CLINICAL REVIEW

Hyperarousal and insomnia: State of the science

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SUMMARY

In the past few years it has become increasingly clear that insomnia is a chronic disease that interacts with many other medical conditions. As our ability to examine complex physiological activity during sleep has increased, additional evidence continues to suggest that insomnia is associated with inappropriate physiological arousal. It is now known that patients with primary insomnia have increased high-frequency EEG activation, abnormal hormone secretion, increased whole body and brain metabolic activation, and elevated heart rate and sympathetic nervous system activation during sleep. This activation can be measured throughout the day and night and is chronic. Other research suggests that insomnia, probably based upon the associated chronic physiologic arousal, is associated with increased risk for medical disorders such as depression, hypertension, or cardiac disease. An animal model that has used odor stress to produce poor sleep in rats has identified specific activated brain sites similar to those found in human brain metabolic studies to suggest that insomnia is a state in which sleep and arousal systems are both simultaneously active. The animal studies have also shown that the inappropriate arousal can be blocked by lesions in the limbic and arousal systems. It is hoped that these findings can be extended to identify new compounds that improve insomnia by acting at these sites of abnormal brain activation.

In a Sleep Medicine Reviews report published in 1997,1 the case was made that many patients given a diagnosis of primary or idiopathic insomnia suffered from a disorder of physiological hyperarousal that produced both poor sleep and their other commonly reported symptoms. This paper will revisit this hyperarousal hypothesis by re-examining the previous data and including significant new data that have accumulated in the intervening years.

Historically insomnia, like depression, has been viewed as a behavioral or emotional problem. One common view is that insomnia develops when an acute emotional stress produces poor sleep and becomes habitual when inappropriate behavioral responses to the poor sleep (i.e., staying in bed longer, using alcohol, worrying about poor sleep) are learned.2 There is no question that acute emotional stress can produce insomnia in many individuals. However, experimental work has shown that stress exists primarily in the central nervous system of the patient – when many people were exposed to the same stressor, some had very poor sleep while others had little change from their baseline sleep.3

Subjects who reacted to the stress of spending a night in the sleep laboratory by having poor sleep did not differ in mood, personality, or other demographic measures from those subjects who reacted to the same stress by having little change in their sleep. However, those subjects who had poor sleep in response to their first night in a sleep lab were found to have higher heart rates and decreased parasympathetic activity at baseline and greater sympathetic nervous system activation than the good sleepers after phase-advanced sleep. Instead of the traditional Spielman model, which posits a single pre-insomnia state with few predisposing factors,2 even normal sleeping young adults were found to have a wide range of predispositions to poor sleep, and the most meaningful measure of predisposition was baseline level of central nervous system arousal as measured by cardiovascular activation. Those subjects with low levels of sympathetic activation maintained normal, efficient sleep despite the added stress that was sufficient to produce poor sleep in subjects with higher levels of sympathetic nervous system activation. On the second sleep laboratory night, the stress of the first sleep lab night was gone, and sleep normalized in the poor sleepers. Traditional psychological explanations would suggest a psychological response to a new environment, but, in fact, the same poor sleepers also were found to have significantly worse sleep (compared to the original stress insensitive subjects) when their bed time was advanced 3 or 6 hours (to produce a different...
type of physiological activation) and even when given caffeine (versus placebo) prior to a normal bed time. The point is that, given a predisposition to physiological activation, any number of physiological stressors will increase the likelihood of an insomnia response. In addition, sympathetic activation tends to increase with age, physical deconditioning, and numerous medical problems; and this increases the predisposition to chronic insomnia as individuals mature in our society. The implication is that there are numerous factors and widely variable amounts of physiological predisposition to poor sleep that interact with a range of state stressors (that may include both cognitive/emotional stress and state physiological activation) to produce insomnia on a given night.

The goal of this paper will be to 1) review the studies that have examined state and trait physiological responses in patients with insomnia and normals to better understand the significance of arousal level in insomnia and 2) to explore the medical and behavioral implications of insomnia as a chronic physiologic arousal disorder.

