

Evolving Science and Emerging Approaches to Improving Outcomes for Patients With Insomnia

An Educational Monograph Based on an Expert Roundtable Discussion



Stephen H. Sheldon, DO, FAAP
Professor of Pediatrics
Northwestern University, Feinberg School of Medicine
Director, Sleep Medicine Center
Ann and Robert H. Lurie Children's Hospital of Chicago



Andrew D. Krystal, MD, MS
Director of the Insomnia and Sleep Research Program
Department of Psychiatry and Behavioral Sciences
Duke University School of Medicine



Sherri L. Ten Pas, DO, DABSM
Director, Trinity Clinic Sleep Medicine
Trinity Mother Frances Hospitals and Clinics



Phyllis C. Zee, MD, PhD
Benjamin and Virginia T. Boshes Professor of Neurology
Director of the Sleep Disorders Center
Northwestern University

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Target Audience

This activity is for osteopathic physicians and other health care professionals who care for people with insomnia.

Statement of Need

The purpose of the initiative is to provide osteopathic physicians with continuing medical education that offers timely and relevant evidence-based data on the pathophysiology of insomnia and the science behind emerging treatments.

Educational Objectives

At the conclusion of this activity, participants should be able to demonstrate improved ability to:

- Define insomnia as a hyperarousal state vs a lack of sleep
- Explain the sleep/wake cycle
- Review the current status of treatment
- Identify unmet treatment needs
- Discuss the science of emerging treatments
- Explain how orexins fit within the sleep/wake cycle

Faculty

Andrew D. Krystal, MD, MS

Director of the Insomnia and Sleep Research Program
Department of Psychiatry and Behavioral Sciences
Duke University School of Medicine

Stephen H. Sheldon, DO, FAAP

Professor of Pediatrics
Northwestern University Feinberg School of Medicine
Director, Sleep Medicine Center
Ann and Robert H. Lurie Children's Hospital of Chicago

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Director, Trinity Clinic Sleep Medicine
Trinity Mother Frances Hospitals and Clinics

Phyllis C. Zee, MD, PhD

Benjamin and Virginia T. Boshes
Professor of Neurology
Director of the Sleep Disorders Center
Northwestern University

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Monograph

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Abstract

Insomnia is one of the most common problems encountered in primary care, but is rarely cited as the principal reason for an office visit. Patients with comorbid conditions, such as depression, anxiety, cardiovascular, pulmonary, and gastrointestinal disorders often experience symptoms of insomnia. Insomnia is frequently associated with mood disturbances, difficulties with concentration and memory, poor quality of life, increased risk of accidents, and lost productivity. Emerging data suggest that patients with chronic insomnia exhibit a state of heightened arousal that can be documented not only during sleep, but also throughout the 24-hour circadian cycle. Increased awareness of diagnosis and management of insomnia on the part of the primary care physician is critical for reducing its associated burden through timely and effective treatment.

Introduction

Insomnia is a clinical condition commonly seen in primary care. It is characterized by difficulty initiating or maintaining sleep and often accompanied by symptoms such as irritability or fatigue during wakefulness. In the medical literature reporting the results of research studies, “insomnia” is a term frequently identified by the presence of polysomnographic evidence of disturbed sleep. The presence of a long sleep latency, frequent nocturnal awakenings, prolonged periods of wakefulness during the sleep period, or even frequent transient arousals are considered evidence of insomnia.¹ In clinical practice, insomnia is defined by a patient’s report of difficulty falling sleep, staying asleep, or both, accompanied by impairment in quality of life and/or daytime function. For example, critical questions for identifying the presence of insomnia are: “Do you experience difficulty sleeping?” or “Do you have difficulty falling or staying asleep?”

Impact and Burden of Insomnia

Although many patients and their physicians perceive insomnia as a trivial issue, its impact on overall health can be significant. Chronic insomnia affects approximately

10% to 15% of American adults, and an additional 25% to 35% experience transient insomnia.² The elderly appear to be particularly prone to insomnia; noninstitutionalized elderly estimates are as high as 40%.¹ Daytime consequences of insomnia reported by affected individuals include reduced energy, memory problems, and difficulty concentrating.^{3,4} Insomnia is associated with impairments of physical and mental well-being, reflected in higher levels of cardiometabolic disease, depression, anxiety, and diminished quality of life. Insomnia also has a broad societal and economic impact. Despite the high prevalence rates, evidence suggests that insomnia is underrecognized, underdiagnosed, and undertreated.²

Several risk factors for insomnia have been identified,³ including comorbid medical disorders,⁵ psychiatric disorders,⁶ and working night or rotating shifts.⁷ It is important to recognize that these factors do not independently cause insomnia, but rather are precipitants of insomnia in people predisposed to this disorder. Age and sex are also demographic risk factors for insomnia, with an increased prevalence in women and older adults. Importantly, the presence of comorbid medical conditions is also a significant contributor to the increased prevalence of insomnia in the elderly population.

People with insomnia have an increased risk of comorbid medical disorders such as hypertension, diabetes, conditions causing hypoxemia and dyspnea, gastroesophageal reflux disease, pain conditions, depression, and neurodegenerative diseases (Tables 1 and 2).^{5,8,9} Notably, a variety of primary sleep disorders as well as circadian rhythm abnormalities are more likely in those with insomnia. Among the primary sleep disorders, restless legs syndrome,¹⁰ periodic limb movement disorders, and sleep-related breathing disorders (eg, obstructive sleep apnea) can present with insomnia as the sentinel symptom.¹¹ This may be especially true among the elderly population.

People with insomnia have been shown to be at a significantly higher risk for workplace accidents and/or errors, even when controlled for other chronic

Table 1. Patients With Chronic Insomnia Reporting Comorbidities⁵

Comorbidity	Prevalence			
	Chronic Insomnia (%)	No Insomnia (%)	Odds Ratio ^a (95% Confidence Interval)	P Value
Chronic pain	50.4	18.2	3.19 (1.92-5.29)	<.001
Hypertension	43.1	18.7	3.18 (1.90-5.32)	<.001
Gastrointestinal problems	33.6	9.2	3.33 (1.83-6.05)	<.001
Breathing problems	24.8	5.7	3.78 (1.73-8.27)	<.01
Heart disease	21.9	9.5	2.27 (1.13-4.56)	<.05
Urinary problems	19.7	9.5	3.28 (1.67-6.43)	<.01
Neurologic disease	7.3	1.2	4.64 (1.37-15.67)	<.05

^aAdjusted for depression, anxiety, and sleep disorder symptoms.

