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Etiology and Pathophysiology of Insomnia

Michael L. Perlis
Michael T. Smith
Wilfred Pigeon

ABSTRACT

Of all the sleep disorders, insomnia is perhaps the only one where there has been a substantial amount of top-down theorization. This may be the case because a framework is required to comprehend a disorder that has multiple causes and an insidious and progressive course. In this chapter, four general models of the etiology and pathophysiology of insomnia are summarized and critically evaluated. In particular, we review how each model characterizes the hyperarousal that is thought to be responsible for disturbing sleep continuity. Additional information is provided on how sleep homeostasis and circadian considerations may mediate, moderate, or interact with the hyperarousal.

Insomnia is often considered a disorder of hyperarousal; that is, the patient has a level of arousal that is incompatible with the initiation or maintenance of sleep. The concept of hyperarousal is, however, likely to be quite complex. What is meant by arousal? How does it become elevated? Is hyperarousal a tonic phenomenon, and if not, what factors mediate or moderate its occurrence or intensity? Is arousal a singular construct, and are hyperarousal and sleep necessarily mutually exclusive?

In this chapter, we review physiologic, cognitive, behavioral, and neurocognitive models of insomnia. Each of these will be summarized as it pertains to primary insomnia and sleep state misperception insomnia (paradoxical insomnia). These models may also be relevant to the extrinsic or secondary insomnias, which, when chronic, have a great deal in common with primary insomnia.[1,2] In addition to reviewing the four models, we also summarize how sleep homeostasis and circadian considerations mediate, moderate, or interact with hyperarousal. Finally, we review a recent hypothesis that suggests that hyperarousal may be better conceptualized as a failure of wakefulness inhibition.

PHYSIOLOGIC MODEL OF INSOMNIA

The physiologic model suggests that chronic insomnia may be understood as a condition in which the patient has a trait level of arousal, or a level of arousal prior to or during the preferred sleep period, that is incompatible with good sleep continuity. This model assumes that physiologic arousal and sleep are mutually exclusive. Studies evaluating physiologic arousal in insomnia have used a variety of techniques, including basic psychophysiologic measures, whole-body metabolic rate, heart rate variability, caffeine-induced insomnia, neuroendocrine measures, and functional neuroimaging. The studies discussed next support the general concept of physiologic hyperarousal but have yet to be integrated into a formal model that explains how insomnia develops and how arousal effects promote sleeplessness (Fig. 60–1).

Psychophysiolgic Measures of Arousal

Early studies comparing elevated physiologic arousal between poor sleepers and good sleepers were based on electrophysiologic measures of heart rate, respiration rate, skin and core body temperature, muscle tone, skin conductance and resistance, and peripheral blood flow or vasoconstriction.[3-8] Overall, these studies showed that poor sleepers exhibit increased physiologic arousal, and in the case of ECG measures of heart rate, this arousal was particularly evident at sleep onset.

Several methodologic difficulties limit the interpretation of these studies. First, subjects in these investigations would not necessarily meet current definitions for primary insomnia, and the inclusion of subjects with other types of insomnia (e.g., sleep phase delay disorder or insomnia secondary to major depression) could have influenced the findings. Second, it is not clear whether these studies carefully excluded short episodes of sleep prior to consolidated sleep onset or short awakenings after sleep onset. The failure to do so could account for some of the sleep onset and nocturnal findings regarding hyperarousal.

Third, most of the early studies did not distinguish between state and trait hyperarousal. This distinction is important in order to determine whether physiologic hyperarousal is a 24-hour phenomenon or whether it occurs only at night, only during the sleep period, or only in association with sleep-related stimuli. Of the early studies that provided data regarding this last issue, the results varied based on the measures and protocols adopted.[6,7] When examining body temperature, Adam and colleagues found persistent effects across the day.

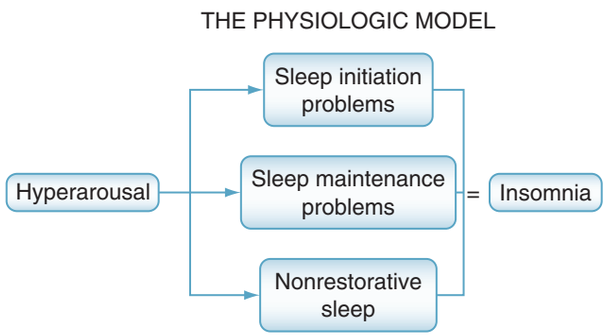

Figure 60–1. The physiologic model.

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When examining heart-rate data, neither Stepanski nor Adam found evidence of hyperarousal outside the sleep period.

In addition to time-of-day effects, it is also possible that hyperarousal may vary in response to situational factors such as stress. Challenge paradigms have also provided mixed results. In one study, there was no evidence that acute stress prior to sleep onset increased physiologic arousal or sleep latency in insomnia subjects.[8] In a second study, patients with insomnia did not exhibit hyperarousal in the morning hours, but they were found to be more physiologically reactive than good sleepers.[7]

Whole Body Metabolic Rate

More recently, Bonnet and Arand undertook two studies to assess arousal using a measure of oxygen consumption ($\dot{V}O_2$), an index of whole-body metabolic rate, in patients with insomnia. In both studies, data were collected during the day and during sleep. In the first study, patients with primary insomnia exhibited significantly higher metabolic rate than good-sleeper controls across the 24-hour day and during the sleep interval.[9] In the second study, patients with sleep state misperception insomnia (paradoxical insomnia) also had higher $\dot{V}O_2$ compared to good-sleeper controls across the 24-hour day.[10] The increased metabolic activity during the night was not significantly correlated with the degree of sleep state misperception.

A major strength of these studies, in addition to sampling across 24-periods, is that the data were not confounded by state interactions (i.e., data from wake intervals included only wakefulness and data from sleep included only sleep). A limitation of these studies is that the $\dot{V}O_2$ measure is strongly influenced by the physical fitness of the individual and by caloric intake, so it is possible that the observed 24-hour effects could have been related to reduced physical fitness of patients with primary insomnia. The negative results of the correlational analyses in the patients with sleep state misperception insomnia are somewhat puzzling and suggest that the subjective-objective discrepancies in these patients are not simply related to physiologic hyperarousal.

