

# **The Impact of Stress on Insomnia and Treatment Considerations**

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## Introduction

Individuals in stressful situations commonly experience difficulty sleeping, and transient insomnia can occur in almost anyone in response to acute stressors, such as illness, personal conflict, work-related stress, environmental factors, and sudden schedule changes. In most cases of transient insomnia, the cause is obvious and sleep improves once the stressor is eliminated. Stress also appears to play a role in chronic insomnia, with severity and frequency of stressors as well as the individual's response to them contributing to the development of persistent difficulties with sleep.

## Association Between Stress and Insomnia

The role of stressors in the genesis of chronic insomnia has been documented in a number of studies. In a retrospective assessment of good vs poor sleepers, those with insomnia reported significantly more negative life events, such as losses and illnesses, during the year prior to the onset of insomnia, and many specifically attributed their insomnia to a major life event.[1] In a prospective study of young adults assessed over a 7-year period, those who experienced more frequent negative life events and interpersonal conflicts were more likely to have occasional insomnia or repeated bouts of brief insomnia.[2] In addition, a Finnish study found that psychosocial stressors were more likely to be associated with insomnia than were health problems,[3] indicating the strong link between stressors and sleep problems.

Although major stressful events can trigger insomnia, chronic exposure to minor stress may also contribute to an increased risk for insomnia and may be particularly important in the genesis of chronic sleep disturbance. In a population-based study in Japan, insomnia was significantly correlated with daily stress levels, whereas regular exercise was negatively correlated with sleep problems.[4] A recent study of over 3400 male civil servants in Japan assessed the relationships of a variety of stressors on 3 aspects of insomnia: difficulty initiating sleep, difficulty maintaining sleep, and poor-quality sleep.[5] Higher perceived stress, the consideration of life as not meaningful/worth living, and a variety of job-related stressors showed the strongest independent associations with all 3 types of insomnia complaints.

Recent work has begun to look more closely at the effects of specific stressors on insomnia. Some of these studies have demonstrated relationships between family conflict and insomnia in children, adolescents, and young adults, consistent with the idea that early and chronic stress may contribute to lifelong sleep problems. In a study of French adolescents, those who had insomnia symptoms came from families with higher divorce rates, had poorer relationships with their families, and reported higher rates of medical and psychological illness or death in parents.[6] A prospective study of undergraduate college students assessed the impact of family, academic, and social events on insomnia;

controlling for depression, negative family events, but not academic or social stressors, showed modest but significant predictive value for insomnia.[7] Furthermore, there appeared to be an interaction between family and academic stress, in that individuals who reported high stress levels in both of these areas had the highest insomnia scores. It is also likely that sleep problems in children may lead to increased family stress, as treatment of children's sleep problems has been shown to improve family satisfaction.[8]

Other studies have focused on the role of work-related stress in the development of insomnia. Individuals with insomnia frequently attribute their sleep problems to work-related stress or job dissatisfaction.[9,10] Job factors, such as shift work and frequent travel, particularly across multiple time zones, are also known to contribute to circadian rhythm sleep disorders and resulting insomnia. In turn, insomnia is significantly associated with decreased productivity and increased absenteeism.[11,12] A Swedish study found that a poor psychosocial work environment led to a more than 2-fold increased risk for the development of a new episode of insomnia.[13] Several studies have suggested that increased workload pressure is a risk factor for sleep problems.[14,15] A prospective, 1-year study examining the effects of specific work stressors found that work demands, leader support, and influence over decisions were significantly related to the development and maintenance of insomnia.[16] A cross-sectional study performed in Japan also found that increased job stress, as indicated by an effort-reward imbalance and overcommitment, was associated with insomnia.[17] Furthermore, another Japanese study reported that high job stress was not only associated with a higher risk for insomnia, but also for short sleep (less than 6 hours per night), suggesting that work-related stress may contribute to a combination of both insomnia and sleep deprivation.[18]

#### Mechanisms for Stress Effects

Although exposure to stressful events is associated with a greater risk for insomnia, individual differences in responding to stressors likely play an important role in the mediation of insomnia. Stress typically activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. There is an increasing body of evidence demonstrating hyperarousal and increased activity of the HPA axis in insomniacs, which may in turn predispose them to greater reactivity to stressors. Not only do stressors lead to insomnia, as discussed above, but activation of the HPA axis, for example, by infusion of corticotropin-releasing hormone, has been demonstrated to produce sleep disruption in normal individuals.[19] Sleep, particularly slow-wave sleep, decreases the responsivity of the HPA axis and waking increases it, such that insomnia is not only exacerbated by HPA axis hyperactivity, but sleep loss also promotes further activation, compounding the problem. In addition, insomniacs reportedly have reduced melatonin levels at night, and corticotropin-releasing hormone has been shown to reduce nocturnal melatonin levels in normal subjects.[20] Taken together, these data suggest the possibility that HPA hyperactivity may also contribute to neuroendocrine abnormalities that could further disrupt sleep at night, including their potential effects on circadian systems.

