New Insights Into the Sleep-Wake System: 
The Neurobiology and Pathophysiology of Insomnia

LEARNING OBJECTIVE
Describe the neurobiology of the sleep-wake system, including the role of neurotransmitters and the nature of the hyperarousal state.

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INTRODUCTION TO THIS TWO-SUPPLEMENT SERIES
This supplement provides the first of two articles that will explore new insights into the sleep-wake system, encompassing revisions in the nosology and nomenclature of insomnia, advances in the understanding that insomnia may be a result of hyperarousal, and how sleep and wake are regulated by classical neurotransmitters and the neuropeptides orexin-A and –B (also known as hypocretin-1 and –2). This supplement will also highlight how insomnia impacts patients with this disorder (“Voice of the Patient” examples) and how to explain to patients the latest understanding of how insomnia occurs. The second supplement, to be published in October 2014, will focus on current treatments for insomnia (encompassing avoidance of stimulating activities and caffeine, cognitive behavioral therapy, and over-the-counter and prescription medications); agents that are on the horizon; and methods to discuss treatment options with patients.

STATEMENT OF NEED
Insomnia can affect many aspects of an individual’s life—impairing concentration and memory, increasing the risk of incident depression or recurrence of a depressive episode, diminishing the patient’s ability to enjoy family and social relationships, and increasing the risk for falls, and motor vehicle accidents.

Clinical research provides evidence that insomnia is a disorder of hyperarousal demonstrated by a number of physiologic measures, such as increased heart rate.1 It is hypothesized that hyperarousal may occur in association with a shift in the balance between systems that promote sleep and those that promote wakefulness.

This neuroscienceCME Clinical Navigator is the first of a two-part series, and will describe the neurobiology of the sleep-wake system so that clinicians understand more about the role of neurotransmitters, including orexin, and the nature of how the hyperarousal state may lead to insomnia.

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NOSOLOGY AND NOMENCLATURE OF INSOMNIA
In 2013, consistent with an advanced understanding of sleep-wake disorders, epidemiology, genetics, and pathophysiology research that occurred since the publication of The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition® (Copyright ©2000; American Psychiatric Association, 2000), the American Psychiatric Association updated the nosology and diagnostic criteria related to insomnia in The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition® (Copyright ©2013; American Psychiatric Association, 2013). The terms primary insomnia and secondary insomnia were replaced with the general term, Insomnia Disorders. Although the terminology changed, it is understood that insomnia typically occurs in conjunction with a mental disorder, medical condition, or sleep disorder (Ancoli-Israel & Roth, 1999).

EPIDEMIOLOGY OF AND COMORBIDITIES ASSOCIATED WITH INSOMNIA
Insomnia is the most common sleep disorder. Studies have yielded a fairly consistent prevalence rate for insomnia, ranging from 9% – 18% in the general population (American Psychiatric Association, 2013; Ford & Kamerow, 1989; Ishigooka et al., 1999; M. M. Ohayon, Caulet, & Lemoine, 1998; M. M. Ohayon & Roth, 2001; Simon & VonKorff, 1997). Sleep-wake disorders as a whole occur far more frequently in patients with psychiatric disorders compared with the general population, as demonstrated by a prevalence rate of approximately 40% (Ford & Kamerow, 1989). Data from participants across the United States in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial demonstrated that 84.7% of those diagnosed with nonpsychotic major depressive disorder (MDD) show clinical features of insomnia (Sunderajan et al., 2010). Insomnia occurs in approximately 24% of patients with anxiety disorders and may also be comorbid, but at lower rate, with dysthymia and alcohol and drug abuse (Ford & Kamerow, 1989). For psychiatrists and other health care professionals caring for patients with psychiatric disorders, it is important to recognize that insomnia occurs frequently in patients with psychiatric disorders.

