The Future Treatment of Insomnia:
Exploring the Mechanisms of Action of Current and Emerging Therapies

An Educational Monograph Based on an Expert Roundtable Discussion

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The Future Treatment of Insomnia: Exploring the Mechanisms of Action of Current and Emerging Therapies

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 a timely and relevant evidence-based update on emerging concepts underlying the neurophysiology of the sleep-wake cycle and the neurobiology of sleep wakefulness. In addition, this activity will compare and contrast the mechanisms of action of current and emerging insomnia therapies.

Educational Objectives
• Define the overall burden of insomnia disorder
• Describe recent advances in the understanding of the underlying pathophysiology of insomnia disorder
• Discuss emerging concepts that relate to the control of the sleep-wake cycle
• Differentiate the mechanisms of action of current and emerging therapies for insomnia disorder

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Unmet Needs in Sleep Medicine and Recent Advances in the Understanding of the Pathophysiology of Insomnia

Abstract

Insomnia is highly prevalent in modern-day society, and sleeplessness is one of the most common symptoms reported by patients in the primary care setting. Insomnia disorder is a risk factor for the development of mental conditions but is also a potential indicator of serious mental or medical issues such as depression, anxiety, congestive heart failure, osteoarthritis, and Parkinson’s disease. Insomnia disorder is diagnosed through comprehensive assessment, including a detailed patient history, physical examination, and questionnaires and sleep diaries. Treatments include behavioral therapies and pharmacological interventions.

Introduction to Insomnia: Unmet Medical Needs

Insomnia disorder is defined as disturbed sleep in the presence of adequate opportunity and circumstance for sleep and is characterized by difficulty initiating sleep (sleep-onset insomnia), frequent or long nighttime awakenings (sleep-maintenance insomnia), and waking up too early without being able to return to sleep (early morning insomnia). A fourth characteristic, nonrestorative or poor-quality sleep, may also be included as part of the definition, although this is not universally accepted.

Insomnia disorder lasts for at least 3 months and may be precipitated by a traumatic event; emotional, personal, or work-related stress; travel across time zones; or other events that initially disrupted sleep habits. Insomnia disorder does not occur secondary to another medical condition but rather is often comorbid with medical conditions such as chronic pain, high blood pressure, obesity or weight gain, obstructive sleep apnea, gastrointestinal problems, urinary problems, osteoarthritis, hip impairment, fibromyalgia, peptic ulcer disease, and breathing problems.

Insomnia disorder can have a negative impact on a person’s daytime functioning and quality of life. In addition to fatigue, insomnia can cause irritability, anxiety, and loss of concentration. It has also been associated with increased rates of motor vehicle accidents and higher rates of occupational injury. People with insomnia disorder have a lower self-reported overall health status and higher level of bodily pain, both of which contribute to reduced quality of life.

Determining the true prevalence of insomnia disorder is complicated because of patient underreporting and the use of different definitions of insomnia. In the United States, an estimated 50 to 70 million adults have chronic sleep and wakefulness disorders. Risk factors for insomnia disorder include female sex; increasing age; low income status; shift work; elevated levels of personal, emotional, and occupational stress; and the presence of medical conditions or sleep disorders that can disrupt sleep. Although older age is associated with an increased risk of insomnia disorder, the condition has been found to peak in middle age (range, 45–54 years), decrease slightly during older age (range, 65–84 years), and increase again in very old age (>85 years).

The annual cost of insomnia disorder in the United States is estimated to range between $30 and $107 billion. This total includes direct costs of $12 to $14 billion for expenses such as medical appointments, over-the-counter sleep aids, and prescription medication as well as indirect costs associated with lost productivity due to absenteeism, reduced quality of life, and accidents and injuries.

The primary care physician or family physician is often the first health care professional to hear about a patient’s sleep difficulties. It is estimated that 52% to 64% of primary care patients have sleep complaints, and 10% to 14% have severe insomnia that interferes with daytime functioning. Insomnia disorder tends not to resolve by itself, and patients often endure it for years without effective help. Although primary care is the ideal place to treat patients with insomnia disorder, the diagnosis can be difficult because of frequent overlap between symptoms of insomnia and disrupted sleep due to lifestyle or environmental factors not associated with insomnia disorder.