Table 2. Patients With Comorbidities Reporting Chronic Insomnia⁵

Comorbidity	Prevalence			
	Chronic Insomnia (%)	No Insomnia (%)	Odds Ratio ^a (95% Confidence Interval)	P Value
Chronic pain	48.6	17.2	2.27 (1.33-3.89)	<.01
Hypertension	44.0	19.3	1.92 (1.06-3.46)	<.01
Gastrointestinal problems	55.4	20.0	2.57 (1.37-4.80)	<.01
Breathing problems	59.6	21.4	3.26 (1.56-6.81)	<.01
Urinary problems	51.5	23.3	2.25 (1.13-4.48)	<.05

^aAdjusted for depression, anxiety, and sleep disorder symptoms.

conditions such as age, sex, and educational level.¹² Work productivity can also be compromised among people with insomnia due to significantly higher rates of absenteeism with reduced job performance and poor safety outcomes.¹³⁻¹⁵

Insomnia also appears to be associated with high levels of health care resource utilization. People with chronic insomnia consume health care services to a greater extent than those without insomnia,¹⁶ including a greater number of hospitalizations and higher use of medications for coexisting cardiovascular, central nervous system, urogenital, and gastrointestinal conditions.¹⁷ Consequently, the direct and indirect costs of chronic insomnia have been estimated at tens of billions of dollars annually.¹⁸ However, it is difficult to separate the effects

of insomnia from the effects of comorbid conditions. For example, a person with joint pain who has problems sleeping may seek health care for the arthritis rather than for sleep problems, assuming that the pain accounts for the sleep difficulty.³

Pathophysiology of Insomnia:
Emerging Perspectives

Research on insomnia has provided a number of important new insights, but mechanisms of insomnia need to be better understood. Insomnia is a heterogeneous disorder with a variety of potential underlying contributing factors that include genetic, psychological, physical, and environmental components. Several lines of evidence suggest that patients with chronic

insomnia exhibit a generalized state of heightened arousal during sleep, but also throughout the circadian cycle.^{19,20} Data on these patients reveal increased high-frequency electroencephalogram activation, elevated cortisol and adrenocorticotrophic hormone secretion, increased core body temperature and metabolic rate, and, during sleep, attenuated nighttime melatonin secretion, increased whole-body and brain metabolic activation, and elevated heart rate and sympathetic nervous system activation.^{19,21}

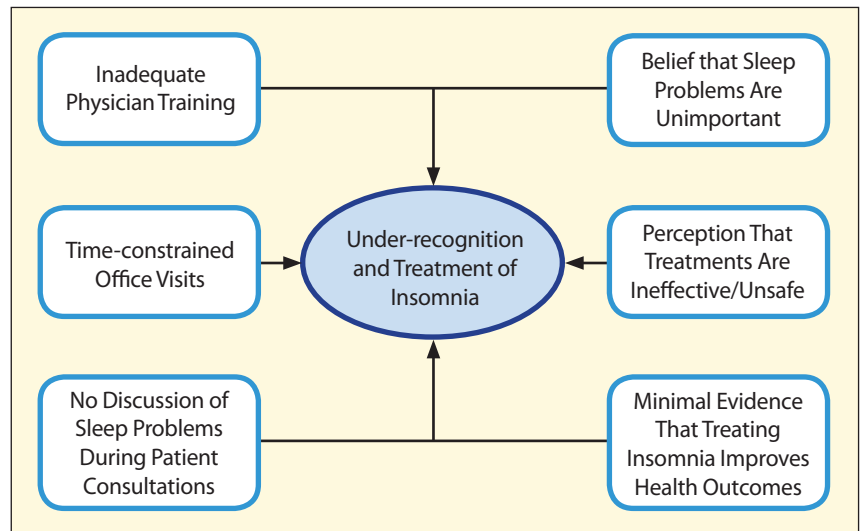


Figure 1. Barriers to Recognition and Treatment of Insomnia³²

The precise physiological mechanism driving the increased arousal remains unclear. However, accumulating data suggest that dysregulation of the orexin system, a central regulator of wakefulness, may be responsible, at least in part, for the clinical symptoms of insomnia.²² Hypocretin/orexin-expressing neurons originate from the lateral hypothalamus, a control center for sleep and wakefulness. Projections from hypocretinergic neurons extend widely throughout the brain to signal activation of key neural centers involved in maintaining the wake-state, including the locus coeruleus and tuberomammillary nucleus, which contain neurons that express hypocretin/orexin peptide receptors and mediate wakefulness signaling.²² Released hypocretin/orexin peptides selectively bind to receptors found on target afferent neurons in cortical, thalamic, and hypothalamic neuronal circuits specifically associated with sleep/wake regulation. There is a circadian rhythmicity to hypocretin/orexin neuropeptide levels, which rise with waking and decrease during the night and are important features of the system.^{23,24} If physiological hyperarousal causes primary insomnia, the hypocretin/orexin system could provide new approaches for the management of this disorder.²⁵ Nighttime administration of hypocretin/orexin receptor antagonists dampens hypocretin/orexin-mediated wakefulness, thereby facilitating sleep.^{26,27} Suvorexant is a hypocretin/orexin receptor antagonist in late phase development for the treatment of patients with insomnia.^{26,27}

Unmet Needs in Insomnia Care

Minimal knowledge of sleep medicine among clinicians, clinicians' time constraints, and patients' reluctance to communicate details about their sleep patterns contribute to the neglect of sleep-related issues during primary care office visits (Figure 1). Results of a collaborative study on general health care indicated that physicians detected insomnia in less than 50% of patients who had symptoms of insomnia.²⁸ A survey of knowledge and attitudes about sleep and sleep medicine among 105 primary care physicians revealed that only 10% reported their knowledge as good, 60% as fair, and 30% as poor. None of the respondents indicated their knowledge was excellent.²⁹

