The Impact and Prevalence of Chronic Insomnia and Other Sleep Disturbances Associated With Chronic Illness

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Abstract

Chronic insomnia may coexist with chronic physical and psychiatric conditions, and its prevalence is often higher among patients with these conditions than in the general population. Evidence suggests that insomnia as a feature of chronic disease tends to be more severe and persistent than insomnia that does not occur in the context of chronic illness. Furthermore, comorbid insomnia can have a profound negative impact on patients' quality of life and overall functioning, and may be associated with greater healthcare resource utilization. In some cases, treatment of the underlying disorder may improve sleep, whereas in other cases, treatment of the sleep symptoms may actually improve the underlying disorder. In addition, chronic insomnia may be a precursor to certain psychiatric comorbidities. Further research is needed not only to clarify the efficacy and safety of specific therapeutic approaches but also to further investigate the possibility that successful treatment of sleep disturbances may improve objective and subjective parameters of the disorders themselves. This article reviews the specific associations between chronic insomnia and a wide range of chronic physical and psychiatric disorders.

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Insomnia is extremely prevalent; community-based surveys in Western countries suggest that about one third of the population reports some form of difficulty falling asleep or staying asleep at any given time.[1,2] For many of those affected, insomnia is a transient phenomenon, resolving within days or weeks; however, a substantial fraction of patients appears to suffer from chronic insomnia.

Chronic insomnia has been variously defined by frequency (usually ≥3 times per week) and duration (usually ≥1 month but sometimes longer), and typically involves some degree of daytime dysfunction. The persistence of insomnia as a complaint appears to be far greater in severe insomnia (ie, insomnia that is more frequent and of longer duration) than in mild insomnia; therefore, to a great extent, severe insomnia and chronic insomnia may describe similar phenomena.[2,3] Prevalence estimates for chronic insomnia are clearly affected by differences in operational definitions. However, it seems reasonable to estimate that about 10% to 20% of the population in the United States and Western Europe experiences chronic insomnia.[1,3]

Chronic insomnia can coexist with a number of chronic physical and psychiatric conditions, including arthritis, cardiovascular (CV) disease, diabetes, and depression; and its prevalence is much higher among patients with such conditions than in the general population.[2-4] Although insomnia is frequently treated as a minor or transient complaint, chronic insomnia has been shown to have a profoundly negative impact on patients' quality of life (QOL) and overall functioning, and is also associated with elevated consumption of healthcare resources.[3,5-7] In addition, chronic insomnia may also be a precursor to, rather than a consequence of, certain psychiatric comorbidities, especially depression.[8,9] This article reviews the specific associations between chronic insomnia and a wide range of chronic physical and psychiatric disorders.

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Insomnia and Specific Disease States

Arthritis. The prevalence of chronic insomnia in patients with various forms of arthritis appears to be substantially greater than its prevalence in healthy controls. In a study of 429 patients with knee pain and osteoarthritis (OA), the proportions of patients reporting problems with sleep onset, sleep maintenance, and early-morning awakenings (all symptoms of insomnia) were 31%, 81%, and 51%, respectively. Predictors of greater numbers of these insomnia complaints included a greater number of involved joints; knee pain severity; CV disease; and poorer self-rated health, physical functioning, and physical performance.[10] An analysis of sleep patterns in patients with OA showed that they spent significantly more time in lighter sleep (ie, significantly more time in stage 1 sleep and significantly less time in stage 2 sleep) than age-matched healthy controls.[11]

The importance of pain as a mediator of insomnia in OA is suggested by a longitudinal comparison of patients with OA before and after total hip arthroplasty (THA). Relative to sleep quality before THA, significant improvements in subjective and objective measures of sleep were observed after THA. Analysis of the results of actigraphy showed that after THA, patients experienced reductions in activity during sleep, as well as less insomnia, specifically more efficient and less fragmented sleep. The study authors concluded that a reduction in post-THA pain was the main factor contributing to improved sleep.[12]

The prevalence of insomnia complaints in patients with rheumatoid arthritis (RA) is greater than 50%.[13] Although these complaints may involve problems with sleep onset, the most significant differences between patients with RA and healthy controls appear to be in sleep maintenance, sleep quality, and restorative sleep.[13-15] Overall sleep architecture in patients with RA, with respect to the classic stages of sleep, resembles that of matched controls; however, these patients experience severely fragmented sleep with frequent awakenings and arousals.[13,15,16]