Insomnia can affect many aspects of an individual’s life. It can impair concentration and memory, increase the risk of incident depression or recurrence of a depressive episode, diminish the patient’s ability to enjoy family and social relationships, and increase the risk for falls and motor vehicle accidents (American Psychiatric Association, 2013; Ford & Kamerow, 1989; Ishigooka et al., 1999; M. M. Ohayon, et al., 1998; M. M. Ohayon & Roth, 2001;
Simon & VonKorff, 1997). Medical conditions, such as sleep apnea, chronic pain, chronic obstructive pulmonary disease, hypertension, diabetes, and arthritis, may exacerbate or be comorbid with insomnia, and insomnia may also worsen these conditions (e.g., prolonged apneas or electrocardiographic arrhythmias during rapid eye movement [REM] sleep or confusional arousals in patients with dementia) (American Psychiatric Association, 2013). It is imperative for clinicians treating sleep-wake complaints to investigate the presence of comorbid conditions. As previously mentioned, insomnia most often occurs in patients with psychiatric disorders. Specifically, insomnia is more likely to emerge prior to the onset of MDD and is associated with a higher rate of lifetime MDD. Its presence and persistence predict future MDD episodes and relapse and also predict a poorer outcome in patients with MDD (i.e., persistence, chronicity, and suicidality) (Chellappa & Araújo, 2007; Ford & Kamerow, 1989; Franzen & Buysse, 2008; Goodwin & Marusic, 2008; Wojnar et al., 2009). In a similar vein, reduced sleep often predated the onset of mania in bipolar disorder (Plante & Winkelman, 2008) and persists following the stabilization or resolution of MDD. Overall, poor sleep is a factor in mood impairment. Drake et al. investigated sleep reactivity (an over-reaction to stimuli related to sleep) among subjects at baseline, insomnia in those same subjects at year one, and the development of depression in year two (C Drake, Mullins, Roth, Alexander, & Mengel, 2013). Subjects who developed insomnia were 38% more likely to subsequently develop depression, as compared with those who did not develop insomnia. These findings highlight the importance of recognizing and treating insomnia to prevent or mitigate MDD and its relapse.

**VOICE OF THE PATIENT**

Patients with insomnia often depict the experience of insomnia as their brain racing and not shutting down. For example, one individual seeking support on a blog wrote, “Even when exhausted, my mind keeps going.” This person also wrote, “My mind will still not shut off. I can’t control it. After a night of this brain activity I wake up feeling wired and tense as if I was given adrenaline even though I did not sleep” ([lanaar2], 2010). This can be very distressing to patients and lead to medical and psychological issues.

Clinicians need to explain to patients that insomnia is generally not a disorder of the sleep system but, rather, a disorder of hyperarousal. This hyperarousal is demonstrated by a number of physiologic measures, such as increased heart rate, increased metabolic rate, and increased core body temperature and diminished capacity to sleep day or night (Stepanski, Glinn, Zarick, Roehrs, & Roth, 1994). The cause of this hyperarousal is unknown; however, it is hypothesized that it may occur in association with a shift in the balance between systems that promote sleep and those that promote wakefulness.

**NEUROBIOLOGY OF SLEEP AND WAKEFULNESS**

The neural pathways that regulate wakefulness arise from cell groups in the brainstem, hypothalamus, and basal forebrain that activate the cerebral cortex and other parts of the forebrain. Historically, the pathway from the brainstem was referred to as the ascending reticular activating system, but over the last 25 years, researchers have established that this pathway is comprised of several neurochemically specific projections that release acetylcholine and monoaminergic neurotransmitters such as norepinephrine, dopamine, serotonin, and histamine (Figure 1) (Saper, Scammell, & Lu, 2005). These cell groups include the histaminergic neurons of the tuberomammillary nucleus, the serotoninergic neurons of the raphe nuclei, and the noradrenergic neurons of the locus coeruleus. Each of these groups likely influences different aspects of wakefulness, and they act collectively to produce full arousal under appropriate conditions. The clinical importance of these pathways is clear as sedation is common with many monoamine antagonists and anticholinergics (e.g. haloperidol, doxepin, diphenhydramine) (Scammell & Winrow, 2011).
Neurons producing orexins are another key element of the wake-promoting system (Sakurai, 2007; Scammell & Winrow, 2011). Orexin-A and orexin-B (also known as hypocretin-1 and -2) are peptide neurotransmitters that bind to the OX1 and OX2 receptors, where they have excitatory effects. Unlike the other wake-promoting neurotransmitters that are produced by a variety of nuclei, the orexins are produced only by a small cluster of neurons in the lateral hypothalamus. Similar to the other wake-promoting systems, the orexins are released during wakefulness (Figure 2), and they excite a wide variety of brain regions, with especially strong effects on the other wake-promoting brain regions. A single injection of orexin-A into the central nervous system of a rat can promote wakefulness for several hours (Hagan et al., 1999). The importance of the orexin system is quite apparent in narcolepsy, in which selective loss of the orexin-producing neurons results in permanent and often severe sleepiness (Burgess, Scammell, 2012).