The nature of insomnia itself contributes to the difficulties associated with its awareness and acceptance as a serious condition by both patients and physicians. Although not typically indicated for evaluation of patients with symptoms of insomnia, polysomnographic studies of patients with insomnia generally show abnormalities such as prolonged latency to sleep onset, frequent arousals, and reduced amounts of total sleep. However, objective measures of sleep do not always correlate well with the patient's experience of insomnia. As a result, we lack an objective test for insomnia that could serve as a clinical tool for practitioners.³⁰

It is often assumed that insomnia results in sleep deprivation, yet this supposition is not supported by studies employing objective tests of daytime sleepiness in patients with insomnia and studies attempting to identify cognitive deficits typically seen in sleep-deprived individuals.³¹ Furthermore, sleep deprivation does not lead individuals to experience symptoms of insomnia; together, these data suggest that a decreased quantity of sleep alone does not constitute insomnia.³²

Summary

Insomnia is a highly prevalent problem that is associated with increased use of health care services and products in addition to functional impairments. However, despite the overwhelming evidence associating insomnia with poor outcomes, increased risk of accidents, and higher socioeconomic burden, primary care has historically overlooked the importance of sleep in maintaining physical and mental health. Increased awareness of insomnia on the part of the primary care physician is a key step toward reducing the burden of insomnia and improving overall health outcomes. It is important to maintain awareness that insomnia may be an unrecognized contributor to functional impairment, symptoms, or difficulty in stabilizing treatment in patients with comorbid medical or psychiatric illness, especially when these conditions worsen.

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Abstract

Although insomnia is rarely the primary reason for an office visit, it is one of the most commonly encountered symptoms in primary care. People with chronic insomnia report difficulty maintaining social relationships, poor concentration, problems with memory, and persistent sleepiness, all of which can negatively affect overall physical health, contribute to loss of productivity, and increase the risk of accidents. Advances in the understanding of the pathophysiology of sleep disorders suggest excessive arousal of brain centers responsible for promoting alertness may contribute to the development of insomnia. This hyperarousal may be attenuated by therapy that antagonizes the action of the orexin (hypocretin) system. Increased understanding of the causes of disordered sleep will allow primary care physicians to more effectively identify and treat their patients with insomnia.

Faculty Introduction

STEPHEN H. SHELDON, DO, FAAP: Welcome to the roundtable discussion titled *Evolving Science and Emerging Approaches to Improving Outcomes for Patients With Insomnia*. I am Dr. Stephen Sheldon, professor of pediatrics at the Northwestern University Feinberg School of Medicine and director of the Sleep Medicine Center at the Ann and Robert Lurie Children's Hospital of Chicago in Illinois.

Joining me are Andrew Krystal, MD, MS, director of the Insomnia and Sleep Research Program at Duke University School of Medicine in Durham, North Carolina; Sherri Ten Pas, DO, DABSM, director of the Trinity Clinic Sleep Medicine of Trinity Mother Frances Hospitals and Clinics in Tyler, Texas; and Phyllis Zee, MD, PhD, Benjamin and Virginia T. Boshes Professor of Neurology and director of the Sleep Disorders Center at Northwestern University in Chicago.

The purpose of our discussion is to provide osteopathic primary care physicians with continuing medical education on the importance of sleep and sleep medicine, as well as the pathophysiology of insomnia and the science behind these emerging treatments.

The Importance of Sleep

STEPHEN H. SHELDON, DO, FAAP: Sleep is imperative for human existence, and our recognition of the importance of sleep continues to grow. However, signs and symptoms of sleep disorders, particularly insomnia, are often subtle and easy to miss in a busy primary care practice. As we understand more and more about the pathophysiology of sleep and its disorders, I think the importance of sleep to the primary care physician will grow.

Dr. Zee, can you give us insight into the importance of sleep for our overall health?

PHYLLIS C. ZEE, MD, PhD: The evidence from both physiological studies and large population-based studies shows that good-quality sleep and adequate amounts of sleep are important for cognition, learning, laying down memories, physical performance, and mental health. It's been known for a while that there is a strong association between sleep deficiency and risk of accidents, depression and anxiety disorders. However, in the past decade or so, there has been increasing recognition of the importance of sleep quality on overall physical health, particularly cardiometabolic, cognitive, and neurological health.

“By improving sleep quality, we may be able to reduce the morbidity associated with cardiometabolic disorders such as diabetes, hypertension, and coronary heart disease.”

— Dr. Zee

STEPHEN H. SHELDON, DO, FAAP: You raise an interesting point about metabolic health, particularly with recently emerging evidence that decreased total sleep time is associated with increased weight gain.

PHYLLIS C. ZEE, MD, PhD: Absolutely; however, I would say it's more than just sleep duration that's important to overall health. The quality of sleep and a lack of deep sleep appear to be most closely associated with obesity, diabetes, cardiovascular disease, and other issues. I think of sleep quality as a modifiable risk factor. By improving sleep quality, we may be able to reduce the morbidity associated with cardiometabolic disorders such as diabetes, hypertension, and coronary heart disease. Considering an estimated 30% of American adults (~50 to 70 million) report a chronic sleep deficit,^{1,2} improving sleep quality could have a significant impact on public health.

The direct and indirect cost of sleep insufficiency is another part of the problem, particularly because the cost of accidents and lost productivity due to sleep deprivation is in the hundreds of billions of dollars.

STEPHEN H. SHELDON, DO, FAAP: That's fascinating. I think the cost of health care can be addressed to some extent by paying attention to sleep. Productivity is also an interesting concept; in an industrialized society such as ours, we think that being awake is tantamount to being productive. Is that true, or are we more productive if we get more sleep rather than sacrifice sleep for work?