Another route by which stress may affect sleep is via interactions between the emotional/cognitive and sleep/wakefulness systems. Emotional regulatory centers, such

as the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the infralimbic cortex, and the lateral septum, project to the ventrolateral preoptic nucleus and orexin neurons -- which are sites involved in sleep and wakefulness, respectively.[21]

Compared with normal sleepers, insomniacs show increases in metabolic rate,[22] body temperature,[23] and heart rate.[24] They also exhibit higher levels of cortisol and catecholamines, suggesting increased activity of the stress-response system.[25,26] Their sleep electroencephalogram (EEG) is characterized by higher levels of fast activity and reduced levels of slow-wave activity, which are thought to represent increased arousal during sleep.[27,28] Not surprisingly, insomniacs also tend to report themselves as being more awake at times when they are behaviorally and physiologically asleep.[29]

In a study of normal sleepers subjected to several stressful conditions, including phase advances or caffeine ingestion shortly before bedtime, those who had the poorest sleep on their adaptation night in the sleep laboratory also had significantly reduced sleep efficiency in response to the stressors compared with those who slept well on the adaptation night[30]; the poor sleepers also had a significantly higher heart rate. These data suggest that individuals show consistent sleep responses to stressors, and that those with greater sympathetic nervous system activation may be more susceptible to developing insomnia. A subsequent study assessed a group of individuals from the general population with a 27-item self-response instrument that asks about sleep disturbance in the context of common stressful experiences (the Ford Insomnia Response to Stress Test).[31] When studied in the sleep laboratory, those with higher scores showed prolonged latency to sleep onset and lower sleep efficiency at night, and took longer to fall asleep during the daytime on the Multiple Sleep Latency Test. The results demonstrated that it may be possible to detect vulnerability to insomnia and that it is associated with hyperarousal.

The important interaction between individual response to stress and external stressors in triggering insomnia was suggested by a prospective study assessing both stressful events and coping skills in insomniacs and good sleepers.[32] In that study, the 2 groups reported similar numbers of stressful events. Higher stress during the day resulted in more insomnia on the subsequent night. Insomniacs, however, rated the impact and the intensity of the stressful events higher, their lives as more stressful, and their presleep arousal as greater than the good sleepers. More importantly, arousal levels at bedtime mediated the relationship between stress during the day and sleep disturbance the following night. These findings are not only consistent with physiologic studies of insomniacs, but they also suggest that treatment for insomnia should include training in stress management and better coping strategies because an individual's response to stress may be one of the key factors in the genesis of chronic insomnia.

An important issue with regard to the association between stress and insomnia is that stress also contributes significantly to depression and anxiety disorders, which themselves are strongly associated with insomnia. HPA axis hyperactivity has been demonstrated in patients with depression and anxiety disorders and is thought to be central to the genesis of these illnesses. Insomnia is both a symptom as well as an

important risk factor for depression and anxiety disorders, suggesting the possibility that the relationship between stress and insomnia may be in part due to comorbid depression and/or anxiety. For example, in a study evaluating stress, depression, and EEG sleep variables in insomniacs, higher depression levels were associated with greater subjective sleep complaints.[33] Furthermore, those with more stress-related intrusive thoughts showed more high-frequency EEG activity during sleep, and those who reported greater subjective stress showed less power in low-frequency, slow-wave activity, again demonstrating the association between stress and objective sleep disturbance. It has been suggested that because stress and subclinical depression are reflected by insomnia, insomnia thus serves as a marker for increasing levels of experienced stress and thus can herald the onset of other stress-induced illnesses; moreover, disturbed sleep likely increases perceived distress.[33]

