the fact that chronic insomnia is not simply a symptom of these other morbidities, but a separate medical disorder requiring treatment in its own right. A marker of this change is the acceptance of the term *comorbid insomnia* to replace the previously used *secondary insomnia*. The report also clearly identified the need to treat insomnia on a long-term basis.[3]

Prevalence estimates for insomnia vary widely. An estimated 4% to 40% of adults experience acute or transient forms of sleep disturbance in any 1-year period, while an estimated 10% of the American population meets diagnostic criteria for chronic insomnia, up to 50% of those receiving medical care.[3,4] At-risk populations include women, the elderly, shift workers, and individuals with comorbid physical and mental disorders.[5] The condition is particularly prevalent in individuals with psychiatric conditions, including major depressive disorder and anxiety disorders.[6,7]

The comorbidities associated with insomnia are many, including altered mood; impaired functionality; increased risk for depression; increased sensitivity to pain; increased risk of falls in the elderly; attention, concentration, or memory impairment; reduction in motivation and energy; increased risk of errors at work and accidents while driving; headaches and gastrointestinal symptoms; and fatigue/malaise.[8]

This supplement reviews the current evidence regarding comorbid insomnia in various populations. The first article, by Thomas Roth, PhD, describes the

incidence and impact of comorbid insomnia from an economic, medical, and treatment perspective. Most importantly, it conveys the emerging body of evidence pointing to the need to treat insomnia and any existing comorbidities as separate conditions, a new paradigm in the treatment of insomnia.

In the second article, Christina S. McCrae, PhD, addresses comorbid insomnia in the elderly, particularly as it relates to pain. She underscores the fact that although changes in sleep architecture occur with age, they are not the primary source of the increased prevalence of insomnia in older individuals. Rather, clinicians need to be aware of the extraordinarily high prevalence of comorbid insomnia in this population, and view an insomnia complaint as a potential marker for other medical or psychiatric conditions. She also details the existing literature on treating comorbid insomnia in this population.

In the final article, David N. Neubauer, MD, addresses pharmacologic and nonpharmacologic treatment options for comorbid insomnia, including emerging new therapies and treatment paradigms. He describes 3 medications that have been specifically studied in comorbid insomnia, as well as several studies examining the use of behavioral therapies to address comorbid insomnia.

These articles provide an opening for a continuing discussion about the need to revisit current assumptions regarding insomnia as an important factor in the overall status of patients with medical and psychiatric conditions. In addition, they appreciate the impact that treating the insomnia *as well as* the comorbid condition may have on both conditions, and on the patient's overall health.

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Comorbid Insomnia: Current Directions and Future Challenges

Thomas Roth, PhD

Abstract

Insomnia is a leading cause of absenteeism, presenteeism (lost productivity when employees are at work), accidents, and errors in the workplace. Overall direct and indirect costs exceed $30 billion annually. A significant portion of these costs are attributable to patients with comorbid insomnia, making these conditions a significant clinical public health issue. These comorbid conditions include mood and anxiety disorders; chronic pain; respiratory, urinary, and neurologic conditions; diabetes; and cardiovascular diseases. Traditional treatment for insomnia with comorbid conditions has focused on treating the comorbid condition with the expectation that the insomnia will resolve. Recent studies, however, suggest this approach is not the most appropriate. Instead, treating both conditions simultaneously may improve the outcomes for each.

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Various studies suggest that the vast majority of insomnia patients seen in psychiatric practices, and about 50% of those seen in primary care practices, have comorbid conditions.[1,2] Thus, the issue of insomnia with associated comorbidities, whether the result of, as a contributing factor to, or as a separate entity from the insomnia appears to be a significant patient as well as public health issue,[3] although to what extent remains unclear given the lack of consistent diagnosis for insomnia in primary care practices.[4] There is also little research on the economic and quality-of-life repercussions of comorbid insomnia versus primary insomnia, defined as insomnia with no identifiable cause.

The phrase "comorbid insomnia" emerged from the 2005 National Institutes of Health's (NIH) State-of-the-Science Conference on the Manifestations and Management of Chronic Insomnia in Adults, to describe the presence of insomnia in the context of a medical psychiatric disorder.[3] Previously, the condition was known as "secondary insomnia." The *International Classification of Sleep Disorders-2 (ICSD-2)* defines it in 2 ways: "Other Insomnia Due to a Mental Disorder," for all psychiatric-related comorbidities; "Other Insomnia Due to a Known Physiological Condition," for all medical comorbidities. The former requires insomnia as well as a mental disorder classified under the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria, with the insomnia related in time to the mental disorder. Although the severity of each varies together, that of the insomnia exists beyond what might be typically expected as a symptom of the psychiatric condition. The latter requires the presence of insomnia as well as a medical condition known to affect sleep.[5] Under *DSM-IV*, however, the insomnia may be "related" to an Axis I or Axis II disorder, but the temporal continuity is not required between the 2 disorders.[6] The problem with both definitions is that each assumes that the insomnia is "secondary" to the primary medical or psychiatric condition. However, as articulated in the 2005 NIH conference, the causal relationships appear to be more complex in most disorders.[3] This article explores that assumption and highlights its implications for treatment.

Impact of Insomnia

Insomnia has a significant impact on individuals' health and quality of life, particularly those with comorbid conditions affecting the central nervous system (CNS).[7,8] The impact appears related to the

effect on daytime functioning as well as the status of their comorbid condition. For instance, various studies found that patients with chronic insomnia have significantly higher risks for falls and accidents.[1,9] One study reported that 8% of workers with severe insomnia were involved in industrial accidents compared with 1% of good sleepers (*P* = .0150).10 Other studies have shown sleep-onset insomnia to be a statistically significant risk factor in being involved in a traffic accident11; in fact, those suffering from insomnia are more than twice as likely to have an automobile accident.[12]

In addition, adults with severe insomnia miss twice as many workdays as those without insomnia, even when matched for work type and schedule.[10] In fact, insomnia may be the greatest predictor of absenteeism in the workplace.[13] Employees with severe insomnia have been shown to make significantly more errors at work (15% vs 6%; *P* <.001), and were more than twice as likely to exhibit presenteeism, or poor efficiency, as those without insomnia (18% vs 8%; *P* = .0004).[10]

People with chronic insomnia also use significantly more medical services than those without insomnia.[4,10,14,15] Leger et al found twice as many individuals with severe insomnia were hospitalized in the year prior to an administered questionnaire (18% vs 9%; *P* = .0017) than those without insomnia. They also found this cohort used more medications than those without insomnia, particularly cardiovascular, CNS, urogenital, and gastrointestinal drugs.[10] There is also data indicating patients with depressive disorders suffering from insomnia have a greater suicide risk than those without insomnia.