People with sleep disorders tend to seek treatment when symptoms such as fatigue, impaired daytime functioning, and the inability to concentrate become bothersome. The American Academy of Sleep Medicine guidelines outline treatment goals for insomnia, including reduction of sleep and waking symptoms and improvement in daytime functioning, and stress the importance of identifying and treating comorbid conditions.

Patients with trouble sleeping often turn to over-the-counter sleep aids and homeopathic remedies such as valerian, chamomile, and St John’s wort prior to discussing their sleep concerns with a health care practitioner. While widely used, few of these agents have been systematically studied in clinical trials. Furthermore, the safety and efficacy of these agents have not been reviewed by the Food and Drug Administration. Once a diagnosis of insomnia disorder has been confirmed by a health care provider, several interventions are available, including lifestyle changes, behavioral and psychological interventions, and prescription medications.

Nonpharmacological treatments with published reports attesting to their efficacy include behavioral and cognitive techniques that modify the precipitating and perpetuating factors that contribute to insomnia. Several classes of prescription agents are also widely used in the management of insomnia disorder, including benzodiazepines, nonbenzodiazepine hypnotics, and ramelteon, as well as antidepressants that target the serotonergic system. Benzodiazepines are known for their effectiveness in increasing total sleep time by reducing the time to sleep onset and the number of nighttime awakenings. However, their long-term use is limited by a negative effect on memory and recall and next-day sleepiness, and continued use may increase the risk of habituation. Nonbenzodiazepine hypnotics such as zolpidem tartrate, zolpidem tartrate extended-release, zaleplon, and eszopiclone have efficacy similar to the benzodiazepines but offer more favorable safety and tolerability profiles. Use of nonbenzodiazepine hypnotics may also be limited by an increased risk of habituation with long-term use. Antidepressants and antipsychotics such as amitriptyline hydrochloride, trazodone
hydrochloride, mirtazapine, and quetiapine are sometimes also used to treat insomnia, although these are used off-label and are associated with dizziness, psychomotor impairment, and other serious adverse events. The selective histamine receptor antagonist doxepin was approved for the treatment of depression in 1969, but more recently, low-dose doxepin received an indication for the treatment of insomnia characterized by difficulty maintaining sleep. Furthermore, few studies have specifically examined the efficacy and safety of antidepressants in the treatment of insomnia.

Pathophysiology of Insomnia Disorder: Recent Advances

Our understanding of the neurobiology of sleep has advanced significantly in recent years with the introduction of experimental techniques that allow access to sleep-wake centers in the brain. One such advance occurred in 1998 with the discovery of the orexin (hypocretin) system. Orexins are neuropeptides synthesized predominantly in the posterior and lateral hypothalamus. Orexinergic neurons activate waking active monoaminergic and cholinergic neurons in the hypothalamus and brainstem regions to maintain a long, consolidated waking period. They also receive abundant input from the limbic system. The clinical utility of the orexin pathway was clarified when studies designed to disrupt the orexin pathway using orexin knockout and orexin receptor 2 gene mutation produced animals with narcolepsy and cataplexy. It has been reported that 90% of humans with narcolepsy and cataplexy have nearly undetectable levels of orexin in their cerebrospinal fluid. Furthermore, humans with narcolepsy have a 90% reduction in brain orexin neurons. Of all the arousal systems discussed, the orexin system seems to have the most potent effect on maintaining wakefulness. These experiments highlighted the consequence of a defective orexin system in the ability to maintain wakefulness. The orexin system thus performs its critical role of maintaining wakefulness. These experiments have provided novel targets for the development of agents to manage clinical sleep disorders such as insomnia.

The first of these agents, the highly selective orexin receptor antagonist suvorexant, was approved by the Food and Drug Administration in August 2014 for the treatment of adults with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Summary

People with sleep disorders tend to seek treatment when symptoms such as fatigue, impaired daytime functioning, and the inability to concentrate become bothersome. Once a diagnosis of insomnia disorder is confirmed, therapeutic interventions such as behavioral and psychological interventions and prescription medications are available. Recent progress has elucidated more clearly the mechanisms underlying the regulation of sleep and wakefulness. Novel insomnia therapies are now being developed to exploit these newly discovered therapeutic targets.