Heart Rate Variability

Heart-rate variability is regulated by sympathetic and parasympathetic nervous system activity and therefore provides another measure of arousal in insomnia. In particular, sympathetic activity is reflected in low-frequency heart-rate variability. To date, this measure has been applied in only one published investigation of primary insomnia. In a 36-hour study, heart period was decreased (i.e., heart rate was increased) and heart-rate variability was decreased in all stages of sleep in patients with insomnia compared with good sleepers.[11] Specifically, spectral analysis of the R-R interval revealed significantly increased low-frequency power (reflecting sympathetic activity) and decreased high-frequency power (reflecting parasympathetic activity) in the insomnia patients across all stages of sleep.

Caffeine-Induced Hyperarousal and Insomnia

Increased endogenous sympathetic nervous system activity may be mimicked by the effects of caffeine, making caffeine administration a potentially useful model for hyperarousal in insomnia. In one study,[12] 400 mg caffeine was provided to good-sleeper subjects three times daily for 7 days. Caffeine administration increased whole body metabolic rate, reduced total sleep time and sleep efficiency, and increased sleep latency, wake after sleep onset, and multiple sleep latency test (MSLT) values. Subjects did not complain of daytime fatigue. By the end of the experimental week the metabolic and sleep continuity effects were reduced. Thus, caffeine-induced hyperarousal appears to be an adequate model of acute insomnia but not necessarily of chronic insomnia. In addition, it is not clear whether the magnitude and specific characteristics of caffeine-induced arousal or the behavioral, mood, and neuropsychological consequences are similar to those seen in primary insomnia.

Neuroendocrine Measures of Physiologic Arousal

Activation of the hypothalamic-pituitary-adrenal (HPA) axis may provide further evidence that insomnia involves, or results from, chronic activation of the stress response system. Other neuroendocrine measures, including norepinephrine and melatonin, have also been examined as potential correlates of insomnia.

Urinary Measures

An early study of urinary free 11-hydroxycorticosteriods in young adult good and poor sleepers found that the mean 24-hour rate of 11-hydroxycorticosteroid excretion over three days was significantly higher in the poor sleepers.[13] A subsequent study of urinary cortisol and epinephrine in middle-aged good and poor sleepers found no significant differences, although poor sleepers showed a trend toward higher urinary cortisol and epinephrine.[6] More recently, Vgontzas et al[14,15] collected 24-hour urine specimens for urinary free cortisol, catecholamines (DHPG [dihydroxyphenylglycol] and DOPAC [3,4-dihydroxyphenylacetic acid]), and growth hormone and correlated these measures with polysomnographic (PSG) measures of sleep continuity and sleep architecture in subjects with primary insomnia. Urinary free cortisol levels were positively correlated with total wake time, and DHPG and DOPAC measures were positively correlated with stage 1 sleep percentage and wake after sleep-onset time. Although not statistically significant, norepinephrine levels tended to correlate positively with stage 1 percentage and wake after sleep onset, and they tended to correlate negatively with slow wave sleep percentage. These data suggest that HPA axis and sympathetic nervous system activity is associated with objective sleep disturbance.

Plasma Measures

Plasma measures of adrenocorticotropic hormone (ACTH) and cortisol have also been compared among patients with primary insomnia and matched good sleepers. In one study, patients with insomnia had significantly higher mean levels of ACTH and cortisol over the course of the 24-hour day, with the largest group differences observed in the evening and first half of the night.[14,15] Patients with a high degree of sleep disturbance (sleep efficiency $< 70\%$) secreted higher amounts of cortisol than patients with less sleep disturbance. In contrast

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to these findings, a recent study of patients with primary insomnia and age- and gender-matched good sleepers found no differences in the mean amplitude or area under the curve for cortisol secretion over a 16-hour period (7 PM to 9 AM).[16]

Like the psychophysiologic studies reviewed earlier, some of the neuroendocrine findings in insomnia could be explained by intrusion of wakefulness into the measured sleep period. This is a particular concern for studies using urinary measures, which integrate biologic activity over long periods of time. This possibility is important when considering causes of insomnia: whether increased HPA activity leads to insomnia, or whether insomnia leads to increased HPA activity.

Although findings from various studies are not entirely consistent, the elevations in ACTH and cortisol prior to and during sleep in insomnia patients may help to shed light on the intimate association between insomnia and major depression, which is also associated with activation of the HPA axis. Specifically, insomnia is a risk factor for,[17-25] a prodromal symptom of,[26] and a ubiquitous[27,28] and persistent symptom of major depression.[28] The common link may be that acute stress leads to both an activation of the HPA axis and insomnia, and that chronic insomnia in turn leads to a persistent activation of the HPA axis.

Functional Imaging and CNS Arousal

Functional neuroimaging methods such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) may be used to identify regional brain blood flow or metabolic activity associated with particular tasks or states. Functional imaging techniques have been used to identify regional brain metabolic changes associated with sleep and sleep stages, and these techniques have recently been applied to the study of insomnia. To date, two studies have been undertaken, one using ^{99m}Tc-HMPAO SPECT and one using fluoro-deoxyglucose PET.

In the SPECT study, imaging was conducted around the sleep-onset interval of patients with primary insomnia and of good-sleeper controls. Contrary to expectation, patients with insomnia exhibited a consistent pattern of hypoperfusion across eight preselected regions of interest, with the most prominent effect observed in the basal ganglia.[29] The medial frontal, occipital, and parietal cortices also showed significant decreases in blood flow compared to those of good sleepers.

In the PET study, imaging data were acquired from patients with chronic insomnia and from control subjects for an interval during wakefulness and during consolidated non–rapid eye movement (NREM) sleep. Patients with insomnia exhibited increased global cerebral glucose metabolism during wakefulness and NREM sleep.[30] In addition, patients with insomnia exhibited smaller declines in relative glucose metabolism from wakefulness to sleep in wake-promoting regions including ascending reticular activating system, hypothalamus, and thalamus. A smaller decrease was also observed in areas associated with cognition and emotion, including the amygdala, hippocampus, and insular cortex as well as in the anterior cingulate and medial prefrontal cortices.