ANDREW D. KRYSTAL, MD, MS: This issue was addressed by a database analysis of employees enrolled in commercial health plans that assessed the costs of workplace and nonworkplace accidents and missed days of work.³ Although the number of missed workdays and accidents due to insomnia was relatively low compared with other disorders, the costs associated with insomnia-related workplace accidents were the highest. In fact, almost one-fourth of the costs of workplace-related accidents were due to insomnia. In addition, employees with insomnia spent approximately 14% of days out of their usual role and were unable to perform their typical daily activities, not just as an employee, but also as a parent or caregiver.

SHERRI L. TEN PAS, DO, DABSM: When looking at accidents and the cost to society, we should also

mention sleepiness and fatigue in regard to motor vehicle accidents. Conservative estimates by the National Highway Traffic Safety Administration indicate that 2.5% of fatal crashes and 2% of injury crashes each year directly result from driver fatigue, and this accounts for \$12.5 billion in monetary losses each year.⁴

“The cost of accidents and lost productivity due to sleep deprivation is in the hundreds of billions of dollars.”

– Dr. Zee

STEPHEN H. SHELDON, DO, FAAP: Insomnia leads to sleepiness during the day. Does sleep deprivation have an impact on, or is it influenced by, insomnia resulting in sleepiness?

ANDREW D. KRYSTAL, MD, MS: That's an important question, because there's a lot of confusion about insomnia and sleep deprivation. Sleepiness during the day is more typical of people with sleep deprivation or with sleep disorders such as obstructive sleep apnea or narcolepsy. Interestingly, while patients with insomnia report being sleepy, their sleep onset latency (or the time it takes them to fall asleep) is actually longer on average than that of the general population when their sleep is evaluated using objective assessments. Therefore, even though patients with insomnia often have loss of sleep, it doesn't seem to manifest itself in sleepiness. This phenomenon is believed to be at least partially attributable to hyperactivation of the sympathetic nervous system and has been termed “hyperarousal syndrome,” which is believed to be mediated by the hypocretin/orexin system.

PHYLLIS C. ZEE, MD, PhD: Dr. Krystal, even though they are not sleepy per se, patients with insomnia are at increased risk for accidents. Do you think this is because they are fatigued or perhaps inattentive?

ANDREW D. KRYSTAL, MD, MS: That's a really interesting question, Phyllis. I will tell you my view on it, but I don't know the answer because it's very difficult to study the specific antecedents of accidents in patients with insomnia. Many studies have attempted to identify whether patients with insomnia exhibit impairments in cognitive function and performance. We conducted a study in which we challenged subjects with a complex attention switching task; the subjects had to focus on one part of a screen and simultaneously be prepared to respond to things they saw in another part of the screen. The subjects with insomnia demonstrated impairments that were proportionate to the amount of sleep they received in the preceding nights. My guess is that those with insomnia do in fact perform more poorly, but it isn't immediately evident. In general, our laboratory studies suggest that insomnia may be at least partially responsible for impairments and/or accidents that arise when people are asked to perform tasks they consider either boring or complex and challenging.

PHYLLIS C. ZEE, MD, PhD: Another important point with regard to sleepiness and accidents is that we shouldn't forget the concept of circadian rhythms. Even if a person is sleep satiated, there is still a risk that they can fall asleep while driving at 3 AM because this is the nadir of our circadian timing of alertness level. Therefore, it is the combination of sleep loss and being at a vulnerable time in the circadian cycle that leads to the highest increase in impairments and accidents, particularly during the early morning hours.

SHERRI L. TEN PAS, DO, DABSM: Phyllis makes a good point. Many shift workers, particularly those who work the night shift, have jobs that require them to be physically and/or cognitively active during periods when the body is most prone to sleepiness. A series of laboratory and vehicle studies conducted by Dinges et al in the 1990s⁵⁻⁷ suggested that shift workers who were sleep deprived have slower reaction times, reduced vigilance, and deficits in information processing, all of which could increase the number of work-related incidents.

ANDREW D. KRYSTAL, MD, MS: I agree.

Interestingly, similar studies have been performed in patients with insomnia, and their performance was normal on the same tests. We have this paradox in which patients with insomnia who are getting the same amount of sleep as those in the studies by Dinges et al feel they are performing as poorly as those who are sleep deprived, but their performance is actually not nearly as bad. It was recognition of this paradox that led to the introduction of the hyperarousal concept.

Sleep Homeostasis

STEPHEN H. SHELDON, DO, FAAP: Phyllis, is there a difference in the homeostatic sleep drive between those patients who report symptoms of insomnia and those who don't?

PHYLLIS C. ZEE, MD, PhD: I don't believe the literature suggests that there are alterations or abnormalities in the homeostatic sleep drive in patients with insomnia. More likely, these patients have a state of hyperarousal.

A behavioral approach to treatment of patients with insomnia includes regulating the homeostatic sleep drive. This intervention is referred to as bedtime or sleep time restriction therapy. Most patients with insomnia are able to respond to sleep loss by increasing their homeostatic drive, which ultimately results in rebound (catch-up) sleep.

ANDREW D. KRYSTAL, MD, MS: I agree with Dr. Zee and would like to add one observation that supports the presence of an intact homeostatic sleep drive in people with insomnia. Investigators at the Sleep Disorders and Research Center at the Henry Ford Hospital in Detroit reduced the amount of sleep received by people with insomnia and found that these subjects showed signs of sleepiness.⁸ In fact, their sleep duration rebounded to predeprivation levels, suggesting that their homeostatic sleep capacity was intact and that their sleep set point was perhaps shifted by the hyperarousal process.

This method that Dr. Zee just mentioned, restriction of time in bed, is an intervention that does in fact ramp up the homeostatic sleep drive and works tremendously well. Primary care physicians should be aware of this because it is a quick and remarkably effective intervention for many people with insomnia.

STEPHEN H. SHELDON, DO, FAAP: Is there a genetic influence in insomnia?

ANDREW D. KRYSTAL, MD, MS: There are not a lot of data linking genetic factors and insomnia. We found a link between the polymorphism in the serotonin transporter gene and the tendency for poor sleep under stress, but a formal diagnosis of insomnia was not established. In general, there is only limited understanding of what might predispose people to insomnia.

Insomnia: Definition and Diagnosis

STEPHEN H. SHELDON, DO, FAAP: Andy, what is the definition of insomnia for the primary care physician?