**FIGURE 2:**
OREXIN LEVELS ARE HIGH DURING THE DAY AND LOW AT NIGHT IN SQUIRREL MONKEYS, WHICH HAVE SLEEP-WAKE PATTERNS SIMILAR TO THOSE OF HUMANS

![Orexin Levels](image)

**Findings:** Orexin-A levels are high during the day and lower at night. The dark period is indicated by the light grey bars.


Orexins also promote other aspects of arousal (Figure 3). Orexins enhance activity in brain regions that regulate motivation and reward, and orexin antagonists can blunt drug-seeking in experimental animals. Orexins also increase heart rate, blood pressure, and locomotor activity. Integration of these varied aspects of arousal by orexins may help ensure that an individual is alert, active, and motivated at the correct times of day (Scammell, 2001).

During NREM and REM sleep, the wake-promoting neurons are inhibited by neurons that release γ-aminobutyric acid (GABA). The ventrolateral preoptic (VLPO) nucleus is the best studied of these GABAergic systems, and it is clearly necessary, as injury to the VLPO substantially reduces the amounts of NREM and REM sleep. Most likely, additional GABA-producing cell groups in the rostral hypothalamus and other brain regions also contribute to the production of sleep (Saper, Chou, & Scammell, 2001; Saper, et al., 2005).

**FIGURE 3:**
OREXINS WORK THROUGH A VARIETY OF TARGET NUCLEI TO INCREASE SEVERAL ASPECTS OF AROUSAL

![Orexin Targets](image)

**Behavioral Effects**
- Wakefulness
- Attention
- REM sleep
- Motivation
- Reward
- Feedback
- Locomotion
- Sympathetic tone


REM sleep is characterized by rapid eye movements, vivid dreams, and muscle paralysis. During REM sleep, the monoaminergic neurons fall silent, but a subset of cholinergic neurons in the pons (in the laterodorsal and pedunculopontine tegmental nuclei) becomes active. These pontine neurons play essential roles in producing the cortical activation and muscle paralysis typical of REM sleep. These REM sleep-promoting pathways are strongly inhibited by monoaminergic neurotransmitters, and in clinical practice, REM sleep is often suppressed by medications that increase the levels of serotonin or norepinephrine such as fluoxetine and venlafaxine (Nishino & Mignot, 1997).

The orexins also regulate REM sleep. During wakefulness, orexins activate the monoaminergic neurons and other brainstem regions that suppress REM sleep (Figure 4). However, with the loss of orexins in narcolepsy, REM sleep can occur at any time of day, and elements of REM sleep mix into wakefulness. For example, the dreams of REM sleep can occur when drifting off to sleep or upon waking, and this can mix with waking mentations, resulting in hypnagogic hallucinations. Further, the paralysis of REM sleep can occur upon awakening, or even in the midst of wake, and manifest as sleep paralysis or cataplexy, respectively (Burgess & Scammell, 2012).
REGULATING THE TRANSITIONS BETWEEN WAKEFULNESS AND SLEEP