This translates into higher costs.[16,17] Even controlling for age, sex, and chronic disease score, average total health services are approximately 60% higher in those with insomnia than in those without insomnia.[18] Ozminkowski et al found that average direct (inpatient, outpatient, pharmacy, and emergency department costs) and indirect costs (absenteeism and the use of short-term disability programs) for adults in the 6 months before a diagnosis for insomnia or beginning prescription treatment for the condition were approximately $1253 greater than for those without insomnia (ages 18-64), whereas average direct costs among adults aged 65 and older were $1143 greater.[19]

Although the economic and social costs of comorbid insomnia compared with primary insomnia have yet to be investigated, it is likely that they account for the majority of the annual $30 billion to $35 billion in costs for chronic insomnia simply because comorbid insomnia is so much more prevalent.[17,20]

Comorbid Insomnias: Untangling the Complexities

As noted earlier, the prevalence of comorbidities and insomnia is significant. Kuppermann et al examined the records of 369 employees together with a telephone screen to evaluate various aspects of their physical and mental health and sleep quality, and found those reporting a current sleep problem were 4 times more likely to have a possible mental health problem as those reporting no sleep difficulties. They were also significantly more likely to report gastrointestinal problems, frequent headaches, and muscle, back, or neck pain.[21]

Simon et al evaluated functional impairment and healthcare utilization for patients with and without current insomnia. They found that 24% of patients with insomnia had moderate-to-severe occupational disability compared with 14% of those without insomnia (odds ratio [OR], 1.91). Patients with insomnia were also twice as likely as those without insomnia to have days of restricted activity and days spent in bed due to illness.[18] Overall, 3.5 days of disability per month were associated with insomnia, an amount similar to that seen with anxiety and somatoform disorders.[22]

Finally, our work evaluating sleep problems with comorbid mental disorders and role functioning using the National Comorbidity Survey Replication found all sleep problems were significantly and positively related to 1 or more anxiety disorders, mood disorders, impulse-control disorders, or substance abuse disorders.[8] We also found significant associations between insomnia and self-reported role impairment that cannot be explained only by comorbid mental disorders, all of which supports the NIH conference report's assertion that insomnia is a significant patient and public health problem.[3]

Evaluating Comorbid Insomnia

Differentiating between primary and comorbid insomnia can prove challenging for the clinician. Does the accompanying condition play a causal role in the insomnia, is it the consequence of the

insomnia, is it incidental to the insomnia, or is it comorbid? The complexity increases when the influence of sleep-related disorders on sleep quality and insomnia are considered, including sleep apnea and periodic limb movements. Similarly, circadian rhythm disorders, such as shift work disorder (Drake Sleep) or phase delay, are associated with disturbed sleep. These result in insomnia symptoms and represent special cases of comorbid insomnia. Thus, insomnia may be comorbid with medical, psychiatric, circadian, or sleep disorders.

An accurate history from the patient and possibly even the bedpartner is paramount in correctly diagnosing comorbid insomnia. Clinicians should consider comorbid insomnia when the onset of the sleep disturbances coincides with or shortly follows that of the comorbid condition; when the course of the insomnia remits and recurs in conjunction with fluctuations in the comorbid disorder; or can be directly linked to some feature of the comorbid disorder, such as pain from chronic arthritis disrupting sleep. Complicating the diagnosis, however, is the fact that insomnia often *precedes* a comorbid disorder, in some instances serving as an early warning sign of an occurrence or recurrence.[23,24] Finally, it is important to consider that the treatment of the comorbid condition may lead to the insomnia. Thus, respiratory stimulants, selective serotonin reuptake inhibitors (SSRIs), beta-blockers, and many other drugs are associated with reports of disturbed sleep.

Yet, as noted later in this article and in the article by Neubauer[25] in this supplement, the cor-rect diagnosis of comorbid versus primary insomnia is particularly important when determining the appropriate treatment plan.

Medical Comorbid Conditions With Insomnia

Becoming aware of the more common comor-bidities, which encompass a wide variety of medical, psychiatric, and sleep disorders, may assist clinicians in managing the condition.

Taylor et al found the following prevalence of conditions in those with chronic insomnia com-pared with those without insomnia: chronic pain (50.4% vs 18.2%), high blood pressure (43.1% vs 18.7%), gastrointestinal problems (33.6% vs 9.2%), breathing problems (24.8% vs 5.7%), heart disease (21.9% vs 9.5%), urinary problems (19.7% vs 9.5%), and neurologic disease (7.3% vs 1.2%) (Table 1).[20]

In addition, they found that people with the following medical problems reported significantly more chronic insomnia than those without insom-nia: breathing problems (59.6% vs 21.4%), gastro-intestinal problems (55.4% vs 20.0%), chronic pain (48.6% vs 17.2%), high blood pressure (44.0% vs 19.3%), and urinary problems (41.5% vs 23.3%) (Table 2).[20]

Leigh et al found insomnia in 31% to 81% of those with osteoarthritis,[26] while other stud-ies found high levels in those with other chronic pain conditions, including rheumatoid arthritis and fibromyalgia.[27] Those with myocardial infarction have a 1.9 OR of mild insomnia, those with conges-

■ **Table 1.** People With Chronic Insomnia Reporting Medical Conditions[20]

| Medical Condition | Prevalence | | | |
	Chronic Insomnia, %	No Insomnia, %	Odds Ratio[a] (95% Confidence Interval)	*P* Value
Chronic pain	50.4	18.2	3.19 (1.92-5.29)	<.001
High blood pressure	43.1	18.7	3.18 (1.90-5.32)	<.001
Gastrointestinal problems	33.6	33.6	3.33 (1.83-6.05)	<.001
Breathing problems	24.8	5.7	3.78 (1.73-8.27)	<.01
Heart disease	21.9	9.5	2.27 (1.13-4.56)	<.05
Urinary problems	19.7	9.5	3.28 (1.67-6.43)	<.01
Neurologic disease	7.3	1.2	4.64 (1.37-15.67)	<.05

[a]Adjusted for depression, anxiety, and sleep disorder symptoms.

