The term insomnia is used in a variety of ways in the medical literature and popular press. Most often, insomnia is defined by the presence of an individual’s report of difficulty with sleep. For example, in survey studies, insomnia is defined by a positive response to either question, “Do you experience difficulty sleeping?” or “Do you have difficulty falling or staying asleep?” In the sleep literature, insomnia is sometimes used as a term to describe the presence of polysomnographic evidence of disturbed sleep. Thus, the presence of a long sleep latency, frequent nocturnal awakenings, or prolonged periods of wakefulness during the sleep period or even frequent transient arousals are taken as evidence of insomnia. Thus, insomnia has been thought of both as a symptom and as a disorder with the following diagnostic criteria: (1) difficulty falling asleep, staying asleep or nonrestorative sleep; (2) this difficulty is present despite adequate opportunity and circumstance to sleep; (3) this impairment in sleep is associated with daytime impairment or distress; and (4) this sleep difficulty occurs at least 3 times per week and has been a problem for at least 1 month.

What qualifies insomnia to be considered a disorder? A disorder is a condition associated with negative consequences, and Importantly, the presence of comorbid medical conditions is also a significant contributor to the increased prevalence of insomnia in the elderly. Additionally, in women, insomnia is more prevalent with both the onset of menses and menopause.

Disclosures
Dr. Roth has received research support from Aventis, Cephalon, GlaxoSmithKline, Neurocrine, Pfizer, Sanofi, SheringPlough, Sepracor, Somaxon, Syreex, Takeda, TransOraI, Wyeth, and Xenoprotect; is a consultant for Abbott, Accadia, Acoglix, Actelion, Alchemers, Alza, Ancil, Arena, AstraZeneca, Aventis, BMS, Cephalon, Cypress, Dove, Eli, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Jazz, Johnson & Johnson, King, Ludbeck, McNeil, MedicNova, Merck, Neurim, Neurocrine, Neuron, Novartis, Orexo, Organon, Orgner, Prestwick, Proctor and Gamble, Pfizer, Purdue, Restiva, Roche, Sanofi, SheringPlough, Sepracor, Servier, Shire, Somaxon, Syreex, Takeda, TransOraI, Vanda, Vivometrix, Wyeth, Yamanuchi, and Xenoprotect; and has participated in speaking engagements supported by Sanofi and Takeda.

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Journal of Clinical Sleep Medicine
Consequences of Insomnia

Due to its chronicity, insomnia is associated with substantial impairments in an individual’s quality of life. In several studies, insomniacs reported decreased quality of life on virtually all dimensions of the 36-item Short Form Health Survey of the Medical Outcomes Study (SF-36), which assesses 8 domains: (1) physical functioning; (2) role limitation due to physical health problems (role physical); (3) bodily pain; (4) general health perceptions; (5) vitality; (6) social functioning; (7) role limitations due to emotional health problems (role emotional); and (8) mental health.16-18 One study compared SF-36 results in groups of mild and severe insomnia patients with groups of patients diagnosed with depression or congestive heart failure (CHF).19 Severe insomnia patients had numerically greater loss of function than patients with CHF in reported pain, emotional effects, and mental health effects. Additionally, insomnia patients also reported more physical problems than patients with depression.20

Research has shown that among the daytime consequences of insomnia, the increased occurrence of accidents poses the greatest health risk. Insomniacs are 2.5 to 4.5 times more likely than controls to have an accident.20,21 In a sample of 8,625 community respondents in France, Léger et al. reported that 8% of insomniacs and 1% of non-insomniacs had an industrial accident in the last 12 months.22 Work productivity is also compromised among insomniacs due to work-related problems (ie, higher rates of absenteeism, decreased concentration, and difficulty performing duties). Kupperman and colleagues23 found that individuals reporting a current sleep problem were more likely than good sleepers to have decreased job performance and to have been absent from work in the last month due to health problems. Simon and VonKorff24 evaluated insomnia in a staff-model health maintenance organization population (N=1,962). After adjusting for age, gender, and chronic disease, days of restricted activity due to illness and days spent in bed were about twice as common among insomniacs compared with non-insomniacs. Additionally, mean total health care expenditures were 60% higher in the insomnia group relative to the controls.

Population- and clinic-based studies have demonstrated a high rate of psychiatric comorbidities in patients with chronic insomnia. In fact, insomnia is more frequently associated with psychiatric disorders than any other medical illness.25 For example, in the Epidemiologic Catchment Area study, 40% of insomniacs had a comorbid psychiatric disorder compared with 16.4% of those with no sleep complaints.6 Additionally, depression and anxiety are the most common comorbid psychiatric disorders in insomniacs. It has traditionally been assumed that insomnia is secondary to the psychiatric disorder; however, given the chronicity of insomnia, it is possible that in some, if not most, cases the insomnia precedes the psychiatric disorder. In fact, it is possible that insomnia represents a significant risk for the development of a subsequent psychiatric disorder. In a large-scale European population-based study (N=14,915), it was found that insomnia more often preceded rather than followed incident cases of a mood disorder.26 This effect is even more pronounced for relapses of the mood disorder, where in 56.2% of cases, insomnia symptoms preceded symptoms of a mood disorder relapse. In contrast, in chronic insomnia patients with a comorbid anxiety disorder, the first occurrence of anxiety or a relapse preceded insomnia in most instances.