Although results from these studies appear to be inconsistent, numerous methodologic differences may help to explain differences in the findings. For instance, the SPECT study, with its short time resolution, may have captured a more transient phenomenon that occurs when subjects with chronic and severe insomnia first achieve persistent sleep. The PET study, with its longer time resolution, may have captured a more stable phenomenon that occurs throughout NREM sleep in subjects with moderate insomnia. In addition to the temporal resolution issues, the PET study used a sample of insomnia patients who did not show objective sleep-continuity disturbances in the laboratory, whereas the SPECT study included patients with objective sleep continuity disturbances. Thus, the samples may have differed with respect to the type of insomnia, the degree of partial sleep deprivation, and the degree of sleep-state misperception. Although further studies are needed, these preliminary investigations clearly demonstrate the feasibility of using functional neuroimaging methods in the study of insomnia, and they suggest that insomnia complaints may indeed have a basis in altered brain activity.

COGNITIVE MODELS OF INSOMNIA

Like the physiologic model of insomnia, the cognitive model suggests that insomnia occurs in association with arousal and that arousal and sleep are mutually exclusive. Unlike the physiologic perspective, the central tenet of these models is that cognitive arousal in the form of rumination and worry predisposes the individual to insomnia, precipitates acute episodes, and perpetuates the chronic form of the disorder. The "three-factor" framework (predisposing, precipitating, and perpetuating factors), although not an explicit part of any of the cognitive models, is applied here for its heuristic value (Fig. 60–2).

Worry and Rumination

Predisposing Factor

The tendency to ruminate and worry serves as a predisposing factor for insomnia in at least one of two ways. First, individuals given to rumination or worry are more likely to be reactive to life stressors. Second, individuals with high trait levels of cognitive arousal may require less activation to reach the level of arousal that is incompatible with sleep. Put differently, individuals prone to worry and rumination are more likely to react to life events, and less of a reaction is required to trigger a level of arousal that is incompatible with sleep.

Support for this position is found in patients with chronic insomnia who exhibit higher scores on instruments measuring personality factors related to trait worry.[31-33] These data are consistent with the possibility that worry and rumination are predisposing factors for insomnia. Only longitudinal studies, however, will be able to determine whether stable premorbid traits for worry and rumination actually predispose the individual to insomnia, or whether these features appear as a state-related characteristic during bouts of insomnia.

Precipitating Factor

Worry and rumination may also act as precipitating factors for insomnia. In this instance, life stress (acting alone or in combination with premorbid personality factors) triggers both physiologic and cognitive activation. The former presumably serves as the biologic basis for the "fight or flight" response that inhibits sleep. The latter is also thought to result in sleep-continuity disturbance but via a more subtle process.

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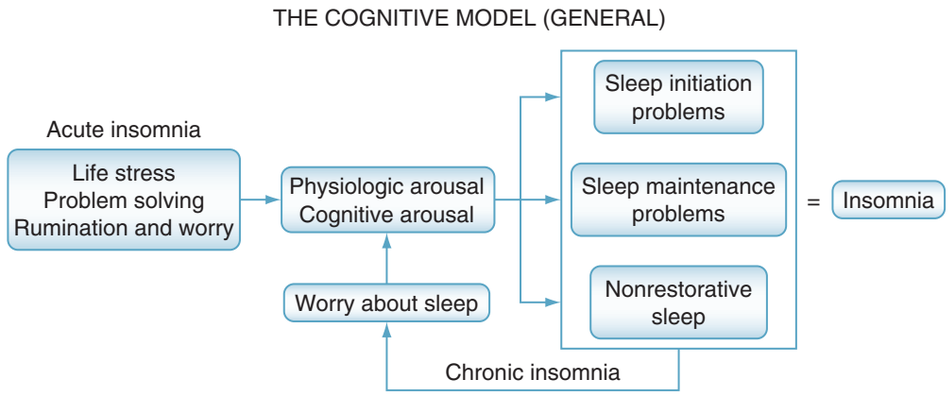

Figure 60–2. The cognitive model (general). Whether physiologic arousal and cognitive arousal independently contribute, or interact, to produce sleep continuity disturbance is often not well delineated within the cognitive perspective. This schematic allows for both types of arousal but does not distinguish between the two constructs.

Life stress presumably initiates an increase in problem solving. During the day, such a response is adaptive. During the night, such a response may be adaptive but has the consequence of sleeplessness. The effects of sleepiness, sleep loss, and sleep inertia on cognitive function may in turn increase the probability that effective problem solving will give way at night to rumination and worry, setting the stage for persistent cognitive activation and chronic insomnia.[1]

Empirical data support the role of life stress as a precipitating factor for insomnia. Patients with chronic insomnia report that life stress events often precede and precipitate their insomnia,[34,35] and epidemiologic studies show that job stress is related to sleep disturbance.[36] Insomnia patients also attribute their insomnia to cognitive activation more often than somatic arousal.[37-39] Finally, good sleepers in experimental stress paradigms show increased worry and sleep disruption.[7,40,41] Such data prospectively support the links among stress, cognitive activation, and sleep disturbance.

Perpetuating Factors

Worry and rumination may serve as perpetuating factors for insomnia. When insomnia becomes chronic, worry and rumination may acquire a different focus; that is, a person worries about the inability to sleep and the consequences of sleep loss. This shift in content may be one of the most important etiologic factors for chronic insomnia, setting up a self-perpetuating cycle wherein insomnia fuels worry and worry fuels the insomnia.[42] Although there are no longitudinal studies to demonstrate that patients actually shift the content of their worry in the transition from acute to chronic insomnia, empirical data do support the hypothesis that worry in chronic insomnia is often "worry about sleep." For instance, studies that sample thought content around sleep onset in chronic insomnia patients[38,43] and studies that differentiate between good and poor sleepers' presleep cognitions[44] show that the worry content of insomnia patients is indeed focused on sleep-related issues including worry about not falling or staying asleep and concerns about the next day's performance or the catastrophic consequences of extended sleep loss.