■ **Table 2.** People With Medical Conditions Reporting Chronic Insomnia[20]

Medical Condition	Prevalence			
	Chronic Insomnia, %	No Insomnia, %	Odds Ratio[a] (95% Confidence Interval)	P Value
Chronic pain	48.6	17.2	2.27 (1.33-3.89)	<.01
High blood pressure	44.0	19.3	1.92 (1.06-3.46)	<.01
Gastrointestinal problems	55.4	20.0	2.57 (1.37-4.80)	<.01
Breathing problems	59.6	1.4	3.26 (1.56-6.81)	<.01
Urinary problems	41.5	3.3	2.25 (1.13-4.48)	<.05

[a]Adjusted for depression, anxiety, and sleep disorder symptoms.

tive heart failure a 1.6 OR of mild insomnia and 2.5 OR of severe insomnia.[28] Over a 2-year period, Katz and McHorney showed that more patients with hip impairment, osteoarthritis, and peptic ulcer disease reported new or worsened insomnia compared with those without these conditions.[28]

Patients with chronic obstructive pulmonary disease (COPD) have a particularly high prevalence of insomnia, with more than 50% complaining of difficulties initiating or maintaining sleep, and 25% reporting excessive daytime sleepiness.[29] Insomnia may also hold significant implications for pulmonary function in those with COPD and other respiratory conditions. Phillips et al showed small but statistically significant falls in forced expiratory volume in 1 second (1.06 ± 0.11 to 1.00 ± 0.09 L; P <.05) and in forced vital capacity (2.56 ± 0.20 to 2.43 ± 0.17 L; P <.05) following a single night of sleep deprivation. Over time, this could have a significant impact on patients' overall pulmonary status.[30]

Patients with diabetes also report high rates of insomnia. Skomro et al found that 50% of adults with diabetes had insomnia compared with 31% of controls (P = .04), and 15.5% had high Epworth Sleepiness Scores compared with 6% of controls (P = .02).[31] Other work finds impaired glucose regulation with shorter sleep times in those with and without diabetes, as well as an increased risk of diabetes.[32]

Given that the prevalence, morbidity, and mortality of COPD and diabetes have been increasing in the United States and other countries in recent years,[33,34] and the impact of insomnia on clinical parameters, the comorbidity of insomnia with COPD and diabetes will present a significant challenge to employers and clinicians and will be an increased burden to the healthcare system in coming years.

Psychiatric Comorbidities

Insomnia is frequently (about 40% of the time) comorbid with psychiatric conditions.[1] Ford and Kamerow first reported this link in 1989.[2] They found that approximately 40% of patients with chronic insomnia met the diagnosis for 1 or more psychiatric disorders compared with 16% of patients without insomnia. Twenty-four percent had anxiety disorders compared with 10% without insomnia (P <.001); 14% were diagnosed with depression (compared with <1% without insomnia [P <.001]), and 8.6% were diagnosed with dysthymia (compared with 2.1% without insomnia [P <.001]).[2]

In a random sample of 1200 young adults (21- to 30-year-olds) in a 400,000-member health maintenance organization, Breslau et al found a lifetime prevalence of insomnia of 24.6%, with increased prevalence of major depression (31.1% vs 2.7%), any anxiety disorder (35.9% vs 19.1%), alcohol abuse (30% vs 16.7%), and drug abuse (14.4% vs 7.7%) in those with insomnia compared with those without insomnia.[35]

Crum et al assessed the risk of alcohol-related problems among 1537 individuals at risk for problem drinking. Those who reported sleep disturbances because of worry were twice as likely to develop an alcohol-related problem as those without a sleep disturbance (OR, 2.32; 95% confidence interval [CI], 1.31-4.09). The risk was higher for those with any lifetime history of anxiety disorder or dysphoria (OR, 3.82; 95% CI, 1.56-9.38; and OR, 2.71; 95% CI, 1.25-5.91, respectively).[36]

The timing of insomnia vis a vis psychiatric disorders may depend on the disorder itself. Most studies find that insomnia tends to precede or appear at the same time as a mood disorder episode (whether initial or relapse). In one, insomnia preceded the onset of depression in 69% of cases evaluated.[37] In contrast, insomnia tends to appear at the same time or to follow an anxiety disorder episode (whether initial episode or relapse).[38]

Insomnia and Major Depression

Several studies of comorbid insomnia show that depression appears as the condition most likely to exist in conjunction with chronic insomnia (Figure).[35,39-42] Patients with physician-diagnosed major depression have a 2.6 OR of mild insomnia and an 8.2 OR of severe insomnia.[28] Meanwhile, Pigeon et al, in evaluating elderly patients with major depressive disorder (MDD) and/or dysthymia found those with persistent insomnia were 1.8 to 3.5 times more likely to remain depressed compared with those without insomnia (P = .05).[43]

In addition to the above-reported link between insomnia and depression persistence and recurrence, concurrent insomnia and depression may contribute to the higher rates of cardiovascular disease associated with MDD and depressive symptoms.[22] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study of 4041 outpatients with MDD found cardiac disease associated with symptoms of sympathetic arousal and early-morning insomnia.[44]

This is particularly interesting given that patients with chronic insomnia do show physiologic signs of hyperarousal, including increased levels of catecholamines, increased basal metabolic rate[45] and elevated core body temperature, altered heart rate, increased level of CNS as well as systemic metabolic rate, and elevated fast frequency electroencephalograph activity.[46] Many of these variables are also implicated in the development and progression of cardiovascular disease.[47]

Treating Comorbid Insomnia

The treatment paradigm for comorbid insomnia has traditionally focused on treating the medical or psychiatric disorder with the expectation that the insomnia will also resolve.[48]
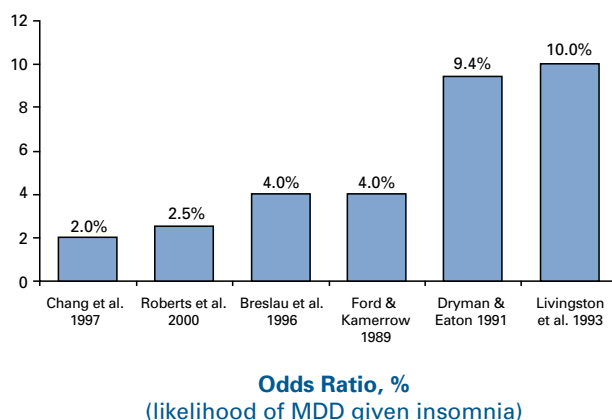
This paradigm has affected treatment modalities for insomnia, with cognitive behavioral treatment (CBT) and hypnotics as monotherapy typically used only in those with primary insomnia, and psychiatric interventions reserved for those with comorbid insomnia.[49] It has also affected research on the appropriate treatment for comorbid insomnia.[48]