Although data on insomnia are reliable, there is conflicting evidence about the relationship between RA disease parameters and sleep architecture. Although no correlation was identified between inflammatory disease activity and sleep disruption in 1 study,[15] a longitudinal study of sleep architecture and clinical symptoms demonstrated significant correlations between disrupted sleep architecture (including less restorative slow-wave sleep), pain, and morning stiffness.[17] Patients with RA also experience more periodic movements of the legs (PML), a symptom that has been associated with a number of disease states.[13,15,16]

Similar patterns of insomnia have also been observed in children with juvenile rheumatoid arthritis (JRA). Patients with JRA demonstrated 90% more arousals and awakenings than age-matched controls, as well as more shifts from deeper to lighter sleep and longer afternoon naps.[18] Pain, but not disease activity, has been correlated with insomnia in patients with JRA, similar to the pattern observed in adults with RA.[19]

Insomnia is extremely prevalent (>75%) among patients with fibromyalgia and those with primary Sjögren's syndrome. In fibromyalgia, as in RA, insomnia has been associated with pain and morning stiffness.[20,21] It is important to emphasize that the consistent associations between poor sleep and pain in various arthritides may involve bidirectional causation: Pain can disrupt sleep, but poor sleep (especially loss of restorative sleep) can also lower the pain threshold and may contribute to increased daytime pain.[20]

Gastroesophageal Reflux Disorder (GERD). Patients with GERD frequently experience nighttime gastroesophageal reflux (GER) because of several factors: continued contact of stomach contents with the lower gastroesophageal sphincter, reduced esophageal motility, increased intra-abdominal pressure, and decreased gastric volume. These conditions are exacerbated by obesity, which is a risk factor for GERD and is common among patients with this disorder.[22,23]

The occurrence of GER events during sleep almost invariably leads to arousal, and sometimes to awakening. In a study of nighttime GER events using polysomnography, it

was found that 45% (31/69) of such events occurred during periods of wakefulness after sleep onset. Of the 38 events that occurred during sleep, only 1 did not result in subject arousal.[23] Although estimates of the prevalence of sleep complaints and/or insomnia among GERD patients are hard to find in the existing literature, the nearly invariant association of GER events with arousal suggests that these patients experience frequent insomnia and loss of restorative sleep.

Many patients with GERD also demonstrate obstructive sleep apnea (OSA).[22-24] The frequent association between GERD and OSA has led researchers to postulate a direct causative link between respiratory events (apnea or hypopnea) and GER events.[22] However, a polysomnographic study that recorded both respiratory and GER events failed to confirm such a link; GER events tended to occur independent of respiratory events.[23] Both GERD and OSA share obesity as a common risk factor, and it is possible that the association of each condition with obesity provides a sufficient explanation for the association between the 2 conditions.[22]

Coronary Artery Disease (CAD). A number of studies have demonstrated an association between sleep disorders and the incidence of, and/or mortality caused by, CAD; the risk ratios for CAD associated with subjective insomnia complaints generally ranged from 1.5 to about 4.[25] In some but not all of these studies, a gender association has also been identified, suggesting that men are at higher risk.[26]

In 1 of the few prospective studies of middle-aged adults, a general link between complaints of insomnia and CAD mortality was identified in a population-based study of 1870 subjects who had responded to a health survey. After a follow-up period of 12 years, difficulty in initiating sleep was associated with a 3-fold risk of CAD death in men; no such link was identified in women. The association in men remained significant after controlling for other CAD risk factors, including depression.[26] However, in a number of other studies, adjustment for other CAD risk factors (especially depression) attenuated the relationship between insomnia and CAD, making it difficult to ascertain whether insomnia is an important causative factor in CAD or simply reflects the impact of risk factors common to both.[25,27]

The evidence base linking CAD to sleep disruption that is secondary to OSA or respiratory dysfunction is much firmer than that for more general sleep complaints. OSA has also been broadly linked to hypertension and other CV conditions.[28] In 1 study, the prevalence of OSA (apnea index >10/hr) among 60 patients with angiographically confirmed CAD was 42% (25/60); 8 of the patients with OSA also demonstrated excessive daytime sleepiness.[29]