ANDREW D. KRYSTAL, MD, MS: Patients who report difficulty falling asleep, staying asleep, or early morning awakening often have insomnia, particularly if the lack of sleep leads to impaired function or decreased quality of life. Other signs include patients who state they are not thinking as clearly as usual or who are feeling irritable or moody. These signs are often seen in patients with insomnia, and they are an important part of the diagnosis.

There are a couple of parts of the diagnosis that are often missed and may lead to misdiagnosis. For instance, it's important to determine if the person has an appropriate opportunity to sleep. I may decide arbitrarily that I should be getting 10 hours of sleep and start spending 10 hours in bed to achieve this goal. If it takes me 2 hours to fall asleep, this is not insomnia because I changed my habits beyond what I am actually capable of normally sleeping. Furthermore, failure to sleep in a nonconductive environment and not having an opportunity to sleep are not insomnia.

Another critical aspect of diagnosis is that a sleep study is not needed to identify whether a person has insomnia because the diagnosis is symptom based. The reasons for this are beyond the scope of our discussion, but we rely on a patient saying that he or she has had trouble falling asleep or staying asleep for 1 month or more. There is no test that needs to be performed to assess whether or not that is the case.

“Insomnia is actually very common and the diagnosis of insomnia in a medical practice population is significantly higher than in the general population.”

– Dr. Krystal

PHYLLIS C. ZEE, MD, PhD: Another important point regarding diagnosis is impairment in daytime function and/or the distress experienced by the patient. Data suggest that patients with insomnia have a quality of life worse than that reported in patients with congestive heart failure and similar to that of patients with clinical depression.⁹

STEPHEN H. SHELDON, DO, FAAP: Phyllis, you mentioned that 50 to 70 million Americans have sleep-related disorders. How commonly do primary care physicians see patients with insomnia?

PHYLLIS C. ZEE, MD, PhD: Insomnia is probably one of the more common sleep disorders. The prevalence of chronic insomnia in the overall US population is between 10% and 15% and is as high as 50% in older people.

ANDREW D. KRYSTAL, MD, MS: To add to Dr. Zee's point, the diagnosis of insomnia in a medical practice population is significantly higher than that in the general population. More than 50% of young adults and a much higher proportion of older adults had a diagnosis of

insomnia in one study of a primary care setting.¹⁰ The investigators attributed this to an increased prevalence of comorbid conditions among patients seeking care. That is, those with medical and psychiatric conditions represent the bulk of patients with insomnia.

PHYLLIS C. ZEE, MD, PhD: We conducted a survey of general medicine practices in Chicago in which we interviewed older patients sitting in waiting rooms. We found that almost 70% of these patients reported a chronic sleep problem. Unfortunately, in an overwhelming number of cases, this problem was not identified by the physician and/or sleep was never even mentioned in the medical record.

STEPHEN H. SHELDON, DO, FAAP: Is this because patients are not reporting sleep problems because they think there is nothing to be done or because physicians are not asking questions about sleep or insomnia?

PHYLLIS C. ZEE, MD, PhD: There are multiple reasons for this. It could be that the clinicians are not asking about sleep as part of a routine history and physical examination. Also, patients may think it's normal to have problems with sleep because it is so common, especially older patients. In addition, even if patients know that a sleep disturbance could be considered a medical problem, many are not aware that there are effective treatments.

“Many patients do not consider their sleep difficulties to be a true medical condition.”

– Dr. Ten Pas

SHERRI L. TEN PAS, DO, DABSM: In my experience, many patients do not consider their sleep difficulties to be a true medical condition. According to the National Sleep Foundation's Sleep in America Poll, only 23% of patients reported sleep problems to their physicians. In this survey, women reported difficulty sleeping more often than men. What I found interesting was that even though women

more frequently reported symptoms to their physicians compared with the men in the study, the percentage of women diagnosed and treated for a sleep disorder was the same—approximately 7%. This makes me wonder about physicians' perceptions of sleep disorders across the sexes.¹¹

STEPHEN H. SHELDON, DO, FAAP: Do you think there is a difference between sexes in practice?

SHERRI L. TEN PAS, DO, DABSM: Based on the survey data, it appears that women are more likely to report sleep symptoms than men. However, the proportion of women with a diagnosis and treatment plan for a sleep disorder is about the same as for men, so there seems to be a disconnect somewhere.

STEPHEN H. SHELDON, DO, FAAP: What about age? Elderly people tend to spend more time in bed awake.

ANDREW D. KRISTAL, MD, MS: It used to be accepted wisdom that insomnia was a normal part of the aging process. This belief was supported by a number of studies conducted years ago. However, on closer scrutiny and on further study with cleaner methods, it was shown that many cases of age-related insomnia are due to the confounding effect of comorbid conditions; examples are pain syndromes, psychiatric disorders, other medical problems, and medications that may disturb sleep. If we control for the presence of a comorbid condition, the prevalence of insomnia in older adults is not nearly as high as once believed.

That said, insomnia is still highly prevalent in older adults, and even in the cleanest of samples, there is a tendency for less slow wave sleep amplitude and more sleep disturbance, that is, less ability to sleep through the night.

Insomnia and Comorbid Conditions

STEPHEN H. SHELDON, DO, FAAP: Let's spend a minute discussing how insomnia affects other medical illnesses such as asthma, chronic pain, certain psychiatric

disorders, and shift work, in which the patient might be sleepless to begin with but also experiences insomnia. What is the role of a comorbid condition in insomnia?

PHYLLIS C. ZEE, MD, PhD: As we touched on earlier, data show that patients with chronic comorbidities are much more likely to experience sleep disturbances. Symptoms of insomnia may be related to medications for the treatment of the comorbid condition, but many patients also have insomnia.

We always tend to think that patients who are in pain are not going to sleep well and that they'll be in even more pain if they don't sleep well. Recent data show that a lack of good-quality sleep lowers the threshold for pain. Thus, the problem isn't just that patients are not sleeping because they are in pain, but the lack of sleep actually can exacerbate the underlying pain condition or comorbid condition.