Evidence for physiological arousal in patients with primary insomnia

Extensive physiological differences between good and poor sleepers were first reported by Monroe, 4 who found increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions 30 minutes prior to and during sleep in poor sleepers as compared to normal sleepers. In the 20 years that followed, several additional differences were reported when patients with insomnia were compared with normal sleepers. Poor sleepers had increased secretion of corticosteroids and adrenaline. 5,6 compared with good sleepers in most but not all studies. Patients with sleep-onset insomnia had increased frontalis 8 and mentalis EMG 9,10; increased heart rate 11; increased finger temperature; and more beta and less alpha frequencies in the EEG. 9,10 Significantly elevated body temperature was reported in some but not all studies of poor sleepers. 4–6,12

More recent experiments, often using carefully selected patient populations, have extended the range of physiological findings. These findings will be reviewed by category: cardiac measures, hormone measures, body temperature, metabolic measures, evoked and spectral EEG measures, and multiple sleep latency test measures.

Cardiac measures

A number of studies have replicated and refined the earlier experiments. In addition to the early study that showed a significantly higher heart rate in insomnia patients compared with normals, 13 two of three more recent studies have shown significantly higher heart rate during both sleep and wake periods in carefully selected insomnia patients. 13,14 Another more recent study that did not show a significant increase in heart rate 15 did document a 4-beat increase in the insomnia group (Effect Size [ES] = 1.04). When data were combined from these latter three studies, mean heart rate was 69.8 bpm in insomnia patients versus 64.1 bpm in controls (tES = 3.476; p < 0.001 and ES = 2.80). Two studies have examined heart rate variability in insomnia patients versus controls. One found significantly decreased high-total frequency spectral power (parasympathetic activation) and increased low/high-frequency spectral power (sympathetic activation) in wake and all sleep stages in insomnia patients as compared with normal controls. 11 The other study did not find significant differences in Heart Rate Variability based upon a single 5-min recording from a waking afternoon session. 16 Vgontzas et al. 17 have shown a significantly increased risk for hypertension in insomnia patients with a polysomnographic sleep time of 6 hours or less. Risk was greatly reduced for patients without an insomnia complaint who slept for less than 6 hours and patients with an insomnia complaint who actually slept for more than 6 hours.

Hormone measures

Several measures including cortisol, ACTH, melatonin, norepinephrine, and IL-6 have been measured in matched groups of insomnia patients and controls. In addition to initial positive results, 7,8 at least seven newer studies, 8–24 have examined cortisol levels, and all except one 25 have found evidence for increased cortisol secretion in insomnia patients compared with controls. In the two studies with a large number of cortisol observations, 22,23 overall increases in cortisol were large (average ES = 2.32). One study with frequent sampling has found increased ACTH in patients with primary insomnia. 22 Studies have shown that patients with insomnia have decreased melatonin secretion at night. 25,26 One study has shown increased norepinephrine in insomnia patients compared with both controls and depressed patients. 27 Two studies have shown indication of increased IL-6 in insomnia patients, but the points of elevation varied from prior to bed time to 3–7 am. 28,29

Body temperature

Body temperature was significantly elevated in insomnia patients compared with controls in 2 of 6 studies. 4,6,12,20,31 In a recent study that used a constant routine and careful subject selection to examine rectal temperature in older patients with insomnia, 32 a highly significant difference of only 0.29 °C (based upon careful measurement with very small error) was found during the night with patients awake in the constant routine. However, the difference, when measured during sleep, was not significant.

Metabolic measures

Two studies have measured whole-body metabolic rate across the night in insomnia patients and matched controls. 33,34 One showed significantly elevated VO2 in insomnia patients compared with normals across the night, within matched sleep stages, and during daytime waking observation periods. The other study showed that VO2 was also significantly elevated, although to a lesser degree, in patients with paradoxical insomnia (patients with sleep staging that did not differ from the controls). More recently, insomnia patients have been shown to also have elevated global brain metabolism both asleep and awake based upon functional neuroimaging. 35 In addition, insomnia patients had a smaller decline in metabolism during sleep in the reticular system, hypothalamus, thalamus, insular cortex, amygdala, and hippocampus compared with normal, and this suggested increased general arousal and increased activity in emotional arousal areas of the brain. In a following study, the same investigators reported positive correlations between wake time during sleep and brain metabolic rate in areas associated with emotion. 36

