Consequences of Insomnia and Its Therapies

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Insomnia has a number of clinically significant associations. In particular, patients with chronic insomnia have higher rates of psychiatric and medical illnesses, and insomnia is an important risk factor in the development of depression. Insomniacs also have higher rates of health care utilization and reduced quality of life. This article reviews important clinical correlates of insomnia and evidence for possible causal relationships between sleep and health.

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Insomnia is one of the most common medical conditions, yet it often goes undiagnosed and/or untreated; physicians do not regularly ask about sleep problems and patients often do not spontaneously report them. One reason for this may be the belief that insomnia does not have serious sequelae and therefore does not require treatment. In fact, there are a number of clinically significant correlates to disturbed sleep, which should make it a focus of clinical attention (Table 1).

INSOMNIA AND PSYCHIATRIC DISORDERS

Chronic insomnia is generally associated with poorer emotional and physical health. Several large-scale epidemiologic studies of the general adult population have shown that between one third and one half of people who complain of chronic insomnia are also diagnosable with primary psychiatric disorders, mostly anxiety and mood disorders. Mellinger et al.[1] found that 17% of adults reported "a lot" of trouble falling asleep or staying asleep over the past year; 47% of them had high levels of psychic distress, with symptom complexes suggestive of depression and anxiety disorders. In contrast, only 11% of individuals with no history of insomnia showed elevated levels of psychiatric symptoms. In a survey of almost 8000 individuals, Ford and Kamerow[2] reported that 10% suffered from significant insomnia for at least a 2-week period during the previous 6 months. Forty percent of the insomniacs met criteria for psychiatric disorders, with the majority being anxiety disorders and depression; only 16% of those with no sleep complaints had psychiatric illnesses. In their study of young adults, Breslau et al.[3] found a strong correlation between lifetime prevalences of sleep problems and psychiatric disorders, with anxiety, depression, and substance abuse disorders most common.

Insomniacs not only have higher rates of psychiatric disorders, but they also have increased rates of various kinds of psychological symptoms. Patients with insomnia reported increased psychological stress and/or decreased ability to cope with stress according to surveys of American and Japanese populations.[4,5] A recent study[6] found that almost 80% of insomniacs had significant increases on one or more clinical scales on the Minnesota Multiphasic Personality Inventory (MMPI). Even people whose insomnia was due to identified medical factors showed elevations on the MMPI, suggesting a possible causal relationship or specific association between insomnia and psychiatric symptomatology.

Clinical populations have generally shown even higher rates of comorbidity between insomnia and psychiatric disorders. Charon et al.[7] reported that over half of insomnia patients in a general medical setting had psychiatric symptoms. Buysse et al.[8] surveyed patients presenting to sleep or general medical clinics with complaints of insomnia and found that three quarters or more had a diagnosable psychiatric illness. In a comparison of patients with depression and patients with other chronic illnesses (hypertension, diabetes, congestive heart failure, or myocardial infarction), Katz and McHorney[9] found that major depressive disorder and depressive symptoms were more strongly associated with insomnia than were other chronic illnesses, although significant associations between insomnia and other medical conditions were also seen.

Not only are psychiatric disorders more prevalent in individuals with insomnia, but psychiatric patients also frequently complain of sleep disturbance. Furthermore, there is objective evidence of disturbed sleep in psychiatric patients when studied in sleep laboratory settings. Virtually

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Table 1. Correlates of Insomnia

Psychiatric disorders
Medical illnesses
Increased health care costs
Reduced quality of life
Increased absenteeism
Increased risk of accidents
Cognitive impairment

all psychiatric patient groups studied have shown changes in sleep architecture that are associated with insomnia. In almost all psychiatric disorders, however, there is evidence of reduced sleep efficiency, prolonged latency to sleep onset, increased time awake during the sleep period, and reduced amounts of total sleep.[10] Depressed patients have been studied most extensively and appear to have the most robust changes in their sleep patterns. Thus patients with psychiatric illnesses both report insomnia and show objective evidence of sleep disruption. The increase in complaints of poor sleep among psychiatric patients cannot, therefore, be attributed to simple reporting bias, but has in fact a basis in objective measures.