In a prospective study comparing CAD patients with and without OSA (defined as a respiratory disturbance index [RDI] of ≥10/hr), 37% of patients with CAD and OSA died during a 5-year follow-up period, compared with 9% of those with CAD and no OSA (P = .018); both groups were well matched at baseline with respect to other CAD risk factors. In a multiple conditional regression model, the association between elevated RDI and CAD mortality remained significant even after controlling for other risk factors.[30]

Studies of the relationship between OSA and CAD have not yet clarified the relative contribution of OSA per se, versus that of sleep disruption secondary to OSA, to the observed increased risk of CAD and CAD mortality. OSA causes a significant reduction in oxygen saturation, and the resulting CV stress may be sufficient to explain OSA-associated cardiac risk. Moreover, the associations between OSA and other CV conditions (such as hypertension), as well as the congruence between risk factors for CAD and for OSA (such as obesity), make it challenging to isolate and assess OSA-attributable risk.[25] It is important to note that treatment of OSA with continuous positive airway pressure (CPAP) has been shown to reduce hypertension and nocturnal angina and to improve cardiac output in patients with congestive heart failure (CHF).[31-34] These results tend to strengthen the causative link between OSA and CAD, even if the link is mediated through other CAD risk factors.[25,28]

CHF. Abnormal breathing patterns in patients with CHF were described independ-

ently in the early 19th century by Cheyne and Stokes, whose names were applied to a specific pattern known as Cheyne-Stokes respiration (CSR). CSR is characterized by a recurring pattern of central apneas and hypopneas, and is strongly associated with left ventricular insufficiency.[35,36] The prevalence of CSR in patients with stable CHF ranges from 45% to 50%. Most CHF patients with CSR are men, but the significance of this finding is not yet known.[35]

Prospective studies have demonstrated a strong link between nocturnal CSR and increased mortality. In a comparison between CHF patients with and without nocturnal CSR, the mortality rate over 3 to 4.5 years was 56% (5/9) in the CHF group with CSR, compared with 14% (1/7) in the CHF group without CSR; in addition, there was 1 heart transplant in the CSR group. In addition to CSR, mortality in this study was positively correlated with apnea-hypopnea index (AHI), arousal index, and the amount of time spent in stage 1/2 non-REM [rapid eye movement] sleep; mortality was inversely correlated with total sleep time.[37] Another prospective study showed that AHI was an independent predictor of mortality among patients with moderate CHF (New York Heart Association class II/III) during a mean follow-up of 28 months; patients with AHI >30/hr were at especially high risk.[36]

As with the relationship between sleep problems and CAD, elucidating the relative contributions of CSR and secondary sleep disruption to declining health status and mortality among CHF patients presents a significant challenge. Hall and Bradley have proposed a mechanistic model in which sleep disruption secondary to CSR-induced arousal contributes to overall fatigue and daytime somnolence but does not contribute directly to CHF status.[38] In contrast, Kaneko et al have proposed that respiratory dysfunction is a direct contributor to ventricular decline, based on the positive effect of CPAP sleep apnea treatment on several measures of ventricular function.[33]

End-Stage Renal Disease (ESRD). The prevalence of insomnia is high among patients with ESRD who are undergoing hemodialysis (HD). Parker reported that as many as 80% of patients receiving HD complain of insomnia; also, the prevalence of PML and sleep apnea are far higher in this population than in the community.[39] In the Kidney Outcomes Prediction and Evaluation (KOPE) study, nighttime awakenings and early-morning awakenings were the most prevalent complaints (57% and 55%, respectively).[40]

The KOPE cohort study also showed that pain, depressive symptoms, and physical functioning demonstrate the strongest and most consistent associations with complaints of insomnia.[40] As in other disorders, it is likely that the cause-and-effect relationship between these conditions is complex and bidirectional. Although no long-term prospective studies have yet assessed the impact of sleep disruption or chronic insomnia on survival and other critical clinical endpoints in patients undergoing HD, insomnia and other sleep abnormalities do have a substantial effect on QOL and functional health status in these patients.[39]