#### Treatment Considerations

The central role that stress and an individual's response to it play in insomnia has been increasingly recognized, highlighting the need for interventions targeted at managing stress levels and reducing the impact of stressors. Assessment of insomnia should always include an assessment of stressors and the patient's perception of and response to them. Whenever possible, lifestyle changes to reduce obvious stressors should be considered. Cognitive-behavioral therapy to diminish arousal levels, intrusive thoughts, and negative cognitions -- particularly those that occur in the evening -- has been demonstrated to be effective in the treatment of chronic insomnia.[34]

Not surprisingly, most US Food and Drug Administration (FDA)-approved treatments act on the benzodiazepine receptor complex, and many of these have antianxiety as well as hypnotic effects. Little work has been done, however, to assess the effects of benzodiazepine receptor agonists on central systems involved in stress responses. One recent study studied the effect of alprazolam on the HPA axis and sympathetic nervous system responses to a psychosocial stressor[35]; activation of the HPA axis in response to stress was blunted, but secretion of catecholamines and increases in heart rate and blood pressure were not affected.

Benzodiazepines approved for use in treatment of insomnia include triazolam, temazepam, estazolam, flurazepam, and quazepam; nonbenzodiazepines acting at the benzodiazepine receptor include zaleplon, zolpidem/zolpidem modified release (MR), and eszopiclone. Zaleplon and zolpidem have greater binding affinity for the GABA-A1 receptor subtype, which is not thought to be primarily involved in anxiolysis. Nevertheless, all of these agents are effective in promoting sleep onset, and those with longer half-lives also improve sleep maintenance.

Ramelteon, currently the only FDA-approved hypnotic that acts on melatonin receptors, is not known to act on the HPA axis or sympathetic nervous system, or have anxiolytic properties; however, it is helpful in promoting sleep onset, even in a stress-induced model of transient insomnia.[36] Thus, hypnotics may promote sleep without necessarily affecting the responses to the stressors disrupting sleep. Certainly, for patients with

significant anxiety disorders or other psychiatric illnesses, specific treatment for those disorders may be required and could also contribute to improvement in sleep.

#### Summary

Stress and insomnia are strongly linked, with stress playing a major role not only in transient insomnia, but also in many cases of chronic insomnia. Even minor, day-to-day stresses can contribute to insomnia because some individuals may be particularly vulnerable or reactive to a broad range of stressors. Stress reactivity also appears to be central to psychiatric disorders, such as anxiety and depression, which may explain their close connection to insomnia. Treatment approaches should include behavioral methods to reduce stress and its impact. Hypnotic medications can be helpful in both acute and chronic insomnia to promote sleep. Individuals with severe stress-related symptoms, such as anxiety disorders or mood disorders, may require more specific treatments for those disorders as well.

#### References

1. Healey ES, Kales A, Monroe LJ, Bixler EO, Chamberlin K, Soldatos CR. Onset of insomnia: role of life-stress events. *Psychosom Med.* 1981;43:439-451. Abstract
2. Vollrath M, Wicki W, Angst J. The Zurich study. VIII. Insomnia: association with depression, anxiety, somatic syndromes, and course of insomnia. *Eur Arch Psychiatry Neurol Sci.* 1989;239:113-124. Abstract
3. Martikainen K, Partinen M, Hasan J, Laippala P, Urponen H, Vuori I. The impact of somatic health problems on insomnia in middle age. *Sleep Med.* 2003;4:201-206. Abstract
4. Kim K, Uchiyama M, Okawa M, et al. Lifestyles and sleep disorders among the Japanese adult population. *Psychiatry Clin Neurosci.* 1999;53:269-270. Abstract
5. Murata C, Yatsuya H, Tamakoshi K, Otsuka R, Wada K, Toyoshima H. Psychological factors and insomnia among male civil servants in Japan. *Sleep Med.* 2007;8:209-214. Abstract
6. Vignau J, Bailly D, Duhamel A, Vervaecke P, Beuscart R, Collinet C. Epidemiologic study of sleep quality and troubles in French secondary school adolescents. *J Adolesc Health.* 1997;21:343-350. Abstract
7. Bernert RA, Merrill KA, Braithwaite SR, Van Orden KA, Joiner TE Jr. Family life stress and insomnia symptoms in a prospective evaluation of young adults. *J Fam Psychol.* 2007;21:58-66. Abstract
8. Mindell JA, Durand VM. Treatment of childhood sleep disorders: generalization across disorders and effects on family members. *J Pediatr Psychol.* 1993;18:731-750. Abstract
9. Ancoli-Israel S, Roth T. Characteristics of insomnia in the United States: results of the 1991 National Sleep Foundation Survey. I. *Sleep.* 1999;22(suppl2):S347-353.
10. Shochat T, Umphress J, Israel AG, Ancoli-Israel S. Insomnia in primary care patients. *Sleep.* 1999;22(suppl2):S359-365.
11. Ozminkowski RJ, Wang S, Walsh JK. The direct and indirect costs of untreated insomnia in adults in the United States. *Sleep.* 2007;30:263-273. Abstract