Evoked and spectral EEG measures

Increased beta EEG activity has been noted during the night in 7 of 8 studies of patients with insomnia compared with normals. 30,37–41 One study has documented a significant decrease in beta activity in a group of patients with insomnia after 6 weeks of cognitive behavioral therapy. 44 After therapy, relative beta power was reduced to 82% of the pretherapy value (ES = 0.32). In comparison, another study reported that relative beta power in control subjects was 49% of the value found in insomnia patients (ES = 1.60). 37
Studies of evoked potentials have shown increased amplitude to N1 and decreased amplitude for N350 in patients with insomnia compared with controls during the night.55,66 These differences are consistent with hyperarousal and difficulty inhibiting cortical arousal. Other studies have shown increased amplitude of P300 in insomnia patients on poor nights of sleep in comparison with better nights of sleep.47,48

**MSLT measures**

The multiple sleep latency test is particularly interesting with reference to insomnia. Since insomnia patients have reduced sleep time and report daytime deficits related to reduced sleep, it might be expected that these patients would be sleepy during the day and have reduced sleep latencies on nap evaluations. However, this hypothesis was not supported in any of twelve studies that showed daytime sleep latency was not significantly reduced in insomnia patients compared with controls.33,49,50–52,54,55,50,56,57 An alternate hypothesis suggests that, if poor nocturnal sleep occurs secondary to chronic physiological activation, patients would find it difficult to fall asleep anytime including at night and during daytime naps. Indeed, in 6 of the 12 studies above, MSLT sleep latency was significantly increased in insomnia patients as compared to controls. Of the 12 studies, six defined insomnia based upon EEG (as compared to subjective report findings). MSLT results were significantly increased in four of these six studies in insomnia patients compared with normal controls. Four of these studies reported mean and standard deviation data for the groups,33,49,50,51 and this allowed the data from these studies to be combined for a meta-analysis. The average sleep latency for insomnia patients from these four studies (N = 108) was 16.1 (±4.4) minutes versus 13.6 (±4.8) minutes for controls (N = 83). This difference was statistically significant (t = 3.698, p < 0.001), and the power was ES = 0.55.

In addition to the traditional MSLT, numerous studies have shown significant positive correlations between physiological activation and sleep variables, usually measured by heart rate and sleep latency.58–60 Do these results and the significant elevation of MSLT in insomnia patients imply that the MSLT can be a measure of arousal? Studies have shown that MSLT is reliably increased for up to 90 minutes in normal young adults after brief physiological arousal (5 minutes of normal walking) and that increases in MSLT are paralleled by increased heart rate.61,62 Patients with insomnia were also tested in this model, and it was found that the insomnia patients had significantly longer sleep latencies than normals after rest (10.5 versus 6.7 min – t22 = 4.04; p < 0.001), after a brief walk to produce state arousal (16.2 versus 13.0 min – t22 = 3.4; p < 0.01), and in themselves after the walk compared to their own resting baseline.60 The implication is that the insomnia patients have chronic increased physiological activation to account for the resting differences but also continue to respond with additional state physiological activation that produces a further increase in sleep latency after the walk. These sleep latency results were corroborated by heart rate, which increased from 59.4 bpm at rest to 62.3 bpm at the beginning of the MSLT after activity in the normals while increasing from 62.7 bpm to 64.7 bpm in the insomnia patients in the same conditions. These studies directly support the concept of elevated trait physiological arousal in the insomnia patients with additional increase from state arousal following physical activity that produced an elevation in MSLT and heart rate in both groups.

**Summary**

Consistent findings across a broad range of physiological systems support the concept of physiological arousal in patients with primary insomnia. There are occasional studies in these areas that do not statistically support the arousal concept, but non-supportive studies tend to be those with few or less well-defined populations that are infrequently measured or evaluated with less sensitive measures. Consistent physiological and neurophysiological findings increase the possibility of developing animal models and site specific treatment options, and these will be discussed in the sections that follow.