Of importance, correction of certain conditions associated with ESRD and HD has a positive impact on sleep. In the SLEEPO study, it was found that when 10 moderately anemic HD patients were treated with recombinant human erythropoietin to correct their anemia (hematocrit pretreatment, 32%; posttreatment, 42%), all 10 experienced improvement in sleep. Anemia correction was associated with highly significant reductions in PML, sleep arousals, and sleep fragmentation; in addition, daytime alertness improved significantly. Treatment of anemia with recombinant human erythropoietin had previously been shown to improve QOL across a wide range of measures; improvement in sleep may be an important mechanism underlying these improvements.[41]

Obstructive Airway Disease (OAD). Fleetham et al reported that patients with chronic obstructive pulmonary disease (COPD) have a high prevalence of insomnia, especially problems with sleep onset and sleep maintenance.[42] An association between OAD and complaints related to insomnia was also reported in the Tucson Epidemiologic Study of Obstructive Airway Disease, which surveyed 2187 adults in a

community setting.[43] Consistent with other epidemiologic studies, 41% of respondents reported at least 1 symptom of disturbed sleep. Disorders of sleep onset and maintenance, as well as daytime sleepiness, were significantly associated with chronic bronchitis, bronchitis plus asthma, and emphysema (no association was found for asthma alone). This study also demonstrated a higher prevalence of complaints of poor sleep in women and a pronounced increase in complaints of poor sleep with advancing age, especially in patients aged 65 years or older.[43]

The association of OAD with sleep disturbance appears to be related to OAD severity. A study of patients with mild OAD found no association between OAD and sleep apnea/hypopnea, and generally minor effects on sleep quality.[44] However, sleep quality was poor among a group of patients with moderate-to-severe COPD; these patients also demonstrated reduced oxygen saturation.[45] The effects of treating OAD symptoms on sleep quality have been mixed. One study demonstrated a significant improvement in sleep parameters after treatment with the bronchodilator ipratropium bromide, whereas another demonstrated no effect of supplemental oxygen on arousal frequency, despite a positive correlation between oxygen desaturation and arousals while patients were breathing room air.[42,45]

Diabetes. Sleep disorders have been extensively reported in both type 1 and type 2 diabetes.[4,46,47] However, the complexity of diabetes as a disease state, as well as the shared risk factors (especially obesity) for type 2 diabetes and for sleep-disordered breathing, makes it challenging to discern the associations and causative relationships between diabetes and sleep disorders. Relative to healthy controls, significant alterations in circadian patterns of glucose metabolism have been observed in patients with type 1 or type 2 diabetes, and appear to underlie the "dawn phenomenon," an early-morning rise in plasma glucose levels. However, no studies have combined continuous overnight glucose monitoring with polysomnography to analyze the relationship between glucose regulation and sleep.[48]

Most analyses of sleep disruption among diabetic patients have been conducted in those with type 2 diabetes. Despite the cooccurrence of obesity as a risk factor for type 2 diabetes and for OSA, several studies using multivariate analysis have shown a direct association between glucose intolerance or type 2 diabetes per se and sleep-disordered breathing.[47,49,50] Although the link between obesity, type 2 diabetes, and OSA seems to be the most obvious explanation for this association, studies have also suggested disruption of central nervous system regulation of respiration, leading to periodic breathing, a form of respiratory dysfunction, in patients with diabetes.[50,51] In nonobese patients with type 2 diabetes, episodes of OSA/hypopnea have been linked to autonomic neuropathy.[51]

Perhaps most intriguing is the suggestion that sleep and breathing disorders may be causally linked to the onset of type 2 diabetes, based on associations demonstrated in both cross-sectional and longitudinal studies.[49,52] Consistent with this hypothesis are recent studies showing that CPAP treatment of OSA in patients with type 2 diabetes can improve insulin sensitivity and even reduce levels of hemoglobin A1C.[53-55]

Psychiatric Disorders. Depression is the most consistent correlate of insomnia and daytime sleepiness in community-based studies, and insomnia is a diagnostic symptom for depressive and anxiety disorders. Over 40% of patients with persistent hypersomnia or persistent insomnia have a psychiatric disorder.[9,56]

The relationship between depressed mood and insomnia is complex. Longitudinal studies have shown that the presence of insomnia predicts the subsequent onset of clinical depression,[9,57] and at least 1 study has shown that the predictive value remains significant even after controlling for the influence of other previous depressive symptoms.[8] The mechanisms responsible for this link remain unclear. Sleep disturbance may simply be an extremely early symptom of subclinical depression, a direct causative factor in the induction of depression, or the result of other factors involved in the etiology of depression. It is unclear whether intervention aimed at

improving the insomnia may reduce the risk of developing depression, and to date, no controlled clinical study has examined this possibility.[8,9,57]