Yet while treatment may resolve most symptoms of the comorbid disorder, it often does not improve the insomnia. Nierenberg et al reported that 45% of patients treated for 8 weeks with fluoxetine to MDD remission still exhibited disturbed sleep. Given that 91% of patients with posttreatment insomnia also had pretreatment insomnia, the authors concluded that the symptom was a residual one not related to medication side effects.[50] Katz and McHorney showed that the majority of patients with comorbid conditions still had insomnia 2 years later.[28] This compares to 6% in those with primary insomnia at 1 year.[2] They also showed that 23% developed new-onset insomnia at the 2-year follow-up.[28]

Conversely, treating the insomnia as a separate entity may prove more effective.[51-55] A report of several patients receiving CBT for posttraumatic stress disorder (PTSD) showed the therapy successfully resolved the patients' PTSD, but patients still complained of insomnia. After CBT treatment for insomnia, however, their insomnia resolved.[56]

Other research finds that treating the insomnia and other medical or psychiatric condition concurrently improves insomnia in conditions as diverse as alcohol discontinuation,[57] rheumatoid arthritis,[55] menopausal-associated insomnia,[53] and generalized

■ **Figure.** Insomnia as a Risk Factor for Major Depressive Disorder (MDD)[35,39-42]

Odds Ratio, %
(likelihood of MDD given insomnia)

anxiety disorder.[58] Eaton et al hypothesized that 47% of the incidence of depression at the 1-year follow-up could have been prevented by addressing existing insomnia at baseline.[59]

In addition, treating both the insomnia and the comorbid condition simultaneously may improve the comorbid condition more than treating it alone. Krystal et al randomized 545 patients with insomnia and comorbid MDD to either fluoxetine with nightly eszopiclone (3 mg) or placebo for 8 weeks followed by 2 weeks of continued fluoxetine plus single-blind placebo (n = 387).[60] The cotherapy group showed greater improvement in the 17-item Hamilton Depression Rating Scale (HAMD-17) scores at week 8 (P = .0004) than the monotherapy group, an improvement that was maintained at week 10 (P <.0001). The cotherapy group also exhibited significantly higher depression response and remission rates at week 10 (P <.02), specifically, with regard to HAMD-17 ratings of feelings of guilt; early, middle, and late insomnia; work and activities; retardation; agitation; anxiety psychic; somatic symptoms general; and hypochondriasis compared with the monotherapy group. Importantly, the augmentation of the antidepressant was significant even when the sleep items were excluded from the analysis. The cotherapy group maintained the improvements obtained in the double-blind period during the single-blind run-out period. In addition, after patients stopped taking eszopiclone, they continued to maintain improvements in sleep latency, wake after sleep onset, and total sleep time in the 2-week period after discontinuation (P <.05).

The percentage of patients exhibiting clinically significant insomnia was greater in the monotherapy group than in the cotherapy group at weeks 8 and 10 (54.4 vs 36.8 and 58.7 vs 40.0; P <.009). In addition, the percentage of patients with moderate-to-severe insomnia declined from 88% to 15.2% at week 8 in the cotherapy group, but only from 89% to 27% in the monotherapy group, an improvement that continued through week 10 (P <.009).

This improvement in the comorbid condition by improving sleep has also been shown by using CBT for insomnia in conjunction with an SSRI versus an SSRI only, with those patients undergoing CBT showing a more robust antidepressant response.[61]

Conclusion

The prevalence of chronic insomnia coexisting with 1 or more psychiatric or medical conditions is significant, with particularly high rates seen in patients with depression, chronic pain, respiratory conditions, and diabetes. Although the specific economic and quality-of-life repercussions of comorbid insomnia have not been differentiated from those with primary insomnia, they are likely quite significant. It is clear that insomnia and comorbid conditions have a bidirectional effect, with the status of each impacting the other, potentially affecting the treatment course and outcome. Treating insomnia and the comorbid condition simultaneously as separate conditions may result in greater improvements in each than treating either individually. Additional research is required on the outcomes of such a treatment approach.

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Late-Life Comorbid Insomnia:
Diagnosis and Treatment

Christina S. McCrae, PhD

Abstract

Changing sleep architecture in the elderly may increase their vulnerability to comorbid insomnia. Common comorbid conditions include chronic pain, depression, nocturia, and neurological conditions such as Parkinson's and Alzheimer's disease. Diagnosing and treating comorbid insomnia in an older population poses special challenges for clinicians given the variety of coexisting medical and psychological conditions, polypharmacy, and the potential adverse effects of the most commonly used medications for insomnia in this population. Thus, the use of nonpharmacologic treatments, such as cognitive behavior therapy and relaxation techniques, is recommended before any medical approaches.

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For author information and disclosures see end of text.

Although sleep disorders such as insomnia, daytime sleepiness, and frequent awakenings become more common and chronic with age,[1,2] they are not an inevitable result of aging and should not be treated as such.[3]

Instead of linking insomnia in elderly patients to age, then, clinicians should consider the impact of coexisting physical and mental conditions on sleep. Foley et al, whose review of sleep complaints in nearly 7000 community-dwelling older adults forms the basis for most epidemiologic estimates of sleep disorders in the elderly, found that the prevalence of insomnia in this population increased in conjunction with depressed mood, respiratory symptoms, fair to poor health, or physical disability.[1] Reid et al showed that respondents with only one sleep complaint were still 40% more likely to have a poorer physical health summary score and 23% were more likely to have a higher mental health summary score (**Figure 1**).[4] In fact, sleep disorders in the elderly are strongly associated with significant limitations in activities of daily living, declining quality of life, and morbidity and mortality.[2,4,5] For instance, disrupted or lack of sleep may lead to falls and subsequent nursing home placement and affect cognitive functioning.[6] There is also evidence that sleep disturbances may produce physiologic abnormalities and dysfunction in the elderly that can cause physical[7] and mental disorders,[8] and may increase the severity of chronic conditions such as diabetes.[9]

Although current rates of insomnia in the elderly are significant, ranging from 23% to 57% and appearing more frequently in women,[1] practitioners can expect to see these numbers grow given that adults 65 and older make up the fastest growing segment of the US population.[10] Current estimates call for this sector to grow from 13% of the overall 2010 population in the United States to 19.6% in 2030. Thus, understanding the implications and repercussions of insomnia in older adults, as well as treatment issues specific to this population, is important.