**Animal model**

The diagnosis of insomnia is based upon the subjective complaint of poor sleep that is sometimes corroborated by EEG recordings. The requirement of a complaint, of course, makes an animal model of insomnia difficult, but studies of poor sleep in animals in response to expected stressors can add unique insight to human work. In a recent model, rats were placed in a cage previously occupied by a male rat (odor exposure). This is a species specific model that produces an acute stress response. Rats exposed to this stress were found to take longer to fall asleep (59 minutes versus 32 minutes in controls) and to have increased wakefulness during sleep.63 The rats were sacrificed 5.5 hours after being placed in the new cage, and Fos expression was significantly elevated in the cerebral cortex, limbic system and parts of the arousal (specifically locus coeruleus) and autonomic systems in the stressed animals in comparison with controls. However, Fos expression was also found in the sleep promoting areas of the brain. These dual findings suggested that the rats were displaying “simultaneous activation of the sleep and arousal systems” (p. 10173).64 These same animals also showed increased high-frequency EEG (gamma) during their sleep recordings after the odor stress. In another part of the experiment, lesions in the limbic system or arousal system were associated with improved sleep and normal gamma during sleep after odor exposure. These findings directly support the hyperarousal model by showing brain physiological activation in response to stress as demonstrated by gamma increases that are similar to the EEG activation found in human insomnia patients. Of more importance, the finding of activation in sleep centers is an indicator that the poor sleep is not secondary to reduced drive for sleep but rather to the combination of activation in both the sleep and arousal systems when the animals attempted to sleep.

In another animal model, when rats slept in an environment where they had previously received electrical shock,65 both the sleep response (reduced REM) and neural circuits were somewhat different than in the odor model, and this suggests that some of the reported findings in animal models may be specific to the model. Certainly, it is the case that poor sleep associated with stress in the rat is substantially different from chronic insomnia in humans. While the limbic and arousal sites of activation in the rat odor model are in general agreement with the human neural imaging studies,66 there are also cortical sites of activation in humans that are not seen in rats. Nonetheless these animal results provide a starting point for the development of more specific neural models of both pathology and treatment that may be able to target abnormally activated limbic or arousal systems.

**Genetic studies**

Basal level of sympathetic nervous system activity, like many other attributes, could be seen as normally distributed in the population. This would mean that some individuals would probably have a genetic predisposition to greater sympathetic activation and therefore a greater predisposition to develop associated disorders such as insomnia. A good deal of evidence suggests that
insomnia is under strong genetic influence. A recent twin study showed a heritability estimate of 57% for insomnia (as contrasted with 73% for obesity and 38% for sleepiness). These data agree well with earlier studies. Strong heritability implies that insomnia is not primarily a learned or environmental disorder but does not necessarily indicate that insomnia is related to underlying level of arousal. However, it is known that individuals predisposed to significant situational insomnia also have elevated heart rates and sympathetic activation, that these individuals can be identified by the use of the Ford Insomnia Response to Stress Test (FIRST) that there was a strong correlation for FIRST scores (r = 0.61; p < 0.001) between sibling pairs, and that a history of transient sleep difficulty predicts development of chronic insomnia. Together, these studies begin to show how heritable physiological tendency can develop into chronic insomnia.

**Cause versus effect**

Despite the fact that there is now pervasive evidence of physiological arousal in numerous systems during sleep in patients with insomnia, none of the literature cited, except, perhaps, the rat stress–induced model, comments on causality. Insomnia is typically accompanied by numerous changes including cognitive arousal/stress, dysphoria or degraded mood, depression or anxiety and fatigue, in addition to the numerous physiological changes described previously. It has always been difficult to determine which of these variables caused the symptoms reported and which were simply correlates of the underlying pathology. A few studies have attempted to disentangle some of these many variables.

One study sought to model insomnia by administering caffeine 400 mg three times per day to normal young adult sleepers for a week to produce physiological arousal (as measured by whole-body metabolic rate) and to record standard insomnia outcomes. The chronic use of caffeine increased metabolic rate, and sleep efficiency declined significantly. During the initial days of caffeine use, participants had elevated MSLT scores (i.e., took longer to fall asleep) and reported increased subjective vigor. However, by the end of the week of caffeine use, significantly increased daytime fatigue was reported despite MSLT scores that were still significantly elevated as compared with baseline. In addition, anxiety, as measured by the anxiety scale of the Minnesota Multiphasic Personality Inventory (Pt), moved significantly toward psychopathy. This finding that chronic physiological arousal would paradoxically lead to increased fatigue even while objective sleepiness was decreased indicated that physiological activation by itself could be responsible for the same paradoxical reports in patients with insomnia. The increase in anxiety based upon a non-transparent trait measure of personality offered additional evidence that cognitive and personality components frequently seen in patients with insomnia could be significantly influenced by a chronically increased level of CNS arousal.