Neurologic Disorders. A number of neurologic disorders, including Parkinson's disease (PD) and Alzheimer's disease (AD), are associated with a high prevalence of insomnia and other sleep disorders.[58,59] In PD, insomnia may be the result of motor symptoms, psychiatric symptoms, and/or treatment with dopaminergic agents; dopaminergic agents appear to be particularly important in the induction of daytime sleepiness.[59-61] Also, PD is associated with nighttime hallucinations; this phenomenon appears to be separate from, and more progressive than, other forms of sleep disruption.[62]

Restless legs syndrome (RLS) is a sensorimotor disorder associated with a number of other disorders, including PD, as well as with increasing age.[60,63] Many patients with RLS also exhibit PML, although the 2 conditions are not identical.[63] Both conditions cause significant difficulties with sleep onset and sleep maintenance. Treatment with dopaminergic agents has demonstrated effectiveness in some groups of patients with RLS or PML.[63,64]

Difficulty in maintaining sleep is particularly burdensome in patients with AD, and both insomnia and nocturnal agitation/sleep schedule disruption (eg, "sundowning") are significant factors in the institutionalization of AD patients.[65-67] The differential diagnosis and treatment of insomnia in the context of dementia are especially challenging for a variety of reasons, including the patient's declining cognitive capacity; the frequent co-occurrence with PD, CV disease, and other common diseases of the elderly; and the high prevalence of polypharmacy and reduced drug tolerance in the elderly.[58,65,67] The treatment approach must be based on a consideration of underlying and comorbid disorders, as well as specific patterns of sleep disruption. There have been few controlled clinical studies of interventions in patients with AD (in part because of the difficulty of conducting such studies in this population), and there is no indication that successful treatment of sleep problems in these patients has any effect on cognitive functioning.[65]

Summary

The high prevalence of chronic insomnia and other sleep disorders in the general population is elevated still further in the context of numerous chronic disease states. The limited information available suggests that chronic insomnia as a feature of chronic disease tends to be more severe and persistent than chronic insomnia that does not occur in the context of chronic illness. Considered as a whole, sleep problems in patients with chronic disease often involve sleep maintenance rather than sleep-onset latency (difficulty falling asleep); specific forms of sleep disruption tend to be consistent within a given disorder but vary substantially when comparing disorders.

The insomnia described here can be productively grouped into 2 broad categories. In both cases, however, it is important to consider the possibility of bidirectionality of the relationship between chronic insomnia and chronic illness. The first category describes sleep complaints that are clearly linked to a symptom or correlate of the disorder. This category would include insomnia and other sleep disorders due to CSR in CHF, the arousals and awakenings resulting from GER events in patients with GERD, and insomnia associated with neurologic disorders. Effective treatment of the underlying condition or symptom may improve sleep disruption and/or increase the effectiveness of therapy aimed at the sleep symptoms themselves. However, treatment of the sleep symptoms only is unlikely to alter the underlying disease condition.

The second category, which includes insomnia coexisting with type 2 diabetes, depression, and some of the arthritides, is more intriguing from the perspective of intervention. In these disorders, insomnia appears to be a component of either the etiology of the disorder (eg, type 2 diabetes) or the severity of symptoms (eg, RA pain). As with the first category, treatment of the underlying disorder may improve sleep. Unlike the first category, however, treatment of the sleep symptoms in this second group may actually improve the underlying disor-

der, the patient's perception of its severity, and/or the patient's ability to function.

The paucity of well-designed studies investigating sleep disorders associated with chronic illnesses is striking—most of the extant literature is based on cross-sectional studies. The few reported longitudinal studies have made a disproportionate contribution to untangling the complex relationships between primary disorders, associated symptoms, common risk factors, and sleep disruption. It is clear that more such studies are essential to the development and refinement of diagnostic and treatment strategies. Interventional studies are also urgently needed, not only to clarify the efficacy and safety of specific therapeutic approaches but also to further investigate the intriguing possibility that, for at least some disorders, successful treatment of chronic insomnia and other sleep disturbances may improve objective and subjective parameters of the disorders themselves.

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