Individual attitudes and beliefs about sleep may also moderate the propensity for worry.[45,46] For example, if the individual believes that 8 hours of sleep are necessary for optimal daytime function, then when faced with the prospect of getting less than 8 hours of sleep, the individual is more prone to worry. In fact, patients with insomnia endorse more dysfunctional attitudes about sleep, and they believe them more strongly than subjects without insomnia.[46] Treatment outcomes for these patients are related to reductions in negative attitudes and beliefs about sleep.[45,47]

Reconceptualization of the Cognitive Model

Harvey has proposed that the self-perpetuating nature of insomnia may not be related solely to the persistent occurrence, and the shift in the content focus, of rumination and worry. Instead, she has hypothesized that worry about sleep may engage cognitive processes and behavior that mediate the occurrence and severity of chronic insomnia.[48] According to this model, acute insomnia occurs in association with life stress, subchronic insomnia occurs with worry about sleep, and chronic insomnia is maintained by selective attention and monitoring, distorted perceptions of daytime deficits, and counterproductive safety behaviors (Fig. 60–3).

Selective Attention

Some patients selectively monitor the environment for sleep-related threats, including both the internal environment (e.g., monitoring mental alertness or body sensations) and the external environment (e.g., monitoring the bedroom clock or the environment for noise). This selective attention is not conscious but automatic, and it increases the chance of perceiving random environmental events as sleep threats. Increased detection of relevant and random cues, in turn, increases both cognitive and physiologic arousal and reinforces monitoring behavior. Thus, a self-perpetuating cycle is established.

Distorted Perception of Daytime Deficits

Some people with insomnia exhibit increased attention or sensitivity to the consequences of poor sleep. They may worry that they have not obtained sufficient sleep, which causes them to selectively attend to daytime problems such as fatigue, sleepiness, and performance deficits. As with monitoring for sleep-related threats, monitoring for daytime deficits also increases the chance of detecting both occasional relevant cues and random cues. Unlike the monitoring that occurs at night, the detection of fatigue, sleepiness, and performance deficits prompts the patient to engage in safety behaviors. Examples of safety behavior include avoiding work and social

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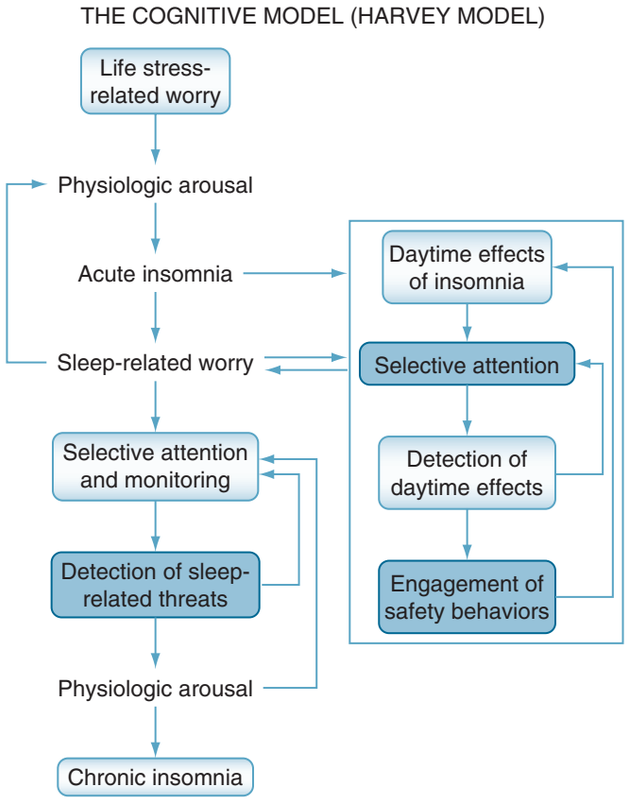

Figure 60–3. The cognitive model (Harvey model). The regions shaded in light blue represent the unique contribution of the Harvey model to the cognitive perspective.

tasks perceived to be too physically or mentally taxing. Such avoidance is thought to reinforce worry and cognitive arousal.

Consistent with this reconceptualization of the cognitive model of insomnia, patients with insomnia do indeed appear to excessively monitor their sleep environment, selectively attend to sleep-related stimuli,[49,50] and engage in daytime safety behaviors.[51] Whether the cognitive and behavioral factors delineated by this perspective represent the primary perpetuating factors for insomnia remains to be demonstrated.

BEHAVIORAL MODELS OF INSOMNIA

In general, the behavioral perspective suggests that although a variety of biopsychosocial factors may precipitate acute insomnia, chronic insomnia results from behaviors that disrupts sleep. A number of specific behavioral models have been proposed, most of which are closely tied to specific treatment techniques.

Sleep Hygiene Model

Sleep hygiene refers to the notion that specific kinds of behavior are conducive to or incompatible with sleep and that modifying behavior may alleviate insomnia. The earliest systematic reference to sleep hygiene can be found in Kleitman's *Sleep and Wakefulness*,[52] which includes a chapter entitled, "The Hygiene of Sleep and Wakefulness." Kleitman reviews evidence regarding factors such as sleep duration, bedtime rituals, sleep surface, ambient temperature, sleep satiety, and body position. The chapter is discursive and in no way resembles the list of do's and don'ts of good sleep that exist today as sleep hygiene instructions. As for the validity of this perspective, poor sleep hygiene apparently is neither necessary nor sufficient for the occurrence of insomnia. Patients with primary insomnia do not necessarily engage in more poor sleep hygiene practices than good sleepers,[53] and monotherapy with sleep hygiene instructions does not reliably produce significant benefit.[54,55]

Stimulus Control Model

Stimulus control, as originally described by Bootzin and colleagues,[56] is based on the behavioral principle that one stimulus may elicit a variety of responses, depending on the conditioning history. A simple conditioning history, wherein a stimulus is always paired with a single kind of behavior, yields a high probability that the stimulus will yield only one response. A complex conditioning history, wherein a stimulus is paired with a variety of reactions, yields a low probability that the stimulus will yield only one response.