Sleep Architecture and Comorbid Insomnia

Differentiating true sleep-related problems from age-related changes in sleep architecture in an elderly population can be challenging. Changes in sleep architecture are generally accepted as a normal part of aging, but, in reality, only a subset develop clinically significant changes in sleep architecture or complain of the subjective symptoms
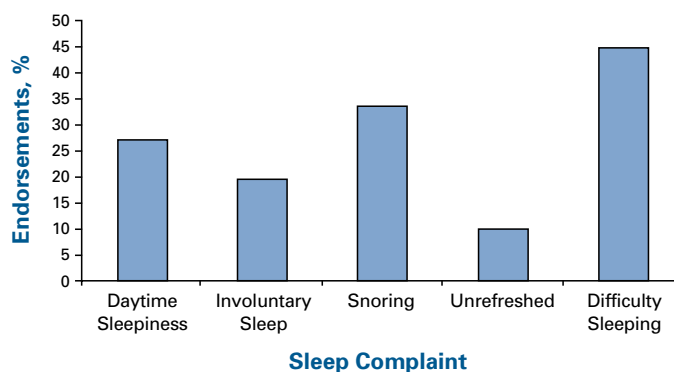
of insomnia. After about age 50, older adults tend to have more awakenings and reduced sleep efficiency. They sleep less (an average of 6-6.5 hours vs 7 hours in middle age); experience more frequent brief arousals; spend more time in the light sleeping stage 1; and have more frequent shifts between sleeping stages. There is also evidence that older adults spend less time in the deeper, slow-wave sleep and rapid-eye movement (REM) sleep, with REM latency also declining with age. By age 60, however, these changes have become fairly constant and do not continue to worsen.[11] Thus, they should not be considered as sleep disorders or insomnia, but as a natural occurrence of aging.[12]

However, the lighter sleep older adults experience makes them more vulnerable to sleep-related interruptions from medical and psychiatric conditions, contributing to the high rates of comorbid insomnia in this population.[13]

The 2003 National Sleep Foundation's Sleep in America Survey, which involved telephone interviews of 1506 participants aged 55 to 84 years of age about their sleep habits and mental and physical health conditions, found that 69% of respondents with 1 or more sleep problems also had 4 or more medical conditions, whereas just 36% of those with no major medical conditions reported sleep problems.[14] Table 1 shows the odds ratio (OR) for insomnia symptoms according to major medical condition.

Other works have found associations between insomnia and arthritis, hypertension, coronary heart disease (CHD), and diabetes.[1,4,14,15] Conversely,

Figure 1. Sleep Complaint Endorsement Rates[a]

[a]Percentage of patients who positively endorsed each complaint on the Five-Item Sleep Questionnaire. Among those reporting complaints with snoring, 29.5% reported feeling unrefreshed as a consequence (ie, 9.8% of the full sample).

improved physical health or even the perception of improved health results in reduced reporting of insomnia.[1] Thus, insomnia in the elderly may be considered a marker for overall mental and physical health.

When assessing older adults for sleep issues, clinicians should consider the severity of the sleep problem; changes in psychosocial, occupational, or physical functioning; and daytime impairment. The latter may manifest as daytime fatigue, irritability, anxiety, feelings of restlessness or other negative effects, cognitive inefficiency, somatic symptoms, errors or accidents while driving, and excessive concerns or worries about sleep.[12]

It is also important that clinicians evaluate patients' overall mental and physical health and

Table 1. Odds Ratio (OR) for Insomnia Symptoms by Major Medical Condition[14]

Medical Condition	Insomnia Symptom, %			
	Difficulty falling asleep (9%), OR (95% CI)	Awake a lot during the night (22%), OR (95% CI)	Wake too early (11%), OR (95% CI)	Wake unrefreshed (14%), OR (95% CI)
Obesity	NS	1.36 (1.02-1.82)	NS	1.45 (1.04-2.01)
Bodily pain	1.89 (1.28-2.78)	2.68 (2.06-3.49)	1.88 (1.32-2.66)	2.11 (1.54-2.90)
Depression	2.44 (1.59-3.73)	1.59 (1.14-2.22)	2.21 (1.49-3.29)	NS
Heart disease	1.99 (1.29-3.07)	1.67 (1.23-2.31)	1.87 (1.27-2.78)	NS
Lung disease	NS	NS	NS	1.50 (1.01-2.24)
Memory problems	1.76 (1.08-2.87)	1.56 (1.07-2.27)	NS	NS

CI indicates confidence interval; NS, not significant.
Reprinted with permission from Foley D, et al. *J Psychosom Res.* 2004;56(5):497-502.

■ **Table 2.** Medications Associated With Insomnia[18,19]

Central nervous system stimulants
Dextroamphetamine
Methylphenidate
Mixed amphetamine salts
Pemoline

Antihypertensives
Alpha-blockers
Beta-blockers
Methyldopa
Reserpine

Respiratory medications
Albuterol
Theophylline

Chemotherapy

Decongestants
Phenylpropanolamine
Phenylephrine
Pseudoephedrine

Hormones
Corticosteroids
Thyroid medications

Psychotropics
Atypical antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors

Anticholinesterase inhibitors

Carbidopa, levodopa

Phenytoin

Alcohol

Caffeine

Nicotine

■ **Figure 2.** Insomnia Comorbid With Pain

N = 18,980; *P* <.001. Based on survey data.

[a]Pain categories included limb pain, backaches, joint pain, gastrointestinal pain, and headaches.
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functioning, as well as all medications, given the high rates of polypharmacy in the elderly[16,17] and the impact of many medications on sleep (Table 2).[18,19]

It is also important to recognize that treating the comorbid medical condition does not necessarily improve the insomnia. This issue is discussed more in depth in the article by Dr Thomas Roth elsewhere in this supplement.[20]
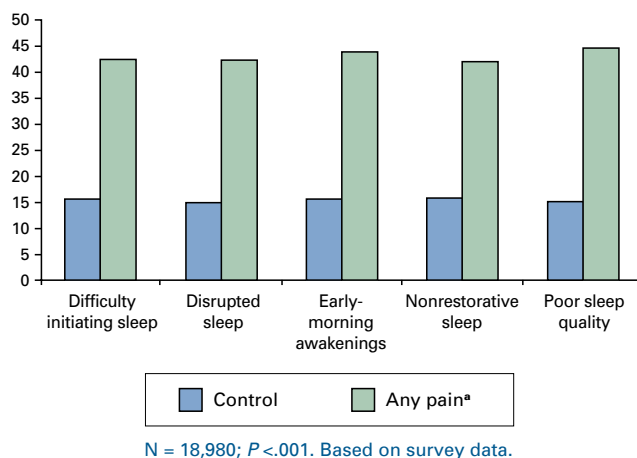
Pain, Depression, and Comorbid Insomnia