INSOMNIA AND MEDICAL DISORDERS

In addition to the strong associations between psychiatric disorders and sleep disturbance, insomnia is also correlated with medical illnesses. Mellinger et al.[1] found that 53% of those with serious insomnia had 2 or more health problems, in contrast to only 24% of those with no trouble sleeping. In the Ford and Kamerow survey,[2] patients with insomnia had higher rates of general medical services utilization. Using particularly stringent criteria for insomnia (i.e., occurring nearly every night, requiring at least 2 hours to fall asleep, waking at least 2 hours early, or lying awake at least 1 hour during the night), Simon and VonKorff[11] reported an insomnia prevalence of 10% in primary care patients. Furthermore, they found insomnia to be associated with significantly greater disability from medical disorders and increased health care utilization. Not surprisingly, insomnia was also associated with depression in this population. A survey of patients in primary care clinics in Hawaii and California[12] found a total prevalence of insomnia of 69%, with 19% reporting chronic insomnia, (i.e., insomnia "occurring on a frequent basis"); a similar poll of adults in the New York City region performed by the Gallup Organization in 1991 found that 36% of those in the general population complained of insomnia.[13]

OTHER CORRELATES OF INSOMNIA

There are a number of other important correlates of insomnia. People with insomnia have higher rates of absenteeism from work and more accidents.[14,15] Various studies[4,12,14,16] have reported deficits in cognitive and psychomotor functioning, including memory, concentration, attention, reasoning, problem solving, and reaction time; it is possible that some of these correlates may be related to the increased prevalence of psychiatric disorders. Subjective reports in these areas have more consistently revealed decrements, whereas objective measures have yielded more variable results. Weissman and colleagues[17] attempted to determine morbidity of insomnia not related to psychiatric illness using data from the National Institute of Mental Health Epidemiologic Catchment Area study between 1980 and 1984. Subjects were divided into groups with no history of insomnia or psychiatric disorders, with insomnia and no lifetime history of a psychiatric disorder (uncomplicated insomnia), and with both insomnia and a psychiatric disorder within the past year. Both complicated and uncomplicated insomnia were associated with greater utilization of general medical and psychiatric services, although higher rates were generally seen with complicated insomnia. Despite the lack of any history of psychiatric disorders, subjects with uncomplicated insomnia were at greater risk for developing major depression, panic disorder, and alcohol abuse in the next year. These data suggest that although associated features of insomnia such as increased health care utilization are not necessarily related to psychiatric illness, insomnia is clearly linked with an increased risk of developing depression.

Many studies have documented poorer quality of life in people with insomnia. Similar results have been reported from various populations, including a National Sleep Foundation/Gallup poll,[4] a survey of U.S. primary care patients in California and Hawaii,[12] and a Japanese study[5]; all groups showed a strong correlation between insomnia and decreased overall well-being. As one might infer from the data presented above, insomniacs appear to have increased rates of various kinds of health problems. This is consistent with their subjective sense of poorer health quality. Not surprisingly, insomniacs showed greater utilization of health care services in several studies.[11,17,18]

In addition to the broad association with psychiatric disorders, insomnia is also associated with poor outcomes in some specific medical disorders. For example, a recent meta-analysis by Schwartz et al.[19] concluded that trouble falling asleep was associated with coronary events independent from other risk factors for cardiac disease. Other correlates of insomnia include decreased productivity at work, increased absenteeism, higher rate of accidents, and complaints of daytime fatigue.

INSOMNIA AS A PREDICTOR OF DEPRESSION

One problem with most epidemiologic studies is that they rely on subjective reports of insomnia rather than on the objective measurement of sleep. The reliance of most of these studies on self-report of insomnia or other symptoms raises the issue of whether self-defined insomnia is

simply part of a larger perception of being unwell or a negative global perception of physical and psychological state. Furthermore, assuming that there are correlations between objective measures of sleep and health or performance, are there causal relationships between sleep and health, and if so, in which direction?

A number of studies have suggested that insomnia may be an important predictor of poor physical and emotional health. Predictive value does not necessarily prove causality, and the problem with many studies is how well the independent contributions of insomnia have been assessed. Most work has looked at the relationship with depression, with the general finding that insomnia has positive predictive value for subsequent development of depression. In a 2-wave study, Ford and Kamerow[2] found that subjects who had insomnia at the time of initial assessment and again 1 year later had a greatly increased risk of developing a new episode of major depression in comparison to individuals with no insomnia, with an odds ratio of 39.8; those whose depression had resolved by the second timepoint, however, had an only slightly increased risk for depression (odds ratio = 1.6). A prospective study[20] of community-dwelling elderly persons over a 2-year period found that sleep disturbance was the best predictor for the development of depression. The longest-term study relating insomnia and depression, The Johns Hopkins Precursors Study,[21] assessed sleep habits of over 1000 men while they were medical students and followed them for a median of 34 years. Individuals with insomnia in medical school had an increased risk of depression later in life (relative risk = 2.0), as did those who reported difficulty sleeping under stress (relative risk = 1.8), in comparison to those with no sleep problems.