In persons with insomnia, the normal cues associated with sleep (e.g., bed, bedroom, bedtime) are often paired with activities other than sleep. For instance, in an effort to cope with insomnia, the patient may spend a large amount of time in the bed and bedroom doing something other than sleeping. Insomnia-related coping strategies appear to the patient to be both reasonable (staying in bed at least permits the patients to get "rest") and reasonably successful (engaging in alternative activities in the bedroom sometimes appears to end the insomnia). These practices, however, set the stage for stimulus dyscontrol, the lowered probability that sleep-related stimuli will elicit the desired response of sleepiness and sleep.

Stimulus control therapy for insomnia is one of the most widely used behavioral treatments, and its efficacy has been demonstrated consistently.[57-59] The therapy, however, includes active components that are not based solely on learning or behavioral theory. For instance, the treatment specifies that the patient should spend awake time somewhere other than the bed, and that the sleep schedule should be fixed. These two interventions also influence the homeostatic and circadian regulation of sleep. Thus, the efficacy of stimulus control therapy does not necessarily provide strong evidence for the stimulus control model. In fact, one investigation found that the reverse of stimulus control instructions also improved sleep continuity.[60]

The Spielman Model

Spielman's model,[61] alternatively referred to as the three-factor model or the three-P model, is a stress-diathesis model that has an additional behavioral component to account for how acute insomnia becomes chronic. A schematic representation of this model is presented in Figure 60–4.

In brief, this model posits that insomnia occurs acutely in relation to both traits (predisposing factors) and life stresses (precipitating factors) and that the chronic form of the disorder is maintained by maladaptive coping strategies (perpetuating factors). Thus, a person may be prone to insomnia due to trait characteristics, may experience acute episodes because

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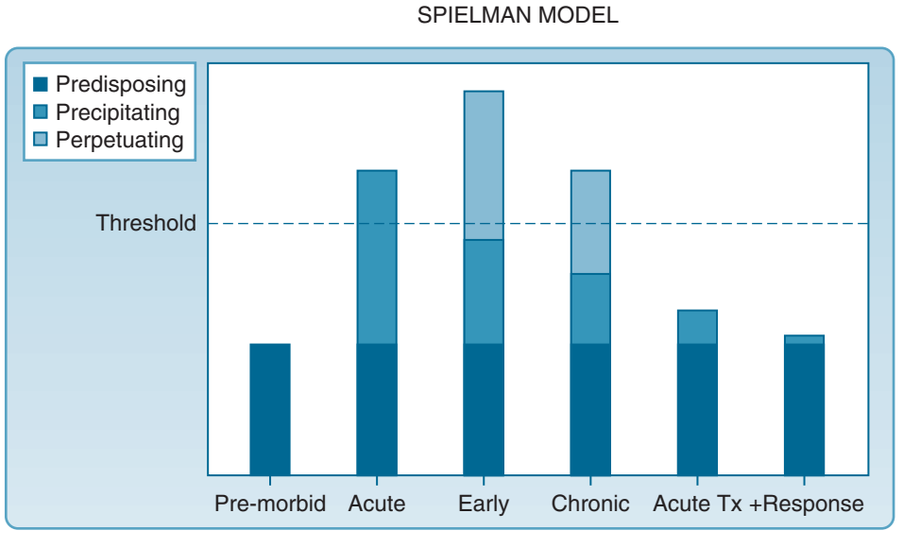

Figure 60–4. The traditional Spielman model does not extend to what occurs with treatment. The model is usually represented as ending with the chronic phase. The "Acute Tx" and "+ Response" intervals are included here so that the reader may appreciate the differences between the three-factor and four-factor models. +, positive; Tx, theories.

of precipitating factors, and may suffer from a chronic form of the disorder because of behavioral factors.

Predisposing factors extend across the entire biopsychosocial spectrum. Biologic factors include trait hyperarousal (e.g., elevated metabolic rate, stably elevated levels of cortisol) and hyperreactivity (elevated startle response or diminished capacity to recover following startle, or both). Psychological factors include worry or the tendency to ruminate excessively. Social factors, although rarely a focus at the theoretical level, include a sleep schedule incompatible with the bed partner's or social pressures to sleep according to a nonpreferred sleep schedule (e.g., child rearing).

Precipitating factors, as the name implies, are acute occurrences that interrupt sleep. The primary "triggers" are thought to be related to medical and psychiatric illness and stressful life events.

Perpetuating factors refer to the strategies that the patient adopts to compensate for sleep loss. Research and treatment have focused on two kinds of perpetuating factors: the practice of staying in bed while awake and the tendency to extend sleep opportunity. The stimulus control perspective speaks mainly to the former. The Spielman model focuses primarily on the latter. Extending sleep opportunity refers to the tendency of patients to compensate for sleep loss by going to bed earlier or by getting up later, or both. Such strategies are intended to "recover what has been lost." These strategies, however, lead to mismatch between *sleep opportunity* and *sleep ability*. The greater the mismatch, the greater the chance the person will spend more time awake during the given sleep period.

Perhaps the most compelling evidence for the validity of behavioral models is the success of treatments based on its principles. Multicomponent therapies composed of sleep restriction and stimulus control therapy reliably produce significant pre-post change[57-59] and effects that are comparable to[62] and more durable than pharmacotherapy.[63] The central tenets of the stimulus control model and the Spielman model, however, have never been evaluated empirically. Such an evaluation would require an experimental or a prospective study. Obviously, a human experimental model to produce chronic insomnia is not viable. A prospective study, while possible, has yet to be undertaken. Such a study would require that subjects at risk for acute insomnia be identified and then studied longitudinally in a way that allows for an assessment of which, if any, of the behavioral factors predict the occurrence of chronic insomnia.

Finally, neither the stimulus control model nor the Spielman model addresses the concept of conditioned arousal. Both models focus on the instrumental side of the behavioral equation—in other words, how behavior fuels insomnia. Neither model addresses the possibility that being awake in bed (for long periods of time and on frequent occasions) may directly elicit arousal responses via classical conditioning. Such conditioned arousal may contribute independently to the self-perpetuating nature of insomnia, even when the original maladaptive strategies are no longer operational.