One of the most common comorbid conditions affecting sleep quality is chronic pain, which is particularly prevalent in the elderly (Figure 2).[21] Between 50% and 88% of patients attending chronic pain clinics (albeit a self-selecting population) complain of impaired sleep.[22]

Medical conditions associated with chronic pain include rheumatoid arthritis, fibromyalgia, and osteoarthritis. In one of the largest community-based studies to explore the link, Power et al analyzed a cross-sectional nationally representative sample of 118,336 participants ≥18 years of age with arthritis pain, insomnia symptoms, and other sleep-related conditions.[23] They found significantly greater numbers of individuals with arthritis reported pain (45.8%), insomnia (24.8%), and unrefreshing sleep (11.9%) than those without arthritis (11.7%, 10.6%, and 6.1%, respectively [all *P* <.001]). The greater the level of pain, the greater the prevalence of insomnia symptoms and unrefreshing sleep, even in those without arthritis. Adjusting for pain reduced the effect of arthritis on unrefreshing sleep and insomnia symptoms by 64% and 53%, respectively.

Roehrs et al reported that sleep loss increased pain sensation, likely as a result of REM sleep deprivation, which is associated with hyperalgesia.[24] Other studies reported insomnia causing headaches and headaches causing insomnia,[25] and sleep deprivation increasing next-day pain receptivity in patients with fibromyalgia and arthritis.[26,27]

Pain often manifests in conjunction with depression. Wilson et al reported that patients with major depression and insomnia were more likely to score higher on severity (*P* = .005), interference (*P* = .041), life control (*P* <.001), and affective distress (*P* = .005) on the Multidimensional Pain Inventory (MPI) than those with insomnia but without major depression, or with neither

insomnia nor major depression.[28] One potential reason for the link could be that patients reporting depression and pain are more likely to exhibit sympathetic nervous system arousal, a factor in insomnia.[29-31]

In addition, patients with insomnia who did not have major depression still showed higher scores on the Beck Depression Inventory (BDI), less life control on the MPI, and higher scores on the sensory-discriminative dimension of the McGill Pain Questionnaire than participants without either major depression or insomnia.[28] There is also evidence that insomnia perpetuates depression in elderly adults, even after treatment.[32]

In older adults, Taylor et al showed that elderly patients with insomnia exhibited more severe symptoms of depression and anxiety than those without, and were 9.82 and 17.35 times more likely to have clinically significant depression and anxiety, respectively.[33]

Comorbid Insomnia in Parkinson's and Alzheimer's Diseases

Sleep disturbances are particularly prevalent in patients with neurologic diseases related to aging, such as Parkinson's and Alzheimer's disease. Up to two thirds of patients with Parkinson's disease experience sleep-related disorders, including problems falling asleep, and nighttime and early-morning awakenings.[34]

Meanwhile, Tractenberg compared sleep quality in 399 healthy elderly individuals without dementia and 263 persons with a diagnosis of possible or probable Alzheimer's disease. They found a lower prevalence of sleep problems in those without Alzheimer's (18.3%) than in those with Alzheimer's (27.6%) (P <.01). Specifically, patients with Alzheimer's had greater prevalence and frequency of waking after sleep onset (WASO), sleep latency (>30 min to fall asleep), waking too early, and waking at night with pain.[35]

Other Comorbid Conditions

Other conditions that may occur comorbidly with insomnia symptoms include nocturia, a common complaint in the elderly. Nocturia is associated with increased mortality, related in part to the consequences of falls resulting from elderly persons awakening in the night to urinate.[36] In one survey of 100 older adults, 59% attributed their sleep disruption to nocturia.[37]

Insomnia and other sleep complaints may be present with CHD. A review of articles on the association between CHD events and sleep complaints exclusive of sleep apnea found risk ratios of 1.47 to 3.90 between "trouble falling asleep" and coronary events after adjusting for age and various coronary risk factors (combined effect, 1.7; P <.0001).[38]

Hypnotic-Dependent Insomnia

Hypnotic-dependent insomnia (HDI) results from chronic use of hypnotics and sedatives as sleep medication. The disorder is particularly prevalent in the elderly, who are most likely to be prescribed hypnotics for sleep-related disturbances and to use them nearly twice as long as younger users.[39,40] It is characterized by a pattern of tolerance and dependence, and marked by rebound insomnia or excessive sleepiness, anxiety, and depression when the medication is stopped.[41] Older adults with HDI are also at risk for seizures and hallucinations.[42]

The condition should be treated with gradual tapered withdrawal from the medication (10%-25% every 1-2 weeks) over 8 to 12 weeks.[43,44] At the lowest possible dose, medication-free nights should be gradually introduced before the medication is completely stopped. Behavioral interventions may also help facilitate medication withdrawal.[45] If tapered withdrawal fails, switching to a longer-acting, cross-tolerant medication such as clonazepam and/or using medication to suppress withdrawal symptoms such as carbamazepine is an option.[44]

Treating Comorbid Insomnia in the Elderly

When determining the appropriate treatment for older adults with comorbid insomnia, it is important to consider the consequences of any treatment on the patient's overall health and interactions with other medications given the high rate of polypharmacy in older adults.[16]

The most commonly used treatments for insomnia in the elderly are medications, primarily benzodiazepine sedative-hypnotics (estazolam, flurazepam, quazepam, temazepam, and triazolam), the nonbenzodiazepine sedative-hypnotics (eszopiclone, zaleplon, and zolpidem), sedating antidepressants (trazodone, nefazodone) used off label, and over-the-counter antihistamines.[46] More recently,

the first nonsedating sleep medication, ramelteon, a selective MT1/MT2 melatonin receptor agonist was approved for the long-term treatment of insomnia characterized by sleep-onset difficulty in the United States.[47] In addition, eszopiclone, zolpidem extended-release, and ramelteon no longer have any implied limitation on the duration of their use. For some patients, long-term use may be successful in improving nighttime sleep and daytime functioning. However, patients taking any of these medications should be regularly observed and evaluated.[48]

In addition, age-related metabolic changes may extend the half-life of these drugs in older adults, leading to cognitive and motor impairment and sleep-related breathing disorders.[49] Sleep medications in the elderly are also associated with falls, fractures, and more days in the hospital (although these adverse effects may, however, be less frequent and severe with the newer benzodiazepine receptor agonists).[49,50] Because of these age-related issues, there is particular need to monitor drug doses and make any necessary adjustments in the elderly. The starting dose of eszopiclone in an elderly individual, for example, is 1 mg and should not exceed 2 mg (compared with 2-3 mg for nonelderly adults).[51]

In 2007 the US Food and Drug Administration requested that manufacturers of all sedative-hypnotic drug products include stronger language on product labeling concerning the potential for severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving.