References

An Expert Roundtable Monograph for Osteopathic Physicians

Abstract

Insomnia is one of the most common symptoms reported in clinical practice. Cardinal features of insomnia include difficulty initiating or maintaining sleep with impairment of daytime functioning. Insomnia results from a variety of genetic, environmental, behavioral, and physiological factors, culminating in hyperarousal. Insomnia is associated with poor quality of life and an increased risk of other medical and mental disorders. Current treatment options include pharmacological therapy and cognitive behavioral therapy for insomnia. Behavioral treatments should be implemented whenever possible, and medications should be used at the lowest effective dose for the shortest duration possible. Among pharmacological therapies, the most evidence exists for the benzodiazepine receptor agonists, but these drugs must be carefully monitored for adverse effects. Neuropeptides arising from the orexin (hypocretin) system have been shown to regulate the sleep-wake cycle, leading to the development of orexin antagonists. Increased understanding of this pathway may lead to novel therapies for insomnia without the side effect profile of currently available agents. In this roundtable discussion, relevant data on the future treatment of insomnia are discussed, specifically the mechanisms of action of current and emerging therapies.

Introduction

STEPHEN H. SHELDON, DO, FAAP: Welcome to the roundtable discussion entitled The Future Treatment of Insomnia: Exploring the Mechanisms of Action of Current and Emerging Therapies. I am Stephen Sheldon, Professor of Pediatrics and Neurology at the Northwestern University, Feinberg School of Medicine and Director of the Sleep Medicine Center at the Ann & Robert H. Lurie Children’s Hospital of Chicago.

Joining me are Dr. Sonia Ancoli-Israel, Professor Emeritus of Psychiatry and Medicine at the University of California, San Diego; Dr. Allen Blaivas, Director of the Sleep Clinic at the Veterans Administration Health Care System in East Orange, New Jersey; and Dr. David Neubauer, Associate Professor at the Johns Hopkins Bayview Medical Center in Baltimore, Maryland.

The purpose of our discussion is to provide osteopathic physicians with continuing medical education that offers timely and relevant data on the future treatment of insomnia, specifically the mechanisms of action of current and emerging therapies.

Insomnia: Defining the Problem

STEPHEN H. SHELDON, DO, FAAP: Sleep difficulties are one of the most common symptoms reported by patients during a primary care office visit. Inadequate sleep is often associated with a decline in health and behavior and can markedly impair a patient’s and their family’s quality of life. Dr. Blaivas, how common is it for an adult presenting to a primary care practice to report some type of sleep disorder?

ALLEN J. BLAIVAS, DO: It is estimated that between 33% and 50% of people in the United States have some form of insomnia over the course of 1 year.1 A recent study by the National Sleep Foundation reported that approximately 22% of American adults experience insomnia on a nightly basis.2 At any given time, approximately 10% of the population has a diagnosis of chronic insomnia.3 Insomnia is also one of the most common sleep complaints reported to pediatric primary care physicians.

STEPHEN H. SHELDON, DO, FAAP: Are you saying that insufficient sleep is a combination of both a sleep disorder and a lifestyle?

SONIA ANCOLI-ISRAEL, PhD: Yes, in some cases it is one or the other, but often it is both.

STEPHEN H. SHELDON, DO, FAAP: Dr. Neubauer, what is the relationship between sleep/insomnia and chronic illness or chronic disease?

DAVID NEUBAUER, MD: Both our clinical experience and the epidemiological research show that those who sleep less are more likely to have chronic illness. The reverse is also true: people with more chronic disorders tend to report disruptions in their sleep patterns, whether it is simply the amount of sleep they get each night, the quality of sleep, or the experience of sleep.

A number of published reports have examined the relationship between reported sleep duration and all-cause mortality. Most of these studies have identified a U-shaped curve, with both short-duration and long-duration sleepers at greater risk for increased all-cause mortality.4
A meta-analysis published in *Sleep* in 2010 pooled data from 16 studies that included 1,382,999 male and female participants (follow-up range, 4 to 25 years) and 112,566 deaths. This analysis identified a 12% greater risk of mortality among short-duration sleepers (commonly <7 hours per night, often <5 hours per night). A long duration of sleep (commonly >8 or 9 hours per night) was also associated with a 30% greater risk of dying compared with those sleeping 7 to 8 hours per night.

Other health conditions can contribute to greater morbidity and mortality in people who do not receive sufficient sleep. The Centers for Disease Control and Prevention (CDC) notes on its website that insufficient sleep is associated with increased risk of depression, obesity, type 2 diabetes mellitus, and cardiovascular disease, including hypertension, stroke, coronary heart disease, and cardiac arrhythmias.