Taking into account conditioned arousal as a possible perpetuating factor can help to explain two reliable findings from the treatment outcome literature. First, cognitive behavior therapy (CBT) for insomnia produces about a 50% reduction in symptoms during the acute treatment phase.[57-59] If only the traditional behavioral factors are responsible for chronic insomnia, a more complete response to treatment might be expected. Second, patients treated with CBT continue to improve over follow-up periods as long as 24 months.[63,64] If only behavioral factors are responsible for chronic insomnia, no additional improvements would be expected beyond the acute treatment phase.

While any number of unaccounted-for factors may be responsible for these clinical phenomena, allowing for the additional behavioral factor of conditioned arousal may help explain why treatment response during therapy is incomplete and why treatment gains appear to occur with time. In the case of the former, acute treatment with CBT may only reduce insomnia severity to the extent that it eliminates the behavioral tendency to extend sleep opportunity, leaving the part of the insomnia ascribable to conditioned arousal in play. In the case of the latter, successful treatment with CBT in the short term may result in counterconditioning in the long term because repeated pairing of sleep-related cues with sleep over

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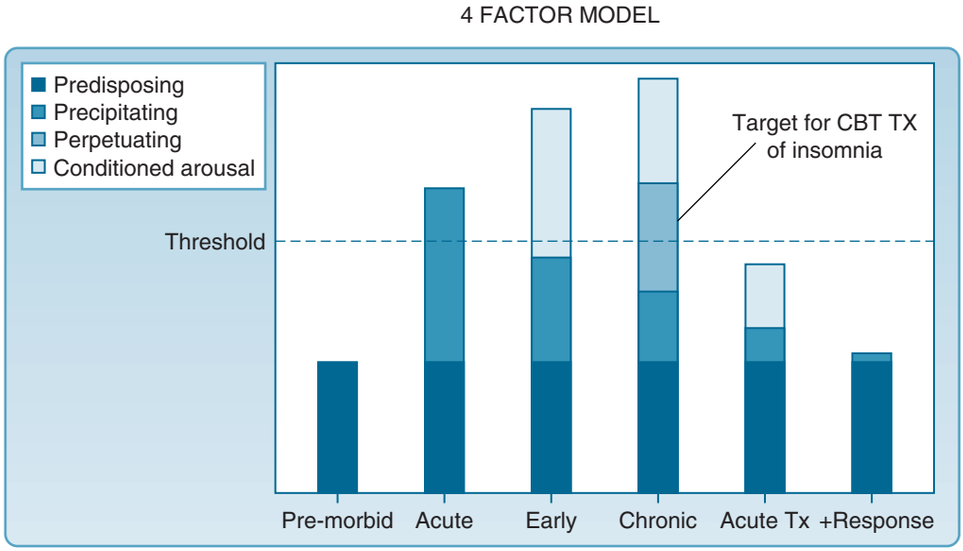

Figure 60–5. The four-factor model. +, positive; Tx, theories.

time extinguishes the conditioned arousal. A version of the Spielman model that includes a conditioned arousal component is shown in Figure 60–5.

NEUROCOGNITIVE MODEL OF INSOMNIA

Central to the neurocognitive model is the view that *acute insomnia* occurs in association with cognitive and behavioral factors and *chronic insomnia* is a reversible central nervous system disorder that occurs in part in relation to behavioral factors and in part as a result of classical conditioning. Accordingly, the neurocognitive perspective[65,66] represents a position counter to the pure cognitive perspective and is an extension of the behavioral model (Fig. 60–6).

As a position contrary to the pure cognitive perspective, the neurocognitive model suggests that rumination and worry may extend wakefulness, but they are not responsible for the inability to initiate or maintain sleep. That is, individuals with chronic insomnia are not awake because they are worrying, but rather they are worrying because they are awake. As an extension of the behavioral model, the neurocognitive perspective acknowledges the role of behavioral factors and attempts both to define arousal and to specify precisely how arousal may interfere with sleep initiation, sleep maintenance, or the perception of sleep.

The neurocognitive model considers arousal along three intersecting dimensions (somatic, cognitive, and cortical) and focuses on the measurement and the consequences of conditioned cortical arousal. Cortical arousal, it is argued, occurs as a result of classical conditioning and may be observed in patients with primary insomnia as high-frequency EEG activity (14 Hz to 45 Hz) at or around sleep onset and during NREM sleep.[65,66] Cortical arousal, it is hypothesized, allows for abnormal levels of sensory and information processing and for the increased formation of long-term memory. These phenomena, in turn, are directly linked to sleep continuity disturbance and sleep state misperception.

Specifically, enhanced sensory processing around sleep onset and during NREM sleep is thought to make the patient particularly vulnerable to perturbation by environmental stimuli, which interferes with sleep. *Enhanced information processing* during NREM sleep may blur the phenomenological distinction between sleep and wakefulness. That is, one cue for "knowing" that one is asleep is the lack of awareness of events occurring during sleep. Enhanced information processing may therefore account for the tendency in insomnia to judge polysomnographically defined (PSG) sleep as wakefulness.[67-73] Finally, *enhanced long-term memory* around sleep onset and during NREM sleep may interfere with the subjective experience of sleep initiation and duration. Normally, subjects cannot recall information from periods immediately prior to sleep,[74-77] during sleep,[78-80] or during brief arousals from sleep.[81,82] An enhanced ability to encode and retrieve information in insomnia would be expected to influence judgments about sleep latency, wakefulness after sleep onset, and sleep duration.

Several components of the neurocognitive model have been empirically evaluated. First, patients with primary insomnia exhibit more NREM high-frequency EEG activity than either good sleepers[83-89] or patients with insomnia secondary to major depression.[88] Second, patients with sleep state misperception disorder exhibit more beta EEG activity than good sleepers or patients with primary insomnia.[89] Third, correlational analyses provide evidence that beta activity is negatively associated with the perception of sleep quality[90,91] and is positively associated with the degree of subjective-objective discrepancy.[88] Taken together, these three lines of evidence suggest that CNS arousal may occur uniquely in association with primary insomnia (versus secondary insomnia) and suggests that this form of arousal is associated with the tendency toward misperception of sleep state.