A meta-analysis of 24 randomized clinical trials in elderly populations (>60 years of age) who used any pharmacologic sleep aids for ≥5 nights for insomnia (over-the-counter medications, benzodiazepine and nonbenzodiazepine sedative-hypnotics) found similar efficacy and adverse effects between the benzodiazepines and nonbenzodiazepines eszopiclone, zaleplon, and zolpidem, but suggested that sedative-hypnotics may have less benefit for older than younger people with similar or greater risk for adverse effects.[52]

Cotroneo et al conducted one of the few, if not the only, published clinical trial to evaluate medical insomnia treatment on elderly patients with comorbid conditions.[51] Researchers evaluated insomnia treatment with zolpidem, triazolam, or oxazepam on 60 subjects aged ≥70 years. Fifteen had insomnia and dementia; 30 had insomnia and depression; and 15 had insomnia only.

After 6 months of treatment, patients with dementia, who were also treated with the anticholinesterase drugs donepezil, galantamine, or rivastigmine, and/or antipsychotic drugs, reported an optimal quality of sleep that positively impacted caregiver satisfaction and quality of life. Patients with depression and insomnia, who were also treated with sertraline, venlafaxine, or escitalopram, reported a sufficient quality of sleep. Finally, those with insomnia only, who were treated only with hypnotic drugs, reported "sufficient" sleep. There were no significant adverse effects with any treatment.[53]

No other trials examine the use of sleep medications in elderly adults with comorbid insomnia. However, it is worthwhile examining published trials of these agents in elderly patients with transient or chronic primary insomnia.

Two published trials examined the effects of eszopiclone 1- and 2-mg dosages compared with placebo on transient insomnia in elderly adults (ages 64-86) during a 2-week period.[54,55] All doses were superior to placebo in improving sleep latency; the 2-mg dose was superior in maintaining sleep. The most commonly reported adverse effect was unpleasant taste. One trial showed a trend toward morning-reported sleepiness.[55] There was no clinically significant evidence of withdrawal symptoms after up to 12 months of eszopiclone use.[56]

Zolpidem has been evaluated in the elderly in one published randomized, double-blind, placebo-controlled trial.[57] This trial evaluated the effect of extended-release zolpidem (6.25 mg) in 205 elderly adults (mean age, 70.2) with primary insomnia during a 3-week treatment period. Patient-reported sleep time and awakening after sleep onset were significantly improved with zolpidem over placebo. Polysomnography showed significantly reduced WASO in the zolpidem group compared with placebo with no residual sedation. However, abrupt withdrawal from zolpidem led to 1 night of rebound insomnia while none occurred after withdrawal from placebo. There did not appear to be any issues with tolerance, however. Although zolpidem is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance, it carries a warning that elderly or debilitated patients may be especially sensitive to its effects.[58] Zolpidem, has also been associated with anxiety and subjective ratings suggestive of abuse potential.[59]

Zaleplon has been evaluated in 3 clinical trials in elderly patients. In the first, zaleplon 5 and 10 mg were evaluated during 2 weeks of active treatment against zolpidem 5 mg in 549 elderly patients (ages 65-92) based on morning questionnaires.[60] Zaleplon 10 mg reduced subjective sleep latency (P <.001) during both weeks; zaleplon 5 mg also reduced it during week 2 (P <.01). There was no clinically significant rebound insomnia after discontinuation with zaleplon, although there was some evidence of rebound effects with zolpidem discontinuation. Central nervous system adverse effects were similar among both agents and placebo.

Hedner et al evaluated 5- and 10-mg zaleplon for 2 weeks (among individuals ≥65 years of age) with results provided via post-sleep questionnaires.[61] Although both doses significantly reduced subjective sleep latency during the treatment period, there was some evidence of rebound insomnia after discontinuation of treatment with the 10-mg dose.

Finally, to evaluate the long-term use of zaleplon in elderly insomnia patients, Ancoli-Israel et al conducted a 1-year, open-label, extension phase of the 2 previously discussed trials. Patients self-administered zaleplon nightly from 6 to 12 months and were then followed through a 7-day, single-blind, placebo-controlled, run-out period. The study showed similar efficacy in terms of sleep latency and duration and reduced nocturnal awakenings (P <.001 for each) with no evidence of rebound insomnia after discontinuation.[62]

Two published trials evaluated ramelteon in elderly subjects (n = 1156) with primary chronic insomnia for 5 weeks. In the first trial, Roth et al compared ramelteon 4 or 8 mg versus placebo in 829 older adults (mean age, 72.4 years). Patient-reported data showed significantly reduced reports of sleep latency throughout the treatment period with no significant rebound insomnia or withdrawal effects.[63] The second trial was a post hoc analysis of the first trial and focused on 327 older adults (mean age, 72.3 years) with severe sleep-onset difficulty (subjective sleep latency ≥60 minutes).[64] Subjects received 8 mg or placebo. Ramelteon significantly reduced self-reported time to fall asleep during nights 1 through 7 of treatment, an improvement that was sustained through week 5.

Table 3 depicts the dosing recommendations and mean half-life elimination of the nonbenzodiazepine sedative-hypnotics and ramelteon for older adults.

Nonprescription Treatment

In contrast to the lack of published literature on medical treatments for comorbid insomnia in elderly populations, at least 5 published studies have evaluated the use of behavioral therapies for older adults with comorbid insomnia.

Lichstein et al exposed 44 participants (≥58 years of age) with comorbid insomnia to four 1-hour sessions of cognitive behavioral therapy (CBT) consisting of relaxation and stimulus control, or to a delayed-treatment control group. The CBT group

■ **Table 3.** Nonbenzodiazepine Sedative-Hypnotics in Older Adults

Medication	Indication	Dosing Patients	Mean Half-Life Elimination in Elderly, h
Eszopiclone[65]	Treatment of insomnia in patients who experienced difficulty falling and/or staying asleep	Sleep-onset difficulty: 1 mg immediately before bed Sleep-maintenance difficulty: 2 mg immediately before bed	~9
Ramelteon	Insomnia characterized by difficulty with sleep onset	8 mg	~1-2.6
Zaleplon	Short-term treatment of insomnia	5 mg	1
Zolpidem[58]	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	6.25 mg once daily immediately before bedtime	2.9

self-reported increased sleep efficiency and sleep quality ratings, both of which were maintained at the 3-month follow-up regardless of the type of comorbidity (psychiatric or medical).[66]

Rybarczyk et al studied comorbid insomnia related to physical medical conditions, screening out patients with psychiatric disorders, in a sample of 38 older adults (mean age, 67.9 years).[67] Participants were randomized to either 8 sessions of group CBT, home-based audio relaxation treatment, or delayed treatment. Based on self-reported measures, the CBT group significantly improved on sleep efficiency, WASO, the Pittsburgh Sleep Quality Index (PSQI) global sleep score, and total score on the Dysfunctional Beliefs and Attitudes about Sleep scale at treatment end and follow-up compared to the control group. The relaxation group improved on sleep efficiency, WASO, and PSQI global score compared with controls. In addition, patients who experienced clinically significant sleep changes also exhibited reduced levels of anxiety.