12. Leger D, Massuel MA, Metlaine A. Professional correlates of insomnia. *Sleep*. 2006;29:171-178. Abstract
13. Linton SJ. Does work stress predict insomnia? A prospective study. *Br J Health Psychol*. 2004;9:127-136. Abstract
14. Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Sleep disturbances, work stress and work hours:a cross-sectional study. *J Psychosom Res*. 2002;53:741-748. Abstract
15. Ribet C, Derriennic F. Age, working conditions, and sleep disorders: a longitudinal analysis in the French cohort e.S.T.E.V. *Sleep*. 1999;22:491-504. Abstract
16. Jansson M, Linton SJ. Psychosocial work stressors in the development and maintenance of insomnia: a prospective study. *J Occup Health Psychol*. 2006;11:241-248. Abstract
17. Ota A, Masue T, Yasuda N, Tsutsumi A, Mino Y, Ohara H. Association between psychosocial job characteristics and insomnia: an investigation using two relevant job stress models -- the demand-control-support (DCS) model and the effort-reward imbalance (ERI) model. *Sleep Med*. 2005;6:353-358. Abstract
18. Utsugi M, Saijo Y, Yoshioka E, et al. Relationships of occupational stress to insomnia and short sleep in Japanese workers. *Sleep*. 2005;28:728-735. Abstract
19. Steiger A. Sleep and the hypothalamo-pituitary-adrenocortical system. *Sleep Med Rev*. 2002;6:125-138. Abstract
20. Rodenbeck A, Hajak G. Neuroendocrine dysregulation in primary insomnia. *Rev Neurol (Paris)*. 2001;157:S57-61. Abstract
21. Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol*. 2005;493:92-98. Abstract
22. Bonnet MH, Arand DL. 24-hour metabolic rate in insomniacs and matched normal sleepers. *Sleep*. 1995;18:581-588. Abstract
23. Lushington K, Dawson D, Lack L. Core body temperature is elevated during constant wakefulness in elderly poor sleepers. *Sleep*. 2000;23:504-510. Abstract
24. Bonnet MH, Arand DL. Heart rate variability in insomniacs and matched normal sleepers. *Psychosom Med*. 1998;60:610-615. Abstract
25. Vgontzas AN, Tsigos C, Bixler EO, et al. Chronic insomnia and activity of the stress system: a preliminary study. *J Psychosom Res*. 1998;45:21-31. Abstract
26. Irwin M, Clark C, Kennedy B, Christian Gillin J, Ziegler M. Nocturnal catecholamines and immune function in insomniacs, depressed patients, and control subjects. *Brain Behav Immun*. 2003;17:365-372. Abstract
27. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep*. 2001;24:110-117. Abstract
28. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry*. 1992;49:651-668. Abstract
29. Edinger JD, Krystal AD. Subtyping primary insomnia: is sleep state misperception a distinct clinical entity? *Sleep Med Rev*. 2003;7:203-214.
30. Bonnet MH, Arand DL. Situational insomnia: consistency, predictors, and outcomes. *Sleep*. 2003;26:1029-1036. Abstract
31. Drake C, Richardson G, Roehrs T, Scofield H, Roth T. Vulnerability to stress-related sleep disturbance and hyperarousal. *Sleep*. 2004;27:285-291. Abstract

32. Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. *Psychosom Med.* 2003;65:259-267. Abstract
33. Hall M, Buysse DJ, Nowell PD, et al. Symptoms of stress and depression as correlates of sleep in primary insomnia. *Psychosom Med.* 2000;62:227-230. Abstract
34. Morin C, Culbert J, Schwartz S. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry.* 1994;151:1172-1180. Abstract
35. Fries E, Hellhammer DH, Hellhammer J. Attenuation of the hypothalamic-pituitary-adrenal axis responsivity to the Trier Social Stress Test by the benzodiazepine alprazolam. *Psychoneuroendocrinology.* 2006;31:1278-1288. Abstract
36. Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep.* 2005;28:303-307. Abstract