In addition to these findings, there is also evidence that increased high-frequency activity appears to be limited to the beta and gamma portions of the EEG spectrum and that patients with chronic insomnia, as compared with good sleepers, have heightened recognition recall in the morning for words presented at sleep onset and from awakenings during the night.[92] The former suggests that the primary source potential for the signal is electroencephalographic, not

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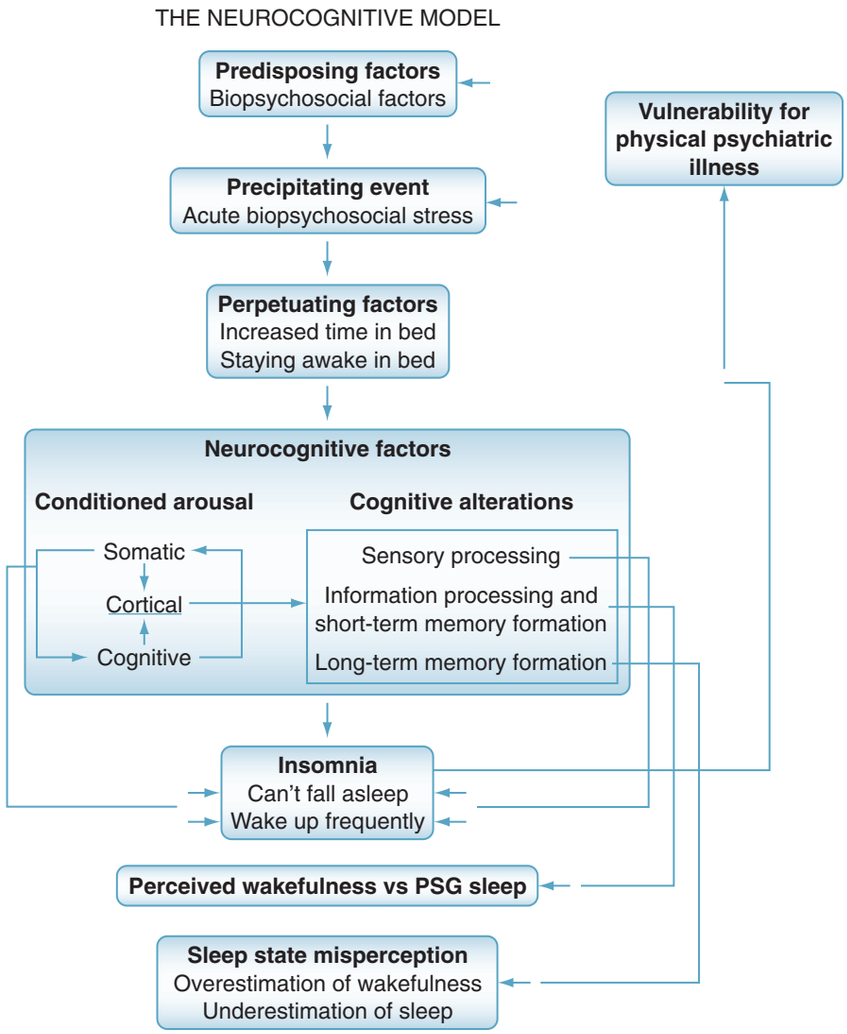

Figure 60–6. This version of the neurocognitive model is slightly different from the schematic representations previously published. The primary differences are that this model explicitly incorporates the three-factor model; long-term memory formation is explicitly linked to the phenomenon of sleep-state misperception; and sleep-state misperception itself is allowed to be related to either the overestimation of wakefulness or the underestimation of sleep, or both.

electromyographic, and that therefore cortical and somatic arousal may be distinct phenomena. The latter provides support for the hypothesis that there is an attenuation in the normal mesograde amnesia that accompanies sleep in patients with primary insomnia.

The major strength of the neurocognitive model is that it provides for an integrated perspective on primary insomnia, allowing for behavior, neuropsychological function, and neurobiologic considerations to be taken into account as contributing to the etiology and pathogenesis of insomnia. The primary limitations of the model are that it does not account for the importance of homeostatic and circadian influences on sleep or for the likely possibility that cortical arousal may constitute a permissive factor for worry, rumination, and monitoring behavior.

FACTORS THAT MAY MEDIATE, MODERATE, OR INTERACT WITH HYPERAROUSAL

All of the models so far discussed provide good frameworks for understanding the nature of the hyperarousal that produces poor sleep continuity. None of the models, however, address factors that may mediate, moderate, or interact with hyperarousal. Such factors may explain heterogeneity among insomnia patients. For instance, some factors must account for how hyperarousal results in initial insomnia in some individuals, middle insomnia in others, and late insomnia in still others. Moreover, some factors must account for how these forms of insomnia occur variably within the individual. The two most likely factors are related to sleep homeostasis and the circadian control of sleep and wakefulness.

Sleep Homeostasis and Physiologic Arousal

Although a number of investigators have suggested that impaired sleep homeostasis may be an important etiologic factor in insomnia,[29,93-95] few empirical studies have addressed this factor. Only one investigation supports the possibility that patients with primary insomnia exhibit reduced slow-wave sleep,[96] although decreased delta activity has been observed in insomnia secondary to major depression[27,97-99] and chronic pain.[100]

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Impaired sleep homeostasis in patients with insomnia would also be supported by evidence of reduced levels of sleepiness following sleep deprivation in comparison with healthy subjects. Stepanski and colleagues[101] demonstrated that patients with primary insomnia and good sleepers had similar responses to sleep deprivation on the MSLT, suggesting that the sleep homeostat may be functioning normally, at least with respect to generating daytime sleepiness.

Finally, impaired sleep homeostasis in insomnia would be supported by smaller increases in total sleep time or in amount of slow wave sleep following sleep deprivation in comparison with healthy subjects. Two experimental studies have shown that compared to healthy control subjects, insomnia patients had similar increases in total sleep time during recovery from sleep deprivation, but they had smaller increases in slow wave sleep percentage or delta power.[95,101] These results, as well as the efficacy of sleep restriction treatments for insomnia, suggest that homeostatic dysregulation may be an important feature of primary insomnia.

