

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 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* 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

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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 comor-

bid 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 and VonKorff 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 Neubauer²⁵ 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 comorbidities, 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 compared 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 insomnia: breathing problems (59.6% vs 21.4%), gastrointestinal 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 studies 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 Conditions²⁰

Medical Condition	Prevalence		Odds Ratio ^a (95% Confidence Interval)	P
	Chronic Insomnia, %	No Insomnia, %		
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	9.2	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

^aAdjusted for depression, anxiety, and sleep disorder symptoms.

■ **Table 2.** People With Medical Conditions Reporting Chronic Insomnia²⁰

Medical Condition	Prevalence			P
	Chronic Insomnia, %	No Insomnia, %	Odds Ratio ^a (95% Confidence Interval)	
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	21.4	3.26 (1.56-6.81)	<.01
Urinary problems	41.5	23.3	2.25 (1.13-4.48)	<.05

^aAdjusted 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 à 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 episode or relapse). In one study, 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 that 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 rate⁴⁵ 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

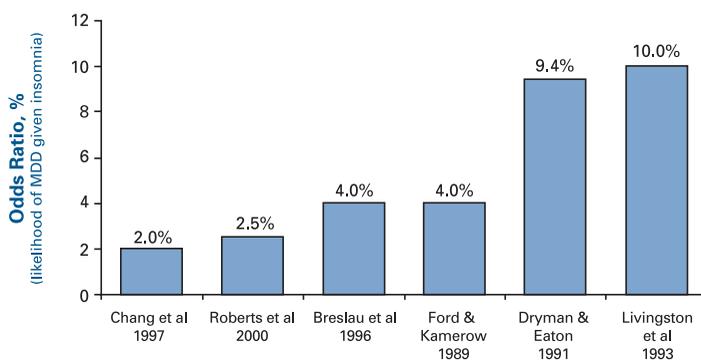
This paradigm has affected treatment modalities for insomnia, with cognitive behavioral therapy (CBT) and hypnotics as monotherapy typically used only in those with primary insomnia, and psychiatric interventions reserved for those with comorbid insomnia.⁴⁹ It has also affected research on the appropriate 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 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}



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, respectively; $P < .009$). 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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Author Affiliations: From the Henry Ford Hospital Sleep Disorders and Research Center, Detroit, and Department of Psychiatry, University of Michigan, Ann Arbor.

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Address correspondence to: Thomas Roth, PhD, Director, Henry Ford Hospital Sleep Disorders and Research Center, 2799 W Grand Blvd, Detroit, MI 48202. E-mail: TRoth1@hfhs.org.

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