To further understand the relation of sleep and psychiatric disorders, several longitudinal studies have examined the evolution of psychiatric disorders among insomnia patients. These studies used follow-up periods ranging from 1 to 40 years, with the majority using a 1- to 3-year follow-up period. In all of these studies, insomnia has been found to confer a substantial risk for the development of a depressive disorder.27,28 Typically, the relative risk was approximately 5 (range 2-40), and in all cases it was statistically significant. While some studies also reported an increased risk for anxiety or drug abuse, neither of these was consistently found. Finally, longitudinal studies in subjects with affective disorders show that depressed patients who experience improvements in sleep will also experience a more rapid antidepressant response; while those patients whose insomnia persists will have a short time to relapse.29,30 What is clearly needed are clinical trials to assess the impact of insomnia therapy on incidence of depression as well as the time to relapse in depressed patients who are in remission.

The question then arises as to whether insomnia causes depression, vice versa, or both. The close association of insomnia with depression is likely related to common underlying pathophysiological mechanisms for sleep and mood regulation that make the individual vulnerable to both conditions. Data have shown that both the diagnosis of insomnia and the severity of the sleep disturbance are related to overactivation of the hypothalamic-pituitary-adrenal (HPA) axis and the hypersecretion of cortisol.31 Recent evidence suggests that there may be some neuroendocrine and clinical similarities between insomnia and depression. Corticotropin-releasing factor (CRF) dysregulation has been implicated in the pathogenesis of psychiatric disorders such as depression32 as well as in the mediation of hyperarousal seen in primary insomnia.33 This abnormality might represent the common risk factor, and therefore, it is quite possible that both disorders would respond to the same therapeutic intervention (eg, corticotropin-releasing hormone antagonists).

Pathophysiology of Insomnia

Insomnia is thought to be a disorder of hyperarousal experienced throughout the entire day. This hyperarousal may exhibit itself as a state of hypervigilance during the day and difficulty initiating and maintaining sleep at night.34,35 This arousal is currently explained by both cognitive and physiological models of insomnia. The cognitive model suggests that worry and rumination about life stresses disrupt sleep, creating acute episodes of insomnia, especially in initiating sleep and returning back to sleep.
after an awakening. Then, once an individual begins to experience sleep difficulties, worry and rumination shift from life events to worries about sleep itself and about the daytime consequences of not getting enough sleep. This negatively-toned cognitive activity is further fueled if a sleep-related threat is detected or a sleep deficit is perceived.

In parallel with the cognitive models, another model of the evolution of insomnia proposes that hyperarousal is primarily due to physiologic or neurophysiologic factors. Physiologic arousal has been evaluated through measurements of the whole body metabolic rate, heart rate variability, neuroendocrine measures, and functional neuroimaging. Whole body metabolic rate may be measured by oxygen consumption ($V_O_2$). Recent studies compared good sleepers with patients diagnosed with insomnia. The insomnia patients exhibited significantly higher metabolic rates (measured at intervals across the 24-hour day) than the healthy controls. Heart rate variability may provide a measure of arousal in that it is regulated by both sympathetic and parasympathetic nervous system activities. A 36-hour study found that average heart rates were increased and variability was decreased in all stages of sleep in insomnia patients compared to healthy normal sleepers.

The neuroendocrine system may also provide evidence of arousal as demonstrated by chronic activation of the stress response system. Several studies measuring 24-hour urinary free cortisol excretion have found high levels in poor sleepers. Urinary free cortisol levels have also been positively correlated with total wake time, and urinary catecholamines have been correlated with stage 1 sleep percentage and wake time after sleep onset. Plasma measures of cortisol and adrenocorticotropic hormone (ACTH) have been evaluated in insomnia patients and healthy normal sleepers. Although the evidence is somewhat mixed, primary insomniacs appear to have higher levels of these compounds in their plasma, with the most significant differences seen in the evening and the first half of the night. Both the urinary and plasma measures of cortisol and ACTH suggest that the HPA axis is associated with the pathology of chronic insomnia.

Finally, positron emission tomography (PET) has been used to assess cerebral glucose metabolism, an indirect measure of whole brain metabolism, in patients with insomnia. Compared to healthy subjects, patients with insomnia exhibited greater cerebral glucose metabolism during waking and non-rapid eye movement (REM) sleep states. Furthermore, the insomnia patients demonstrated smaller reductions in relative metabolism from waking to non-REM sleep in wake-promoting regions of the brain. These findings suggest interacting neural networks involved in the inability to fall asleep, which include a general arousal system, an emotion-regulating system, and a cognitive system.

**CONCLUSION**

Chronic insomnia is highly prevalent and affects approximately 30% of the general population. Insomnia impairs cognitive and physical functioning and is associated with a wide range of impaired daytime functions across a number of emotional, social, and physical domains. Compared with good sleepers, people with persistent sleep disturbances are more prone to accidents, have higher rates of work absenteeism, diminished job performance, decreased quality of life, and increased health care utilization. Various risk factors associated with increased prevalence of chronic insomnia include older age, female gender, and comorbid medical and psychiatric conditions. Approximately 40% of adults with insomnia also have a diagnosable psychiatric disorder—most notably depression. A comorbid psychiatric disorder such as depression or anxiety may be a consequence of—as well as a risk factor for—disrupted sleep. Recent research suggests that insomnia and depression share common pathological processes that make individuals vulnerable to both conditions—specifically, abnormal regulation of CRF. CRF regulation has been extensively implicated in the pathogenesis of depression, and hyperactivity of the HPA axis and CRF neurons could account for the hyperarousal and sleep disturbances associated with chronic insomnia. Studies that improve the knowledge of the neurobiological mechanisms controlling regulation of sleep homeostasis, circadian rhythms, physiological hyperarousal, genetics, stress, and cognition are needed to adequately evaluate the causes and mechanisms of insomnia. Effective pharmacologic and behavioral interventions to treat insomnia rely on accurate neurobehavioral and neurobiological information.

**REFERENCES**