Circadian Dysrhythmia and Physiologic Arousal

Sleep initiation and maintenance problems may result from circadian rhythm abnormalities, as is the case in circadian rhythm sleep disorders. It is less clear whether circadian rhythm factors may also contribute to the occurrence or severity of primary insomnia. Normal developmental phase shifts and acute phase shifts occurring as a part of jet lag or shift work may act as precipitating factors for acute episodes of insomnia and set the stage for the development of a chronic form of the disorder, as suggested in the Spielman model.

The more substantive question is whether chronobiologic factors contribute to chronic insomnia. Lack and colleagues[102,103] found that primary insomnia patients exhibit phase shifts that are consistent with their presenting complaint: Patients with sleep-onset insomnia exhibit a phase delay of the core body temperature rhythm,[102] and patients with early-morning awakening exhibit a phase advance of the core body temperature rhythm.[104,105] In addition to, and consistent with, these data are the studies that suggest that elderly patients with insomnia exhibit attenuated melatonin levels.[106] Taken together, these observations suggest that, at least for some patients with chronic insomnia, hyperarousal may not be a constant phenomenon but may have a specific temporal patterning that reflects the influence of circadian factors.

While it seems likely that circadian factors play a role in the etiology and pathogenesis of primary insomnia, it is perplexing that phase shifts have not been observed in the numerous studies of physiologic arousal using such measures as core body temperature and cortisol. One possible explanation is that most studies include samples of patients with either sleep-onset insomnia, sleep-maintenance insomnia, or mixed symptoms, rather than with one symptom profile alone. Combining subjects with different insomnia phases would obscure circadian phase shifts among individuals. That is, if patients with initial insomnia are phase delayed and patients with late insomnia are phase advanced, averaging across the two samples could yield a 24-hour oscillation that appears relatively normal. Failure to control for the masking influences of posture, activity, and light could also obscure circadian abnormalities in studies of insomnia. Protocols such as the 90-minute-day and constant routine could help to address potential circadian abnormalities in primary insomnia.

Finally, behavioral factors are likely to interact with normal circadian functioning to produce circadian abnormalities that in turn perpetuate and exacerbate primary insomnia. Individuals with acute insomnia caused by factors other than circadian ones may alter the way they are exposed to light, and this may have phase-shifting effects. For example, when people compensate for sleep loss by "sleeping in" or napping, they reduce their exposure to light during the diurnal phase. One or both of these compensatory strategies may cause a phase delay that reinforces the initial and middle insomnia problems. In this way, individuals with chronic insomnia could have observable circadian dysfunction without an inherent defect in the circadian system.

INHIBITION OF WAKEFULNESS VERSUS HYPERAROUSAL

The majority of insomnia models conceptualize insomnia as a disorder of hyperarousal. Espie,[107,108] however, has proposed an important alternative point of view, suggesting that insomnia occurs, at least initially, in association with the failure to inhibit wakefulness. This psychobiologic inhibition model suggests that in the early stages of chronic insomnia, problems with sleep initiation or sleep maintenance may occur because of dysfunction in the neurobiologic mechanisms that normally inhibit wakefulness and permit sleep to occur.

The failure to inhibit wakefulness is thought to result from two cognitive phenomena. First, when people are unable to sleep, their attention is drawn to an otherwise automatic process. The very process of attending, in turn, prevents perceptual and behavioral disengagement and sleep initiation. Second, when people are unable to sleep, effort is expended "trying" to fall asleep, and this effort, like enhanced attention, serves only to extend wakefulness. This increased attention and intention result in sustained wakefulness, which undermines what is normally an automatic process and sets the stage for additional cognitive and behavioral changes as discussed earlier.

Additional findings from other areas of research suggest the utility of the psychobiologic inhibition model. Merica and colleagues propose that cortical arousal may occur in insomnia patients as a failure to downregulate normal levels of cerebral activity before and during NREM sleep. Cortical arousal may indicate that the "wake off" system is not functioning properly,[66,109] the result being an intermediate state in which the dominant mode is consistent with sleep, but with neuronal groups related to the wake state still active.

Saper and colleagues[110] have proposed a similar idea that may be more closely related to the occurrence of PSG wakefulness. These investigators propose that homeostatic and circadian regulatory systems are regulated by a "flip flop circuit" in the ventrolateral preoptic area of the hypothalamus. The wake-promoting and sleep-promoting halves of the circuit each strongly inhibit the other, creating a bi-stable feedback loop that reinforces wakefulness and sleep and prevents intermediate states. The failure to inhibit wakefulness in insomnia could be related to a defect in the "sleep switch," favoring the occurrence of wakefulness relative to sleep both at the beginning and during the middle of the sleep period.

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Distinguishing between hyperarousal and the failure to inhibit wakefulness may allow for better definitions of insomnia, greater precision in the search for the neurobiologic basis of insomnia, and better understanding of treatment mechanisms. The distinction between these two constructs, however, requires further clarification.

CONCLUSION

While each model of insomnia provides us with a deeper appreciation for the fact that insomnia is a complex and multiply determined disorder, it is unlikely that any one of these models is entirely correct or that all are equally correct. In the final analysis, if there ever is a unified theory of insomnia, it will likely be the case that physiologic, cognitive, and cortical arousal each play a role in the etiology of insomnia and that these factors are mediated or moderated by homeostatic and circadian considerations.

Clinical Pearls

The factors responsible for acute and chronic insomnia are different, and acute insomnia does not necessarily result in the chronic form of the disorder. This suggests that early detection and treatment may have substantial prophylactic value.

Hyperarousal is not likely to be a single factor, but rather a construct comprised of several factors including the somatic, cognitive, and cortical domains. In addition, homeostatic and circadian influences probably moderate and/or mediate the extent to which somatic, cognitive and cortical arousal produce insomnia symptoms. Taking into account these concepts may help the clinic tailor treatment to the individual.

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