“Clinicians need to ask their patients about insomnia and institute effective treatment because we can provide treatment that will really help these patients in a short time.”

– Dr. Krystal

ANDREW D. KRYSTAL, MD, MS: In my clinical experience, people often try to treat pain at night with an insomnia medication because they don't want to use a pain medication, or they try to treat poor sleep with a pain medication because they don't want to use an anxiety or insomnia therapy. However, I have found that treating one condition but not the other doesn't work very well, particularly in patients with chronic pain.

Data show that treating insomnia and depression improves both sleep and depression outcomes. The same

is true for generalized anxiety disorder. Treating sleep problems in patients with generalized anxiety, along with therapy for generalized anxiety, results in better outcomes for both anxiety and sleep, but the data are not as robust as for the concomitant treatment of pain and disordered sleep.

PHYLLIS C. ZEE, MD, PhD: Asthma can certainly disrupt sleep. When patients with asthma come to our sleep clinic, the first thing I do is review their asthma medications because bronchodilators and corticosteroids can disrupt sleep and exacerbate insomnia.

SHERRI L. TEN PAS, DO, DABSM: There is a lot of good information on insomnia and depression, and again we're faced with the same chicken and egg scenario. A multinational study performed in 2003 in Europe showed that insomnia predates the onset of the first episode of depression in approximately 40% of cases and follows the onset of depression in approximately 30% of cases. In approximately 30% of cases, the onset of both conditions was recorded at about the same time. At some point in the future, when we have a better understanding of the molecular basis of insomnia and its comorbidities, I think we're going to be surprised at how closely related some of these conditions might be.

STEPHEN H. SHELDON, DO, FAAP: Could you expand on the molecular basis of insomnia?

ANDREW D. KRYSTAL, MD, MS: I don't think we have an understanding of that, but it's very clear from the available data that people with insomnia are at risk for future depression and that people with depression have a high rate of insomnia. What we don't currently understand is whether these are causal or correlative relationships. There may be a common underlying predisposing factor that makes one prone to both poor sleep and depression, or these two conditions may be causally related. We just don't know at this point.

PHYLLIS C. ZEE, MD, PhD: The prevailing hypothesis is that there is a shared vulnerability at a genetic level. One idea that has piqued some interest is the relationship

between circadian clock gene polymorphisms and the vulnerability for both depression and insomnia. To be clear, it's not causative, but this type of thinking may ultimately yield evidence that suggests there is a common or shared vulnerability.

The Physiological Basis of Insomnia

STEPHEN H. SHELDON, DO, FAAP: Let's now turn our attention to the physiological underpinnings of insomnia. Dr. Zee, can you give us a brief review of the neurotransmitters involved in regulating the sleep/wakefulness cycle?

“The hypocretin/orexin system innervates brain structures involved in both sleep and wakefulness.”

— Dr. Zee

PHYLLIS C. ZEE, MD, PhD: The sleep/wake cycle is regulated by brain centers that control sleep and centers that control wakefulness. Consequently, we should think about sleep and wakefulness in terms of how these centers interact to create a state of wakefulness or one of sleepiness.

Wakefulness is promoted by several brain centers, including the basal forebrain, the tuberomammillary nucleus, the raphe nucleus, and the locus coeruleus of the brainstem.

On activation, neurons in these centers produce neurotransmitters that promote wakefulness. For example, the basal forebrain produces acetylcholine, the tuberomammillary nucleus produces histamine, and the structures in the brainstem produce monoamines, serotonin, and, most importantly, norepinephrine. When neurons innervating these centers are activated, the person is awake and alert.

Conversely, neurons found primarily in the hypothalamus actively promote sleep, including the ventrolateral preoptic nucleus, which is GABAergic. Incidentally, the ventrolateral preoptic nucleus is often a therapeutic target of treatments for patients with insomnia, specifically the benzodiazepine receptor antagonists, which modulate gamma-aminobutyric acid (GABA) production.

The hypocretin/orexin system innervates brain structures involved in both sleep and wakefulness. Orexin-expressing neurons originate from the lateral hypothalamus and extend throughout the brain, where they innervate neural centers involved in wake-state control.

The orexin neurons fire rapidly during active wakefulness and progressively decrease firing from quiet wakefulness to sleep. It is important to note that activity of the orexin system stabilizes the state of wakefulness. Conversely, removal of the alerting stimuli produced by orexin neurons stabilizes sleep. Thus, insomnia may be at least partially explained as an instability or imbalance in the neuronal communication between wake-promoting and sleep-promoting sensors.

“There are sleep-promoting and wake-promoting regions that are in balance with each other. Insomnia can be seen as a function of an imbalance between these systems.”

— Dr. Krystal

ANDREW D. KRISTAL, MD, MS: We have wanted to develop a model of insomnia based on the existence of an abnormality in a single neurotransmitter system or region of the brain that has not been identified. It appears more likely that the model Phyllis described is correct—that there are sleep-promoting and wake-promoting regions

that are in balance with each other. Insomnia can be seen as a function of an imbalance between these systems. The fact that we can use benzodiazepines to enhance sleep, as Phyllis said, is presumably because they can shut down a lot of these wake-promoting systems.

The wake-promoting systems function relatively independently of sleep-promoting systems and we now have reason to believe that, based on indirect evidence, there is some increased activation in several of these systems during sleep. For example, if we block the histamine system with doses of a selective antihistamines such as mirtazapine or doxepin that is below the approved dosages for depression, we see specific sleep-enhancing effects in people with insomnia, which, interestingly, is greater toward the end of the night.

A better understanding of how orexins affect the sleep-wake cycle has led to the development of a new class of therapies that antagonize the physiological effects of orexin (ie, orexin antagonists). Recently presented data show that sleep can be improved with orexin antagonism. These data suggest that an increase in orexin neuronal activity and/or diminished activity in GABA neurons may create an imbalance that can be corrected with orexin blockade.¹²⁻¹⁴ We also have similar data suggesting that blocking the adrenergic system improves sleep in patients with anxiety disorder.

These data suggest that wake-promoting systems are more active in patients with insomnia, but we just don't know at this point whether this a specific cause of insomnia or an imbalance between the wake- and sleep-promoting systems.