The results of the 2009 CDC Behavioral Risk Factor Surveillance System survey indicated that approximately 33% of the 54,000 adults older than 45 years of age who completed the survey slept ≤6 hours each night (ie, "short sleepers"). On the other end of the spectrum, approximately 4% reported sleeping ≥10 hours each night (ie, "long sleepers"). After controlling for sex, age, race, ethnicity, and education, both the short sleepers and long sleepers had an increased risk of obesity, coronary heart disease, stroke, diabetes, and frequent mental distress.

What is causing the excess mortality? This is difficult to measure in larger population studies, but a number of smaller laboratory-based sleep deprivation studies suggest that abnormalities in hormonal, immune, and inflammatory processes may be driving the increased mortality. For example, the satiety hormone leptin is decreased with a short duration of sleep, leading to increased appetite and perhaps obesity. In a complementary manner, ghrelin, along with various inflammatory markers including tumor necrosis factor alpha, interleukin-6, and C-reactive protein, are all elevated with a short duration of sleep. Various types of cancer are associated with short duration of sleep or abnormal sleep-wake schedules, such as with shift work, including breast, thyroid, prostate, and colorectal cancers. In addition, people who sleep less are of course more likely to be sleepier and inattentive during the day, increasing the risk of various types of accidents.

The bottom line is that sleep interfaces with nearly all aspects of our physical and mental health, and we should encourage our patients to make it a high priority in their lives.

"...a number of smaller laboratory-based sleep deprivation studies suggest that abnormalities in hormonal, immune, and inflammatory processes may be driving the increased mortality."

– Dr. Neubauer

**STEPHEN H. SHELDON, DO, FAAP:** It appears that there may be a bidirectional cause and effect with comorbidity. What is the recommended amount of sleep for an otherwise healthy adult?

**SONIA ANCOLI-ISRAEL, PhD:** We generally recommend 7 to 8 hours of sleep per night. We work with our patients to help them determine the amount of sleep they need to function at their optimal level. The challenge is that the sleepier people are, the less aware they are of their level of sleepiness and dysfunction. It is not uncommon for a patient to say "I sleep 5 hours a night and I’m doing just fine." However, if you ask the people around that patient, they will note that the patient’s performance is decreased or there are other problems. Therefore, we encourage people to try to get 7 to 8 hours of sleep each night.

**STEPHEN H. SHELDON, DO, FAAP:** Is this related to the homeostatic sleep need or circadian mechanisms? Is there a basal sleep need? And what about sleep debt?

**ALLEN J. BLAIVAS, DO:** The amount of sleep a person needs to be at his or her best is what we consider basal sleep time: between 7 and 9 hours. There is always a competition between sleep debt and basal sleep. Most people do not sleep enough; the total average duration of sleep is usually less than 7 hours. A lack of sleep causes sleep debt, which is defined as the difference between our basal sleep need and the total amount of sleep we lose each night.

"The amount of sleep a person needs to be at his or her best is what we consider basal sleep time: between 7 and 9 hours. There is always a competition between sleep debt and basal sleep."

– Dr. Blaivas

**STEPHEN H. SHELDON, DO, FAAP:** Can a sleep debt be “paid back”?

**SONIA ANCOLI-ISRAEL, PhD:** Yes, it can, but if a person has chronic partial sleep deprivation, it could take as many as 5 days of sleep beyond his or her basal needs to make up the sleep debt. Unfortunately, sleeping in a few hours on Saturday or Sunday morning will not make up for sleep lost during the week.

**STEPHEN H. SHELDON, DO, FAAP:** Does the quality of sleep affect daytime performance as much as the quantity of sleep?

**SONIA ANCOLI-ISRAEL, PhD:** Sleeping 8 to 10 hours each day can indicate the presence of a sleeping disorder, particularly if the patient reports feeling drowsy or fatigued during the day.
The Future Treatment of Insomnia: Exploring the Mechanisms of Action of Current and Emerging Therapies

**ALLEN J. BLAIVAS, DO:** I agree. If a patient who reports sleeping 8 to 10 hours has symptoms of tiredness, he or she should be evaluated for a sleep disorder in the sleep laboratory to rule out the presence of sleep apnea or another condition that might be causing the problem.