Of course, it was possible that the outcome variables were related to the pharmacological effects of caffeine or to the poor sleep produced by the caffeine rather than a direct relationship with the physiological arousal that was produced. One major question was whether the secondary effects of insomnia such as mood/personality differences and daytime sleepiness differences were actually produced by poor sleep at all (or whether both the poor sleep and daytime consequences were produced by another underlying factor such as physiological arousal level). Insomnia patients report that their poor sleep leads to their symptoms of fatigue and dysphoria. However, it is possible to determine empirically what outcomes occur as a result of poor sleep independent of other influences by using a yoke-control design to produce the same poor sleep in normal sleepers as that seen in primary insomnia patients by awakening the normals or disturbing their sleep to the same extent. In a study to address this issue, primary insomnia patients were identified by standard sleep criteria, and the sleep parameters of those patients were used to produce comparable sleep in matched normal sleepers. It was hypothesized that if the yoked normal sleepers developed the secondary symptoms seen in the “true” insomnia patients after sleeping like them for a week, then those symptoms could be seen as secondary to the poor sleep. On the other hand, if the yoked normal sleepers did not develop the symptoms seen in the “true” insomnia patients, then some factor other than poor sleep would be responsible for the secondary symptoms. Sleep patterns were matched by making experimental arousals and awakenings throughout the night in normal sleepers to match the pattern of wake time and arousals seen in the patients with insomnia. The EEG sleep produced in the experimental subjects was similar to that found in patients reporting insomnia, so changes in the outcome variables should have reflected the consequences of pure “poor” sleep. Insomnia patients have difficulty falling asleep both at night and during the MSLT. But, both sleep latency and MSLT data from the yoke-control study supported significantly increasing ease of falling asleep as the nights of experimental insomnia increased. Insomnia patients frequently have them on both temperature and whole body metabolic rate. Except for an increased nocturnal metabolic rate probably associated with the experimental sleep disturbance itself, the trends in the yoke-control study showed lower metabolic rate and decreased body temperature during the day. Insomnia patients typically report increased stress, anxiety, or depression. However, in the yoke-control study, the state measures of tension and depression decreased significantly during the study. Patients with insomnia typically have elevated MMPI scales, but the MMPI measures, including the anxiety subscale, were unchanged in this study. Insomnia patients report increased fatigue and decreased vigor, and similar changes were found in the yoke-control study. However, these changes are also found during simple sleep deprivation. Finally, insomnia patients overestimate their time spent awake during the night. Despite increased awakenings and wake time in the current study, the normal sleepers continued to appropriately estimate their wake time during the night.

The most parsimonious explanation for these results was that pattern of experimental insomnia given to normals resulted in partial sleep deprivation. The decreasing MSLT values and increase in REM percent and rebounds of REM and SWS that were found during recovery are clear signs of sleep loss. Decreases in vigor and body temperature also suggest simple sleep loss. Since total sleep time in the study was reduced to 6 hours for a week, this should have resulted in partial sleep deprivation. So the results suggest that patients with mild insomnia might have mild sleep deprivation but that the symptoms are masked by their inappropriate level of arousal. Of more importance, these data suggest that “the poor sleep itself is not the basis of the secondary symptoms” because those insomnia symptoms could not be reproduced in normal individuals given that pattern of sleep.

One criticism of the above study is that it may be that patients with primary insomnia suffer from the combination of poor sleep and a specific learned background that determines the relationship between their poor sleep at night and residual insomnia symptoms. This hypothesis was tested in a study that identified a group of patients with primary insomnia characterized by EEG-defined poor sleep and then subjected them to seven successive nights of very poor sleep (defined as allowing them only 80% of their already defined decreased total sleep time). This sleep reduction was accomplished by waking patients up at the end of each quarter of the night if they accumulated more than 80% of their baseline sleep for that quarter of the night (while holding time in bed for the night...
at the baseline level) resulting in very poor sleep (average total sleep of 4.2 hours per night for the week).