STEPHEN H. SHELDON, DO, FAAP: Is it fair to say that this imbalance ultimately results in the hyperarousal state that we discussed earlier?

PHYLLIS C. ZEE, MD, PhD: Increased activity of wake centers contributes to the imbalance, but there is perhaps also the potential for hyperarousal at a cognitive or cortical level that interacts with sleep/wake centers in the hypothalamus and in the brainstem.

SHERRI L. TEN PAS, DO, DABSM: To follow up on what Dr. Zee was saying, there are some studies that suggest a neurocognitive role in the pathophysiology of insomnia. In other words, insomnia may develop from conditioned cortical arousal developed between the association of sleep, related stimuli, and encountered sleep difficulties.

There is also a psychological model theorizing that insomnia is not just heightened cortical arousal, but also an inability to disengage or de-arouse. Certainly other medical, behavioral, and environmental factors play a role as well.

ANDREW D. KRISTAL, MD, MS: These are interesting models, but the factors that predispose a patient to insomnia are still poorly understood. We briefly discussed earlier that patients with insomnia have trouble falling asleep due to a state of hyperarousal; they have a problem shutting down regardless of the time of day or night. Part of the hyperarousal model includes factors beyond sleep that have been identified in a series of studies conducted by Bonnet et al.¹⁵ These investigators identified that in patients with primary insomnia—the subgroup of patients without associated medical or psychiatric conditions and who are the easiest to study due to a lack of comorbidities and concomitant medication use—had elevated 24-hour metabolic rates, elevated 24-hour core body temperatures, and elevated heart rates, all indicators of systemic arousal. These patients also had difficulties falling asleep within the 24-hour period. Hyperactivation of the sympathetic nervous system may have caused the heightened arousal observed in these patients, and contributed to their inability to fall asleep. However, it is possible that increased nervous system activity is a manifestation and not a cause of the sleep disorder.

These same investigators also conducted a study in which they yoked a group of patients with primary insomnia to a group of healthy controls to test the hypothesis that the hyperarousal state might actually be created by a poor sleep experience. Yoking the control patients to the patients with insomnia forced those with previously normal sleep patterns to have the exact same

sleep schedule as the patients with insomnia for 1 week. Despite the disruption in their normal sleep pattern, the control patients did not show any of the hyperarousal signs observed in patients with insomnia. The control patients showed sleep deprivation and daytime sleepiness, but they fell asleep faster and did not exhibit any changes in core body temperature or metabolic rate compared with those with insomnia. An argument can be made that the sleep disruption in the yoking study wasn't long enough to cause insomnia, but as far as we know at this point, it seems that insomnia disorder is associated with an alteration in physiology and is not a consequence of poor sleep.

“Recent evidence suggests insomnia is associated with inappropriate physiological arousal, and this hyperarousal may be minimized with treatments that target the hypocretin/orexin system.”

— Dr. Sheldon

Concluding Thoughts

STEPHEN H. SHELDON, DO, FAAP: This has been a fascinating discussion. To close our session, I would like to ask each of the panelists to provide a take-home message for our colleagues who care for patients with insomnia in the primary care setting.

SHERRI L. TEN PAS, DO, DABSM: A simple screen for insomnia can start with 2 easy questions: Do you have trouble sleeping at night? Do you feel refreshed upon awakening?

Also, before considering prescription medications for insomnia, be sure to conduct a thorough review of the

patient's sleep history to determine the etiology of the sleep disruption. It's critical to make sure that underlying conditions such as sleep apnea and periodic limb movements are not missed. A hypnotic agent can help temporarily for these conditions, but they are more of a bandage than an appropriate treatment, so the differential is really important.

STEPHEN H. SHELDON, DO, FAAP: Appropriate diagnosis is the key. Phyllis?

PHYLLIS C. ZEE, MD, PhD: Ask every patient how satisfied they are with their sleep, whether they are getting adequate hours of sleep and quality of sleep, and go from there. It's really important to identify sleep difficulty because it is so common and because proper management and treatment begins with identification of the problem.

ANDREW D. KRYSTAL, MD, MS: I would reiterate that physicians should ask their patients about insomnia and institute effective treatment. Physicians should also appreciate that they can provide therapies that will really help these patients in a short time.

We need to be aware that there is a subgroup of patients who have lifelong, chronic insomnia—idiopathic insomnia—and we don't know the cause. These patients should be treated despite not knowing the etiology of their condition.

SHERRI L. TEN PAS, DO, DABSM: That's a very important point, Andy. We need to determine whether a patient has primary insomnia or insomnia secondary to another condition. It's important to approach a patient who comes into the office saying, “I've never slept well,” a little differently than you would one who reports new problems sleeping at night.

STEPHEN H. SHELDON, DO, FAAP: Summarizing briefly, primary care physicians are well positioned to identify and manage patients with insomnia. Patients rarely come to the office because they are sleep deprived. Rather, sleep disorders are frequently identified with simple questions about sleep habits and careful probing of symptoms.

Insomnia has potentially serious consequences and is frequently comorbid with several other chronic diseases, including cardiometabolic disorders.

Recent evidence suggests that insomnia is associated with inappropriate physiological arousal, and this hyperarousal may be minimized with treatments that target the hypocretin/orexin system.

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Monograph Postactivity Test

The purpose of this postactivity test is to provide a convenient means for osteopathic physicians to assess their understanding of the scientific content in the monograph that accompanied the September 2013 issue of *The Journal of the American Osteopathic Association*.

To apply for 2 credits of Category 1-B continuing medical education (CME), osteopathic physicians may take this postactivity test online at <http://www.osteopathic.org/docmeonline> by September 30, 2014. Postactivity tests that are completed online will be graded and credited to DOs' CME activity reports.

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CME credit will be applied to the following CME cycle: 2013-2015.

1. Choose the correct answer: Which of the following statements regarding the incidence of insomnia is FALSE?

- ☐ a. Chronic insomnia affects 5% to 10% of American adults.
- ☐ b. Chronic insomnia affects 10% to 15% of American adults.
- ☐ c. Chronic insomnia may be present in 25% of older adults.
- ☐ d. Transient insomnia is experienced by 25% to 35% of American adults.
- ☐ e. Insomnia is present in 40% to 50% of noninstitutionalized elderly persons.