One of the problems with many of the survey studies is that since disturbed sleep is part of the diagnostic criteria for depression, insomnia may simply indicate the presence of a subclinical depression and not have any particular etiologic role in the development of depression. To investigate the insomnia-depression relationship further, Breslau et al.[3] assessed the incidence of depression over a 3.5-year period in young adults with a history of insomnia versus no prior history of insomnia. As in the previous study,[21] a history of insomnia was associated with a significantly increased risk of developing major depression (odds ratio = 3.95). Controlling for the prior history of other depressive symptoms naturally reduced the odds ratio somewhat. Nevertheless, the risk for developing depression with a history of insomnia remained significantly elevated (odds ratio = 2.1). Remarkably, insomnia ranked third, behind psychomotor retardation or agitation and suicidal ideation, when the independent contributions of specific depressive symptoms to subsequent depression were assessed.

Another study that attempted to control for the independent contributions of various depressive symptoms was performed in older adults.[22] Again, other depressive symptoms were found to have higher predictive values; insomnia ranked third among women but last (eighth) among men. Independent associations between insomnia and subsequent depression suggest a primary causal role between sleep disturbance and depression, although other contributing factors are quite likely involved as well.

On the other hand, there is also evidence that depression may predict insomnia. In another study of geriatric subjects, Foley et al.[23] studied incidence and remission of insomnia over a 3-year period. Not only did they find that persons with insomnia were more likely to develop depression, but also that incident insomnia was most strongly associated with depression. A number of other medical conditions and use of medications were also predictive of insomnia, again suggesting that the relationships between insomnia and depression are quite likely confounded somewhat by other associated factors.

Overall, these studies show a strong association between sleep disturbance and depression. Furthermore, they suggest that sleep disturbance contributes to the development of depression and that depression may cause insomnia. Alternatively, it is possible that insomnia and other depressive symptoms may appear causally related as the result of some other primary process. To determine the nature and direction of causality, it will be necessary to demonstrate that elimination of insomnia decreases the incidence of subsequent depression and vice versa. In fact, some evidence suggests that insomnia and depression can be manipulated independent of one another.[24,25] For example, in depressed patients, it has been shown that both nefazodone and fluoxetine have equivalent antidepressant effects. Nevertheless, nefazodone leads to subjective and objective improvement in sleep, whereas fluoxetine disrupts sleep.

Several studies attempting to look at the associations between insomnia and medical illness have demonstrated that sleep disturbance tends to change in concert with health status. In a study of geriatric subjects, Foley et al.[23] found that resolution of insomnia was significantly associated with improvement in self-perceived health. A study of patients with irritable bowel disorder[26] reported that severity of symptoms was predicted by the prior night's sleep, suggesting a potential causal relationship.

INSOMNIA AND SLEEP DEPRIVATION

It is generally assumed that patients with insomnia are sleep deprived and that perhaps some of the morbidity and mortality associated with insomnia may be mediated by the effects of sleep deprivation. Certainly, insomniacs tend to complain of daytime fatigue, but there is controversy as to whether the effects of chronic insomnia are similar to the effects of sleep loss. Acute sleep deprivation has been shown to produce increased daytime sleepiness (i.e., reduced sleep latency on multiple sleep latency testing [MSLT]) and decrements in psychomotor performance;

these effects can be seen both with sleep restriction and following frequent awakenings.[27–30]

In contrast, people with chronic insomnia have generally shown hyperarousal, with normal to prolonged daytime sleep latencies on MSLT in comparison to control subjects.[31–34] Results from some studies have even suggested that the less insomniacs sleep at night, the less likely they are to fall asleep during the daytime,[32] which runs counter to the behavior of normal subjects. On the other hand, 2 recent studies[35,36] have demonstrated that insomnia patients will respond to a challenge of acute sleep deprivation by falling asleep more quickly during naps on MSLT, showing that they can respond to a strong homeostatic challenge.

To determine if daytime correlates of chronic insomnia are due to sleep loss, Bonnet and Arand[37] used a yoked study to reproduce the sleep patterns of insomniacs in a group of normal sleepers for a period of 1 week. In comparison to baseline sleep patterns in normal subjects, the insomnia patients showed prolonged MSLT values; abnormalities on psychometric testing (MMPI and Profile of Mood States) including increased tension/confusion, decreased vigor, and MMPI score elevations; increased body temperature; and overestimation of time awake. The sleep-deprived normal subjects, in contrast, showed significantly reduced sleep latency on MSLT; decreased tension/confusion, depression, anger, and vigor, but no change in MMPI scales; decreased body temperature; and no change in estimate of time awake. The authors concluded that poor sleep alone does not produce the symptoms associated with chronic insomnia, but rather that hyperarousal is the primary problem that leads to insomnia and related symptoms.