A larger study in 92 participants with coronary artery disease, osteoarthritis, or chronic obstructive pulmonary disease showed a 78% treatment efficacy across a wide range of sleep-related parameters for participants undergoing CBT compared with a 24% treatment efficacy in the control group, which received stress management training. The results held regardless of the comorbid disease.[68]

Rybarczyk et al also conducted a pilot study in 12 older adults with comorbid insomnia who received a home-based video CBT program. They compared the 12 to 24 participants who received classroom CBT or no treatment and found improvements in the video CBT group similar to those who received the classroom CBT. Attrition in the video CBT group was, however, higher, and the number of participants who achieved clinically significant change was lower (50% vs 73%).[69]

Finally, McCurry et al evaluated a sleep education program in 36 dementia patients in which caregivers received either general dementia education (control) or recommendations about sleep hygiene and training in behavior management skills. Patients also took daily walks and increased their light exposure. Those participating in the education program showed greater reductions in nighttime awakenings and total time awake, and

increases in weekly exercise days than control (P <.05). The treatment gains continued at the 6-month follow-up with continued improvement in night awakenings.[70]

In addition to studies of behavioral interventions in comorbid insomnia in the elderly, a meta-analysis of behavioral interventions for primary insomnia in adults aged 55 and older found these interventions (CBT, relaxation training, or behavioral intervention only) were all effective in reducing sleep latency and WASO, and improving sleep quality and efficiency (P <.001), and somewhat effective in improving total sleep time (P <.038).[71] Two studies compared CBT with pharmacologic study in older adults. In one study, 78 older adults with primary or chronic insomnia received either 8 weeks of CBT (stimulus control, sleep restriction, sleep hygiene, and cognitive therapy) (n = 18), temazepam (n = 20), temazepam with CBT (n = 20), or placebo (n = 20). The 3 active treatments were more effective than placebo, with those receiving the combined treatment showing a nonsignificant trend to a slightly higher improvement in sleep continuity measures. However, participants receiving CBT were most likely to show sustained improvement at 6 and 24 months of follow-up than those receiving other treatments.[72]

Sivertsen et al compared CBT to zopiclone or placebo in 46 older adults with chronic primary insomnia. After 6 weeks, participants receiving CBT improved on 3 of 4 outcome measures (sleep efficiency, slow-wave sleep, time awake during the night) than those receiving medication or placebo. Total sleep time was similar in all 3 groups. At 6 months, those who received CBT continued to show greater improvements in sleep efficiency than those who received zopiclone.[73]

Thus, it is recommended that clinicians begin any treatment for comorbid insomnia in the elderly with behavioral therapies, with an attempt at medications after these approaches have failed.

Conclusion

Comorbid insomnia is a prevalent problem in the elderly population. However, misperceptions continue to exist that age-related changes in sleep architecture underlie sleep disturbances in this population. Instead, comorbid medical conditions

are likely to be the most common cause of sleep disturbances. Thus, it is important that clinicians consider patients' overall medical and psychological status when evaluating, diagnosing, and treating insomnia. Several effective medications exist for the treatment of primary insomnia in older adults. Although they have not been specifically studied for the treatment of comorbid insomnia in this population, studies in older adults with primary insomnia suggest they are safe for short-term use. However, because the use of hypnotics in this population may lead to falls, cognitive changes, and other morbidities, nonpharmacologic approaches should also be considered.

Acknowledgment

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Current and New Thinking in the Management of Comorbid Insomnia

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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 resolving 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.

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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 9.4% of patients with 1 disease, 8.5% with 2 diseases, and 7.1% with 3 diseases woke 3 to 4 nights a week compared with 6.4% of patients with no comorbid conditions (*P* <.001 for all). 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 Medications[13]

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).[16]

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.[4] 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.[17-20]

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.[21] 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.[22] 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, with the exception of ramelteon, concerning the potential for severe allergic reactions and complex sleep-related behaviors, including sleep-driving.[17,18,20]

Melatonin receptor agonists. Ramelteon is the only approved insomnia treatment medication that is not classified as a controlled substance. It is a nonsedating 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.[19]

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 demonstrated better anxiety score response than the placebo group (63% vs 49%; P = .001) and remission (42% vs 36%; P = .09).[21]

Krystal et al [AU: KRYSTAL OK? "FAVA ET AL"? CHECK "584" PATIENTS.] evaluated eszopiclone in a double-blind, placebo-controlled clinical trial involving 584 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 [HAMD-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).

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]

Other recent study results showed 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 total sleep time over the course of 8 weeks.[24]

Patients given zolpidem 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 ER zolpidem (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 showed significant improvements in TST, WASO, number of awakenings (NAW), sleep quality, and sleep latency compared with placebo (P ≤.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 did not significantly affect improvements in depression and there was no evidence of rebound insomnia upon discontinuation.[25]

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.[28] 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.[29-33] A modified-release formulation of indiplon has been shown to be effective in treating subjects with sleep maintenance insomnia.[33] 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 M_1/M_2 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.[33] 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.[34] 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.[35]

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 H_1 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.[36] 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.

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.[37] 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.[38-40]

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.[37]

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.[37] 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.[41] 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 each succeeding night. A drop below 85% requires

■ **Table 2.** Sleep Hygiene Elements[38-40]

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 behavior therapy.[42] 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.[43] These outcomes are similar to those cited in the insomnia treatment CBT and pharmacologic literature.[43]

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.[43] 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. 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.[41]

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.[45] 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.[46]

Insomnia associated with various medical conditions may also be relieved through CBT.[26] 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.[47] 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.[48] 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 obses-sive-compulsive disorder has been studied and shown to have moderate-to-large treatment effects (Cohen's d, range 0.35-2.2). 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.[27]

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 appear 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.

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