2. Choose the correct answer: Which of the following is NOT a risk factor for the development of insomnia?

- ☐ a. Comorbid medical disorders
- ☐ b. Psychiatric disorders
- ☐ c. Ethnicity
- ☐ d. Working nights or rotating shifts
- ☐ e. Age and sex

3. Choose the correct answer: Which of the following statements regarding insomnia in patients during sleep is TRUE?

- ☐ a. During sleep, patients have heightened arousal but not throughout the circadian cycle.
- ☐ b. During sleep, patients have increased high-frequency electroencephalogram activation and elevated cortisol secretion but not adrenocorticotrophic hormone secretion.
- ☐ c. During sleep, patients have attenuated nighttime melatonin secretion.
- ☐ d. During sleep, patients have increased whole-body and brain metabolic activation and elevated heart rate but no sympathetic nervous system activation.
- ☐ e. All of the above are true.

4. Choose the correct answer: In patients with insomnia, the circadian rhythmicity of hypocretin/orexin neuropeptide levels decreases with waking and rises during the night. Suvorexant is a hypocretin/orexin _____.

- ☐ a. specific enzyme
- ☐ b. precursor
- ☐ c. receptor agonist
- ☐ d. receptor antagonist

5. Choose the correct answer: Which of the following statements regarding poor quality of sleep and a lack of deep sleep is FALSE?

- ☐ a. Associated with obesity and diabetes but not cardiovascular disease
- ☐ b. Affect cognition, learning, laying down memories, physical performance, and mental health
- ☐ c. Associated with a higher risk of accidents, depression, and anxiety disorders
- ☐ d. Are modifiable risk factors
- ☐ e. Important to overall physical, cognitive, and neurological health

6. Choose the correct answer: Approximately what percentage of workplace accidents are caused by insomnia?

- ☐ a. 5%
- ☐ b. 10%
- ☐ c. 15%
- ☐ d. 25%
- ☐ e. 50%

7. Choose the correct answer: Which of the following statements regarding insomnia, hyperarousal syndrome, and sleep deprivation is TRUE?

- ☐ a. Patients with insomnia do not typically experience sleepiness during the day.
- ☐ b. Daytime sleepiness is typical of patients with sleep deprivation.

- ☐ c. Daytime sleepiness is typical of patients with sleep apnea or narcolepsy.
- ☐ d. Hyperarousal syndrome can be attributed to hyperactivation of the sympathetic nervous system.
- ☐ e. All of the above.

8. Choose the correct answer: According to a survey conducted by the National Center for Health Statistics

- ☐ a. Women report sleep disturbances more than men.
- ☐ b. The percentage of women diagnosed and treated for a sleep disorder is the same as that of men.
- ☐ c. Women report sleep disturbances less than men.
- ☐ d. The percentage of women diagnosed and treated for a sleep disorder is less than that of men.
- ☐ e. a and b are correct.

9. True or False: Good-quality sleep can improve a patient's pain threshold.

- ☐ a. True
- ☐ b. False

10. Choose the correct answer: Which of the following statements is FALSE?

- ☐ a. Insomnia predates the onset of the first episode of depression approximately 40% of the time.
- ☐ b. Insomnia follows the onset of depression approximately 30% of the time.
- ☐ c. Insomnia and depression are recorded simultaneously approximately 30% of the time.
- ☐ d. The onset of insomnia and depression rarely, if ever, coincide.
- ☐ e. People with depression have a high rate of insomnia.

11. Choose the correct answer: Which of the following neurotransmitters is responsible for promoting sleep?

- ☐ a. Acetylcholine
- ☐ b. Histamine
- ☐ c. Norepinephrine
- ☐ d. Serotonin
- ☐ e. GABA

12. Choose the correct answer: The hypocretin/orexin system, which innervates brain structures involved in both sleep and wakefulness, is located in the

- ☐ a. Basal forebrain
- ☐ b. Lateral hypothalamus
- ☐ c. Tuberonnammillary nucleus
- ☐ d. Raphe nucleus
- ☐ e. Locus coeruleus of the brain stem

Evaluation

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly agree	
Learning Objectives		After participating in this activity, I am now better able to:			
Define insomnia as a hyperarousal state vs a lack of sleep	1	2	3	4	5
Explain the sleep/wake cycle	1	2	3	4	5
Review the current status of treatment	1	2	3	4	5
Identify unmet treatment needs	1	2	3	4	5
Discuss the science of emerging treatments	1	2	3	4	5
Explain how orexins fit within the sleep/wake cycle	1	2	3	4	5

Based on your participation in this activity, choose the statements that apply:

- ☐ I gained new strategies, skills, and information that I can apply to my area of practice.
☐ I plan to implement new strategies, skills, and information into my practice.
☐ I need more information before I can implement new strategies, skills, and information into my practice behavior.
☐ This activity will not change my practice, as my current practice is consistent with the information presented.
☐ This activity will not change my practice, as I do not agree with the information presented.

What strategies and changes do you plan to implement into your practice?

How confident are you that you will be able to make this change?

- ☐ Very confident ☐ Somewhat confident ☐ Unsure ☐ Not very confident

What barriers do you see to making a change in your practice?

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly agree	
The content presentation:					
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Promoted improvements or quality in health care	1	2	3	4	5
Was scientifically rigorous and evidence-based	1	2	3	4	5
Avoided commercial bias or influence (Provide details of any perceived bias in the comments section below.)	1	2	3	4	5
Provided appropriate and effective opportunities for active learning (eg, case studies, discussion, question and answer, etc)	1	2	3	4	5
Provided an opportunity to assess learning which was appropriate to the activity.	1	2	3	4	5

Would you be willing to participate in a post-activity follow-up survey? ☐ Yes ☐ No

Please list any clinical issues or problems within your scope of practice you would like to see addressed in future educational activities or provide details of any perceived bias:

Evolving Science and Emerging Approaches to Improving Outcomes for Patients With Insomnia

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