In addition, it is possible that the chronic, mild sleep deprivation that accompanies insomnia does not trigger a normal sleep rebound response and in fact may feed back positively to worsen the insomnia, through both the establishment of aversive conditioning and maladaptive behaviors and neurochemical changes. For example, sleep deprivation of bipolar patients can lead to manic episodes,[38,39] which are themselves characterized by profound insomnia; sleep loss in mania can thus be viewed as self-perpetuating.[40] This is clearly an extreme case of how sleep deprivation can actually interfere with sleep and may be relevant to insomnia. Overall, these findings suggest an increased baseline level of arousal and/or decreased sleep drive in insomnia. They should not simply be interpreted as implying that insomniacs are not sleepy or that they have decreased need for sleep.

In regard to performance testing, patients with chronic insomnia show equivocal results (as described above) and may be more similar to normal sleepers than to sleep-deprived subjects; this makes it difficult to attribute specific functional impairments to increased sleepiness per se. However, it is possible that chronic sleep loss may result in the morbidity associated with chronic insomnia, e.g., accidents, reduced quality of life, and depression. It is also important to distinguish acute from chronic insomnia. Individuals with acute or transient insomnia may be more similar to normal subjects after sleep deprivation and show comparable effects on daytime functioning.

EFFECTS OF TREATMENT

Clearly, to relate performance deficits to sleep loss in insomniacs, it is necessary to show improved daytime functioning with successful treatment of the insomnia. In the case of transient insomnia, for example, sleep loss related to night shift work, there is evidence suggesting that hypnotics improve sleep during the day and alertness during the night.[41] Limited data are available for chronic insomnia, however. These studies have primarily relied on subjective quality-of-life measures and have yielded variable results. A recent survey of 261 insomniacs and 101 controls by Zammit et al.[14] confirmed that individuals with insomnia reported a number of abnormalities, including impaired cognitive function, poorer physical and emotional health, increased anxiety and depression, increased absenteeism, and decreased optimism regarding career. The insomnia group included 112 subjects currently being treated with medication. A comparison of treated and untreated insomniacs revealed no differences on any scales, suggesting that treatment had no significant effects on these various health and quality-of-life measures. The failure to see differences between treated and untreated insomniacs is difficult to interpret, however, since subjects were solicited by advertisements, which could have created a bias, and they had not necessarily shown an improvement in their sleep in response to treatment.

Other studies[42,43] have reported improved quality of life following treatment with hypnotics. A study[44] on patients with insomnia secondary to rheumatoid arthritis documented increased nocturnal sleep and daytime alertness with short-term use of a hypnotic, suggesting that objective improvement can be seen in some clinical populations. Further longitudinal studies assessing the effects of hypnotic treatment on health outcomes are clearly needed.

Treatment studies using hypnotic agents are often confounded by the effects of the drugs themselves, many of which may have residual effects that actually impair daytime functioning. A recent meta-analysis of the effects of benzodiazepines in the treatment of insomnia[45] found that although hypnotics increased sleep duration, they were also associated with adverse effects, particularly daytime drowsiness and light-headedness. In addition, increased impairment in cognitive function may occur with benzodiazepine use. Newer agents, especially those with ultra-short half-lives, appear to have less tendency to impair cognitive and psychomotor performance the morning after use.[46] For example, the pharmacokinetic profile of zale-

plon gives it the ability to be taken in the middle of the night with minimal risk of next-day impairment. There may even be differences among agents with short half-lives. In one study[47] zaleplon showed less psychomotor impairment in comparison with other hypnotics with short half-lives (e.g., zolpidem and triazolam). This suggests that half-life alone may not be the only factor involved in residual effects of hypnotics; other pharmacokinetic properties, such as receptor selectivity and affinity, may also be important variables.

CONCLUSION

Insomnia has a number of clinically significant associations, including psychiatric disorders, medical illnesses, and increased health care costs. Although insomnia has significant predictive value for some of these associations—most notably depression—it is not clear whether or how insomnia is causally related to any of them. Little is known about the ability of primary treatments for chronic insomnia to reduce any of the associated morbidity. In fact, some hypnotics may contribute to poorer daytime function through carryover effects, even though nocturnal sleep may be improved. However, there are now new agents such as zaleplon and zolpidem, which have shorter half lives that allow for rapid absorption and clearance, minimizing next-day residual effects. Further research is needed to determine the mechanisms relating sleep and health as well as the potential for insomnia treatment to improve medical and psychiatric outcomes.

Drug names: fluoxetine (Prozac), nefazodone (Serzone), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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