This reduction of total sleep time by experimental awakenings resulted in a significant decrease in daytime MSLT values in the patients. After seven nights of 4.2 hours of sleep, MSLT values had decreased from 15.6 to 11.1 minutes. This reduction was statistically significant, but the 11.1-minute value is still within the normal range for the test.\(^{76}\) This value can be compared with the 11.1 minutes sleep latency reported by Dinges et al.\(^{77}\) in normal young adults after baseline sleep. When these normal young adults then had their sleep limited to 5 hours per night for 5 nights, their MSLT was reduced to 3.0 minutes. These results highlight that insomnia patients did become a little sleepier when their sleep was reduced but that the resulting sleepiness was still equal to normal sleepers at baseline and much less than that seen in normal sleepers after similar sleep loss. The difference in MSLT values prior to and after sleep reduction may reflect the degree to which hyperarousal in insomnia can mask sleep tendency. Of equal interest, insomnia patients did not report significant decreases in their sleep quality or show changes in their personality or physiological parameters consistent with more severe insomnia when their wake time during the night was increased by two hours. Again these data are consistent with the conclusion that poor sleep quality and daytime dysphoria in insomnia patients are related to level of arousal\(^{78}\) and not EEG sleep parameters.

If insomnia is primarily related to physiological arousal rather than EEG sleep, one would hypothesize that it should be possible to find a group of patients who complain of insomnia but have perfectly normal sleep as measured by their EEG sleep stages. Such patients, of course, do exist and are currently given the diagnosis of “paradoxical insomnia”. With an understanding of hyperarousal, it can be seen that these patients have a normal sleep system opposed by an activated arousal system. In humans, patients with paradoxical insomnia perceive their laboratory sleep as poor but have EEG sleep stage parameters which do not differ statistically from matched normal controls.\(^{34}\) However, these patients were found to have abnormal MMPI values and were subjectively more confused, tense, depressed and angry than matched normals.\(^{34}\) These observations were similar in direction and magnitude to those seen in patients with primary insomnia. Paradoxical insomnia patients were also found to have significantly elevated 24-hour metabolic rate compared to matched normals.\(^{24}\) The increase in metabolic rate in the patients was about 6% overall compared to their controls. In contrast, an overall increase in metabolic rate of 9% was found in subjects.\(^{33}\) Thus while paradoxical insomnia patients appear to be less aroused than the primary insomniacs, their increased arousal compared with normals suggests a physiological rather than a psychological disorder that may be amenable to treatment by reduction of arousal.

**Medical implications of hyperarousal**

Insomnia has been considered an acute disorder often secondary to other medical pathology such as depression or pain. However, more recently an NIH review of insomnia and treatments has concluded that insomnia can be a primary or comorbid chronic disorder.\(^{79}\) Many studies have shown that insomnia is a predictor for the later development of depression.\(^{80}\) In addition, much evidence has accumulated showing abnormal levels of arousal in patients with depression and other mood disorders.\(^{81}\) Hyperarousal in insomnia has been associated with increased sympathetic nervous system activity\(^{13}\) and/or HPA activation.\(^{22}\) If patients have chronic central nervous system activation, they should also have elevated cardiovascular risk. One study has shown an increased risk for the development of hypertension over a 4-year period in a large group of telecommunication workers who reported either consistent difficulty falling asleep or having many or long awakenings during the night.\(^{82}\) This result was replicated in the Atherosclerosis Risk in Communities Study\(^{83}\) but not in a smaller study that used data from the Cardiovascular Health Study.\(^{84}\) Because questionnaire studies have difficulty controlling for unrecognized sleep apnea in participants and documenting actual sleep, a more recent study has used polysomnography to examine insomnia and blood pressure in 1741 patients.\(^{85}\) Results showed that patients with objective insomnia controlled for apnea had a significant risk for hypertension and that the risk increased as total sleep time decreased. This increased risk was also greater in patients with insomnia than in short sleepers without a complaint of insomnia.

A review of the cardiovascular implications of poor sleep\(^{85}\) found 16 published studies that presented risk ratios for the relationship between either difficulty falling asleep or poor sleep and cardiac events such as first myocardial infarct or cardiac mortality. Virtually all of the studies reported a significant association between one of the insomnia measures and a negative cardiac outcome event with a typical combined risk ratio of about 1.92 (95% confidence interval 1.62–2.31).\(^{86}\) While some of these studies used questionnaire reports of snoring or sleep apnea and BMI among other variables to control for other underlying causes of cardiac disease, none had polysomnographic data available.

Because insomnia has been traditionally viewed as a disorder that only impacts sleep and mood, there has been little interest in measuring other outcome variables. However, as understanding grows that insomnia increases the risk of psychiatric disorders and medical problems, it becomes increasingly important to conduct long-term placebo-controlled trials to show if effective treatment of insomnia can reduce the incidence of hypertension, negative cardiac outcome or depression. It may be equally important to develop medications that can normalize the physiological activation seen in patients with insomnia, perhaps even without significant effects on the traditional sleep measures (sleep latency and sleep efficiency), to determine if such treatment can also reduce the incidence of other significant medical problems.