Mutual inhibition between the wake- and sleep-promoting systems helps produce full arousal and sleep. GABA from the VLPO inhibits the arousal systems, and monoamines and acetylcholine inhibit the VLPO (Figure 5). Thus, during wakefulness, the wake-promoting neurotransmitters inhibit the VLPO, and removal of any inhibition from the VLPO allows the wake-promoting systems to be fully active. Just the opposite happens during sleep when the VLPO neurons are released from any inhibition by the wake-promoting systems. Some researchers refer to this as a neural flip-flop switch because, like the electrical circuit of the same name, the mutual inhibition of the sleep- and wake-promoting systems ensures full arousal or full sleep, with little time spent in intermediate, foggy states (Scammell & Winrow, 2011).

This switching between wake and sleep is stabilized by the orexin neuropeptides. Primarily this occurs through the direct excitatory effects of orexins on other wake-promoting cell groups. In addition, the orexin neurons are autoexcitatory (shown by the recurrent loop in Figure 5); release of orexin promotes local release of glutamate which increases the activity of the orexin neurons. Researchers believe that this positive feedback loop may drive sustained activity in the orexin neurons that then drives sustained activity in the other arousal systems to produce long periods of wakefulness. Conversely, loss of the orexin neurons makes it very difficult for patients or animals with narcolepsy to maintain long periods of wakefulness (Diniz Behn, Kopell, Brown, Mochizuki, & Scammell, 2008; Littner et al., 2005).

DIFFERENCES BETWEEN GABA AND OREXIN DISTRIBUTION AND EFFECTS

It is important to distinguish the differences between GABA and orexin distribution and effects on the brain. GABA receptors are located throughout the brain, whereas the distribution of orexin receptors is more limited. Orexin innervation does not occur at all in certain parts of the brain, such as the cerebellum, where no orexin receptors or fibers exist. Even within the areas that orexin does innervate, orexin is more selective to specific cell groups and does not have nearly as broad an effect as does the GABA system. Orexin affects the brain in a broad fashion, but the consequent effects are generally limited. The primary effects of the orexin system are helping sustain long periods of wakefulness, promoting wake, and suppressing REM sleep. The other effects of orexin are small and have only minimal effects on autonomic tone and on breathing (Scammell & Winrow, 2011).

HYPERAROUSAL AS A MAJOR ASPECT OF INSOMNIA

Substantial clinical research has shown that insomnia is strongly associated with overactivity in the arousal systems (Figure 6). Hyperarousal among subjects with insomnia is evidenced by elevations in core body temperature, heart rate, catecholamine levels, reactivity to stress, and other physiologic changes (Box and Figure 7), compared with healthy control subjects (Bonnet & Arand, 1995, 2001; C. L. Drake, Jefferson, Roehrs, & Roth, 2006; Lushington, Dawson, & Lack, 2000; McClure, Drake, Roth, & Richardson, 2003; Perlis et al., 2001; T. Roehrs, Randall, S., & Roth, T, 2012; Saper, et al., 2005; Stepanski, et al., 1994). These elevations in physiologic measures support the conceptualization of insomnia as a disorder of hyperarousal.
This hyperarousal is not limited to sleep and is present during the day as well. The level of daytime arousal can be measured by the Multiple Sleep Latency Test (MSLT), in which subjects are given five opportunities to nap during the day. Short sleep latencies on this test indicate daytime sleepiness, whereas longer latencies indicate higher levels of arousal. Roehrs and colleagues found that, among patients with insomnia, those who are most alert (i.e., have the longest sleep latency), have the worst nighttime sleep (Figure 8) (T. A. Roehrs, Randall, Harris, Maan, & Roth, 2011). Those with insomnia who are very alert (i.e., have sleep latencies of 15 – 18 minutes) sleep only about six hours a night. The results of this study indicate that prolonged sleep latencies on MSLT are negatively correlated with sleep time in patients with insomnia. This is the opposite of what is seen in normal healthy volunteers, where the less one sleeps or the more severe the sleep disturbance, the greater the degree of subjective daytime sleepiness. Thus, less sleep is associated with decreased alertness in the general population, but reduced sleep in insomnia is associated with increased alertness (T. A. Roehrs, et al., 2011).