**STEPHEN H. SHELDON, DO, FAAP:** Is sleep quality assessed in the sleep laboratory?

**ALLEN J. BLAIVAS, DO:** Not really. Part of the problem is that a good definition of “sleep quality” cannot be found in the literature, and we depend on both subjective patient reports and objective clinical findings to assess sleep quality.

A recent study attempted to assess sleep quality by investigating whether subjects who self-identified as “normal sleepers” might have disturbed sleep when evaluated using objective techniques. The results showed that several people who objectively had “normal” sleep reported always feeling tired and not sleeping well. The group that reported subjective insomnia had more depression and anxiety and had dysfunctional beliefs about their sleep compared with a “normal sleeper.” Therefore, it can be difficult to assess sleep quality because clinical observations and self-reports often do not translate into what we see in laboratory studies.

“...it can be difficult to assess sleep quality because clinical observations and self-reports often do not translate into what we see in laboratory studies.”
—Dr. Blaivas

**DAVID NEUBAUER, MD:** I agree with Dr. Blaivas. We do not have objective criteria that clearly define sleep quality, particularly for a person reporting insomnia. Although it is hard to objectively quantify this, the bottom line is how the person feels the next day and how they retrospectively interpret their nighttime experience. This situation is further complicated by the fact that patients’ subjective descriptions frequently do not correspond to the data generated by a laboratory-based sleep study. In fact, it is not uncommon for patients to report that their sleep experience was poor despite being shown strong laboratory evidence indicating that their sleep quality was high. Conversely, the results of a sleep study may look awful, yet the patient will come in and say “that was a good night of sleep for me.”

**SONIA ANCOLI-ISRAEL, PhD:** This is why we do not conduct an overnight sleep study on our patients with insomnia. A diagnosis of insomnia is really based on what the patients perceive and what they are reporting; it is very subjective.

**STEPHEN H. SHELDON, DO, FAAP:** Is it correct to say that the most important aspect of diagnosis is a clinical assessment and evaluation of the patient?

**SONIA ANCOLI-ISRAEL, PhD:** Yes, and taking the time to listen to the patient.

**ALLEN J. BLAIVAS, DO:** If you talk to patients long enough, they will tell you exactly what is wrong with them.

**DAVID NEUBAUER, MD:** If you are lucky, you can also talk to the family members; they can provide valuable collateral information, which is especially important for sleep problems.

**STEPHEN H. SHELDON, DO, FAAP:** Insomnia seems to be a huge problem, but is it often underreported or undertreated as a chronic condition?

**ALLEN J. BLAIVAS, DO:** By the time a sleep specialist sees these patients, it is already clear that there is a sleep problem. However, it is not so clear in the primary care setting, because most patients have been dealing with fatigue for so long that they are not aware there is a problem; they just assume it is normal. In addition, there often is insufficient time during a typical office visit to ask the questions needed to identify a sleep problem.

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—Dr. Blaivas

**STEPHEN H. SHELDON, DO, FAAP:** How is insomnia defined, and how is it assessed by the primary care physician?

**SONIA ANCOLI-ISRAEL, PhD:** There is no doubt that insomnia is underidentified. As we just heard, physicians frequently do not ask about it and patients often fail to mention it. In fact, we published a paper several years ago on data from a National Sleep Foundation survey showing that of all adults with chronic insomnia, two-thirds...
never discussed it with their physician. Furthermore, only 5% made an appointment specifically to have their sleep symptoms evaluated. Most patients only mentioned it if they happened to be in the clinic for some other reason.  

“…data from a National Sleep Foundation survey showing that of all adults with chronic insomnia, two-thirds never discussed it with their physician. Furthermore, only 5% made an appointment specifically to have their sleep symptoms evaluated.”

– Dr. Ancoli-Israel

STEPHEN H. SHELDON, DO, FAAP: Does the prevalence of insomnia vary by age, sex, and across a patient’s life cycle?

SONIA ANCOLI-ISRAEL, PhD: Yes. More women experience insomnia than men. In older adults, the prevalence is actually quite a bit higher, closer to 25%. In addition, in older adults, insomnia is almost always associated with either a comorbid condition or medications used to treat the comorbidity. Insomnia is also associated with changes in the circadian clock that occur with aging as well as with a higher prevalence of specific sleep disorders in the older population.

STEPHEN H. SHELDON, DO, FAAP: Is there a difference between primary insomnia and secondary insomnia?