**Treatment of hyperarousal as treatment for insomnia**

Although the concept of physiological arousal as a basis for insomnia dates to early studies of poor sleep,\(^4\) treatment strategies have continued to focus on changes in EEG sleep latency and sleep efficiency. Relatively few studies have documented changes in other physiological measures with therapy and even fewer have attempted therapies that target the entire night and day. It is known that benzodiazepines, for example, directly decrease metabolic rate\(^{57}\) and body temperature\(^{88}\) and therefore might improve sleep by direct effects on the sleep system\(^{89}\) or the arousal system. One study of doxepin 25 mg found a significant increase in melatonin in conjunction with improved EEG sleep parameters after three weeks of administration (but not after a single administration) in insomnia patients.\(^{59}\) A more recent study has shown that the same dose of doxepin reduced cortisol both following initial administration and after three weeks of use in patients.\(^{51}\) Another study has documented a significant decrease in beta activity in a group of patients with insomnia after 8 weeks of cognitive behavioral therapy.\(^{45}\) Finally, lorazepam at a dose of 1.5 mg hs versus 0.5 mg TB was administered to determine if there were benefits from 24-hour versus only nocturnal treatment for insomnia. Both doses of medication improved sleep and produced a significant decrease in whole-body metabolic rate during sleep in
the patients. However, the pattern of effects during the day was relatively inconsistent and primarily related to the timing of medication administration with rebound as the medication blood levels declined. 92 There is little published data on medications such as beta-blockers, that directly affect arousal. These medications clearly reduce cardiovascular problems but have not been shown to provide significant improvement in sleep.

Another treatment strategy is to specifically design treatment to reduce physiological activation. For example, a common method used to increase parasympathetic activity and to decrease sympathetic activation is physical training of sufficient magnitude to increase VO2. One study provided a one-year program providing moderate exercise (improvement of maximum oxygen consumption by 10% or more) versus a stretching intervention (1% increase in maximum oxygen consumption) and found significant effects for improved sleep duration and sleep quality in the exercise group, particularly when the exercise was in the morning. 93

Summary

In the last few years, increasingly sensitive measures of central nervous system function have provided a much clearer view of the neurophysiology of insomnia both in man and in newly developing animal models. These new data strongly support the view that primary insomnia is a true conflict between the sleep system and inappropriate activation of central nervous system. Identification of specific sites of brain activation with lesion study confirmation should allow development of increasingly specific medical treatments to control abnormal activation and, perhaps, decrease the risk of developing secondary medical problems to provide improved function for large numbers of patients.

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References


* The most important references are denoted by an asterisk.

Practice points

Patients with a history of chronic insomnia

1) may be at increased risk and should be evaluated for:
   Depression
   Cardiovascular disease including hypertension.
2) may require chronic treatment with the goal of improving sleep, daytime function, and, perhaps, decreasing the probability of other medical illness.

Research agenda

1) Longitudinal, placebo controlled, treatment studies of patients with chronic insomnia are required to document:
   a) Risks of chronic treatment
   b) Reduction in risk, if any, for the development of depression, hypertension, and other cardiac disease.
2) Agents considered for treatment of chronic insomnia should include medications that limit CNS arousal in addition to traditional hypnotics.
3) Poor sleep can be associated with inappropriate behavior (such as attempting to sleep at the wrong circadian time), any type of environmental or medical discomfort (for example noise or pain), or stress. Insomnia can also be a primary problem. A great majority of research has been done with primary insomnia patients, but the neurophysiology of insomnia based upon the other factors listed above may differ as may secondary symptoms and treatment options. Research needs to examine the extent to which these different types of insomnia are linked by similar physiology and outcome.


Campbell SS, Murphy PJ. Relationship between sleep and body temperature in middle-aged and older subjects. JAGS 1998;46:438–62.

Lushington K, Danson D. Lack of core body temperature is elevated during constant wakefulness in elderly poor sleepers. Sleep 2000;23:504–10.


Lamarche CH, Ogilvie RD. Electrophysiological changes during the sleep onset period of psychophysiological insomniacs, psychiatric insomniacs, and normal sleepers. Sleep 1997;20(7):724–33.