Norepinephrine levels are higher in some patients with insomnia. Patients with insomnia that have longer sleep latencies on the MSLT have higher levels of norepinephrine than patients with shorter sleep latencies on MSLT (Figure 9). In addition, norepinephrine levels, but not epinephrine levels, are significantly elevated in patients with insomnia relative to control subjects (Figure 10) (Ford & Kamerow, 1989; McClure, et al., 2003; Vgontzas et al., 2001). Therefore, there is a synchrony among elevated norepinephrine levels, increased daytime alertness, and decreased total sleep time.
A study by Vgontzas et al. (1998) has shown that subjects with insomnia have elevated cortisol, relative to controls, that is most pronounced around sleep onset, further demonstrating that insomnia is a disturbance of hyperarousal (Figure 12). It is interesting to note that cortisol levels in subjects with and without disturbed sleep differed primarily before sleep onset, a time at which thinking about going to sleep may act as a stressor and increase cortisol levels. In a separate study of patients with insomnia, the researchers monitored heart rate while putting subjects’ hands in a cold bucket of water (a stressor) while awake, and heart rate rose higher in those with insomnia compared with control subjects (Figure 13). All of these findings are consistent with insomnia as a disorder of hyperarousal rather than one of an impairment of the sleep system per se.

This hyperarousal has also been documented in imaging studies. Overall, insomnia is associated with greater brain metabolism. When data from subjects with and without insomnia are compared, positive emission tomography imaging demonstrates greater cerebral glucose metabolism in patients with insomnia when asleep as well as when awake, a smaller decline in relative metabolism from waking to sleep in wake-promoting regions, and reduced metabolism in the prefrontal cortex while awake (Figure 11). Arousal centers, including the midbrain and hypothalamus, show a smaller reduction in activity during the night in patients who have insomnia. It is critically important to understand that these insomnia subjects were asleep during the imaging, demonstrating that people with insomnia have increased brain metabolism during non-REM sleep. This same activity can be seen with increased total brain metabolism across a 24-hour day (Nofzinger et al., 2004). This increase in brain metabolism provides more evidence of hyperarousal in patients with insomnia.
To determine whether some individuals have an inherently higher reactivity to sleep-related challenges, Drake et al. measured “sleep responsivity” in normal sleepers and those who have difficulty sleeping under stress, but do not have insomnia (C. L. Drake, et al., 2006). Those who had difficulty sleeping under stress, as measured by high scores on the Ford Insomnia Response to Stress Test (FIRST), had significantly lower sleep efficiencies and longer sleep latencies than did the control subjects. In addition, their sleep latencies on MSLT the next day were significantly longer, demonstrating that some individuals are more sensitive to stimuli disturbing their sleep and that this effect lasts beyond the sleep period. In another study exploring higher reactivity to sleep-related stimuli, Drake et al. used caffeine as a stimulus and determined its effect on sleep (C. L. Drake, Jefferson, Roehrs, Richardson, & Roth, 2004). The results of a much larger (N = 1,396), three-year study to investigate sleep reactivity demonstrated a 22% increased risk of developing insomnia among subjects with high FIRST scores at baseline even after accounting for age, sex, depression, life events, and number of stressors (odds ratio = 1.15, 95% CI = 1.08 – 1.22; p < .001). This odds ratio translates into an approximately 30% increased risk of developing insomnia among those subjects who had a one standard-deviation–elevated FIRST score, demonstrating that an inherent hyper-reactivity represents an increased risk for insomnia (C. L. Drake, et al., 2013).