SONIA ANCOLI-ISRAEL, PhD: Because there is no way of knowing what is cause and what is effect, we no longer use the terms “primary” or “secondary” insomnia. The new Diagnostic and Statistical Manual of Mental Disorders (DSM-5) refers to the condition as “insomnia disorder.” However, we may refer to insomnia as being comorbid because it occurs at the same time as other conditions.

The terminology is important because it can influence how we approach treatment. Referring to the condition as “insomnia disorder” or “comorbid insomnia” suggests that all conditions should be treated concurrently. For example, if a patient presents with depression and also reports problems sleeping, we do not treat the depression and wait to see what happens to the patient’s sleep; we treat both conditions simultaneously.

STEPHEN H. SHELDON, DO, FAAP: Dr. Blaivas, could you describe a typical patient who presents with insomnia?

ALLEN J. BLAIVAS, DO: It really could be any patient who walks into your office reporting difficulty falling asleep, frequent awakenings, difficulty returning to sleep, waking too early, or just sleep that does not feel restorative. Older people are at increased risk, particularly older women. Patients with comorbid medical and psychiatric conditions are also at higher risk.

In many cases, patients specifically report difficulty falling asleep or frequent awakenings. However, once you start asking questions, it becomes apparent that they are experiencing a whole constellation of sleep issues. Many patients develop maladaptive behaviors in an attempt to solve their sleep problem, but in the end they perpetuate the anxiety that revolves around their inability to fall asleep and the act of going to bed becomes anxiety provoking. For example, a patient with difficulty falling asleep stays in bed trying to get more sleep. Some patients begin to spend time in bed even though they are not sleeping. They talk on the telephone, watch television, use their computer, eat, and even smoke. All the time they are looking at the clock and wondering why they cannot fall asleep.

During the day, these people report feeling more weary than actually sleepy. Patients with true insomnia often are unable to fall asleep during the day no matter how tired they are.

SONIA ANCOLI-ISRAEL, PhD: Dr. Blaivas’ point about patients reporting feeling weary is worth emphasizing. Many patients will say “I have insomnia and I nap 2 hours during the day”; however, a person with insomnia is typically unable to nap during the day. This is a clue that there is something else going on other than insomnia.

“…we no longer use the terms ‘primary’ or ‘secondary’ insomnia. The new Diagnostic and Statistical Manual of Mental Disorders (DSM-5) refers to the condition as ‘insomnia disorder.’”

– Dr. Ancoli-Israel

STEPHEN H. SHELDON, DO, FAAP: Is there a difference between insomnia, sleepiness, and fatigue?

SONIA ANCOLI-ISRAEL, PhD: Yes; fatigue is not the same as sleepiness.

STEPHEN H. SHELDON, DO, FAAP: How do you differentiate fatigue from sleepiness?
DAVID NEUBAUER, MD: Patients often report sleep problems when they realize that their daytime functioning has deteriorated due to their inability to sleep well. Most often, patients say “I’m so tired,” but “tired” is too ambiguous to help establish a diagnosis. The classic patient with chronic insomnia has a decreased ability to sleep. In my practice, I attempt to differentiate whether the patient lacks energy, and perhaps motivation, due to physical or mental fatigue or if he or she typically sleeps during the daytime when given the opportunity.

Most patients will provide several clues to the presence of insomnia when you take their history. Most will describe how, despite not sleeping during the night, it is impossible for them to nap during the day even though they crave sleep. Tiredness is a great starting point to differentiate fatigue from sleepiness. Sleepiness should have the provider thinking about other disorders that might contribute to the sleep disorder, whereas fatigue should drive the physician to consider a differential diagnosis, including chronic insomnia.

STEPHEN H. SHELDON, DO, FAAP: Are there any specific questions the primary practitioner can ask to differentiate fatigue from sleepiness during the few minutes spent with the patient?

DAVID NEUBAUER, MD: The patient’s ability to sleep or nap is a pretty good clue. I would say that most patients with chronic insomnia are rarely able to sleep during the daytime. As a group, people with insomnia maintain a higher level of arousal throughout the 24-hour cycle and their inability to sleep at nighttime likely carries over into the daytime, preventing them from napping as well.

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– Dr. Neubauer

STEPHEN H. SHELDON, DO, FAAP: Dr. Ancoli-Israel, are there any current evidence-based guidelines to guide the treatment of patients with insomnia?