To further explore whether hyper reactivity to sleep-related stimuli predisposes some individuals to insomnia, Drake et al. conducted additional longitudinal studies. In the first study, none of the subjects had insomnia at baseline. Thirteen months later, when subjects were evaluated for the presence of insomnia, roughly 11% of the subjects with a high FIRST score at baseline had developed insomnia (Figure 15). The relative risk for developing insomnia over the next year among subjects with high FIRST scores was roughly three times that of subjects with low FIRST scores (C. L. Drake, Jefferson, Roehrs, Richardson, & Roth, 2004). The results of the first study, none of the subjects had insomnia at baseline. Thirteen months later, when subjects were evaluated for the presence of insomnia, roughly 11% of the subjects with a high FIRST score at baseline had developed insomnia (Figure 15). The relative risk for developing insomnia over the next year among subjects with high FIRST scores was roughly three times that of subjects with low FIRST scores (C. L. Drake, Jefferson, Roehrs, Richardson, & Roth, 2004). The results of a much larger (N = 1,396), three-year study to investigate sleep reactivity demonstrated a 22% increased risk of developing insomnia among subjects with high FIRST scores at baseline even after accounting for age, sex, depression, life events, and number of stressors (odds ratio = 1.15, 95% CI = 1.08 – 1.22; p < .001). This odds ratio translates into an approximately 30% increased risk of developing insomnia among those subjects who had a one standard-deviation–elevated FIRST score, demonstrating that an inherent hyper-reactivity represents an increased risk for insomnia (C. L. Drake, et al., 2013).

To characterize sleep responsivity further, Drake and colleagues investigated whether a genetic component exists in sleep reactivity and the risk for insomnia (C. L. Drake, Friedman, Wright, & Roth, 2011; C. L. Drake, Scofield, & Roth, 2008). In a study of insomnia in siblings, siblings with high FIRST scores, but not insomnia, were interviewed (C. L. Drake, et al., 2008). The familial

**Figure 14:** Hypothalamic-Pituitary-Adrenal Axis Hyperactivity in Insomnia: Cortisol

BMI (25) and age (29 years) matched, 24-h blood sampling every 30 minutes. Findings: Significant 24-h mean increase in cortisol release in those with insomnia compared to those without insomnia (p = .002). Significant mean increase in daytime (07:30-22:30) cortisol release in those with insomnia compared to those without insomnia (p = .006).


**Figure 15:** Incidence of Insomnia and FIRST

<table>
<thead>
<tr>
<th>FIRST Score</th>
<th>Insomnia at Time 1 (Baseline)</th>
<th>Insomnia at Time 2 (~13 Months Later)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low FIRST score ≤ 24 (n = 178)</td>
<td>0%</td>
<td>3.4% (6)</td>
</tr>
<tr>
<td>High FIRST score &gt; 24 (n = 134)</td>
<td>11.2% (15)</td>
<td>Relative risk = 3.32 (CI = 1.32–8.33)</td>
</tr>
</tbody>
</table>

Overall insomnia incidence rate of 6.7% over 13 months.
FIRST = Ford Insomnia Response to Stress Test.
CONCLUSIONS

Insomnia can lead to significant medical problems, psychological distress, and injury. Clinical research provides evidence that insomnia is a disorder of hyperarousal evidenced by increases in heart rate (Stepanski, et al., 1994), metabolic rate (Bonnet & Arand, 1995), fast EEG activity (Bonnet & Arand, 2001; Perlis, et al., 2001), catecholamine levels (McClure, et al., 2003), and increased reactivity to stress (C Drake, et al., 2013). Clinicians need to explain to patients that insomnia is generally not a disorder of the sleep system but, rather, a disorder of hyperarousal. Basic research has shown that the VLPO uses GABA to inhibit the arousal systems, and the arousal systems use monoamines and acetylcholine to inhibit the VLPO. Orexin innervation, in contrast to GABA, does not occur in all areas of the brain. Even within the areas that orexin does innervate, orexin is more selective to specific cell groups. The orexin neuropeptides excite the other wake-promoting brain regions to sustain wakefulness and suppress REM sleep. Though much remains to be learned about the underlying neurobiology of clinical insomnia, it is possible that hyperarousal and poor sleep are due to overactivity of the wake-promoting systems.
REFERENCES


REFERENCES cont.


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