SONIA ANCOLI-ISRAEL, PhD: There is a large evidence base for the use of cognitive behavioral treatment for insomnia (CBTI). CBTI is the most effective and longest-lasting treatment available. The challenge is that the number of trained CBTI therapists is limited, so it can be difficult for patients to find a qualified practitioner.

Several medications are approved for the treatment of insomnia, including benzodiazepines, nonbenzodiazepines, a melatonin agonist, and low-dose doxepin. Patients with insomnia who have been successfully treated with these medications are likely to report improvement in daytime function, better quality of life, and less comorbidity. However, the evidence base for pharmacological therapy is not as robust as that for CBTI.

STEPHEN H. SHELDON, DO, FAAP: Is there any evidence regarding the combination of the two?

SONIA ANCOLI-ISRAEL, PhD: Yes. In certain patients, combining CBTI and pharmacological therapy is very effective, particularly in patients who find it difficult to initially comply with the behavioral intervention. I find it is effective to start with medication and then slowly wean the patient off the drug while continuing with the behavioral intervention.

In some cases, patients are prescribed medication before coming to our clinic. We often initiate behavioral training while they are still taking the medication; as favorable changes in their sleeping patterns occur, they often become willing to discontinue their medication.

Neurobiology of Sleep

STEPHEN H. SHELDON, DO, FAAP: I’d like to shift gears and discuss the neurobiology of sleep. The understanding of neurobiological mechanisms of sleep has increased dramatically over the past decade, driven largely by experimental techniques that allow direct access to sleep-wake centers in the brain. It is now understood that there are multiple neurochemical systems that promote wakefulness and sleep. Dr. Ancoli-Israel, can you briefly describe the sleep cycle and the sleep architecture in a healthy adult?

SONIA ANCOLI-ISRAEL, PhD: There are 4 stages of sleep: Stage (or N) 1, the very lightest stage, occurs just as a person dozes off. N2 and 3 are progressively deeper levels of sleep; N3 is the deepest level. The fourth stage is REM, or dream, sleep.

As the night progresses, the person starts in N1 and then proceeds through N2 and N3. The first REM period generally occurs 90 to 100 minutes after falling asleep. The person continues to cycle in and out of these different stages of sleep throughout the night.

Most of our deep sleep occurs in the first third of the night, and most of our dream sleep occurs in the last third of the night and the early morning hours. This sleep cycle is part of the circadian tendency. A person who takes an early morning nap is more likely to experience REM sleep. If that same person takes a late afternoon nap, he or she is more likely to go into deeper levels of sleep. Sleep is also controlled by the homeostatic drive and the circadian drive. The combination of these 2 processes helps the body determine when to sleep and when to be awake.

STEPHEN H. SHELDON, DO, FAAP: Dr. Neubauer, can you briefly describe the neural pathways involved in generating sleep and generating wakefulness?
DAVID NEUBAUER, MD: There are several ways to model the regulation of sleep and waking. One is to consider the normally coordinated effects of the homeostatic and circadian factors that Dr. Ancoli-Israel mentioned. The homeostatic drive basically represents the balance between wake and sleep; as humans, we are driven to want to sleep about one-third of the time (about 8 hours of a 24-hour period). If we get insufficient sleep, we become excessively sleepy, which can happen either acutely or chronically.

The homeostatic drive for sleep begins when we wake up and increases steadily until we sleep again. During sleep, that process is reversed. Whereas the homeostatic process determines how much sleep is needed, the circadian rhythm, which is biologically synchronized with the day-night cycle, optimizes the ability to achieve the required sleep during the night. The interaction between the homeostatic and circadian systems allows us to get up in the morning and remain awake and functioning for 16 hours and then to sleep for 8 hours at night.

STEPHEN H. SHELDON, DO, FAAP: What are the particular neural pathways that control the sleep-wake cycle?

DAVID NEUBAUER, MD: Our best understanding of the regulation of sleep and waking from a neurobiological point of view is what is sometimes described as the flip-flop switch model. This model highlights the activity of different nuclei in the hypothalamus, particularly the ventrolateral preoptic nucleus (the VLPO), and related regions.

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– Dr. Neubauer

The flip-flop model emphasizes the role of the orexin (hypocretin) system in promoting and stabilizing the waking state. Briefly, there is a mutual inhibition between the systems that promote wakefulness and sleeping. Several different neurotransmitters are involved in the promotion of sleep, with the best evidence for gamma-aminobutyric acid (GABA), the most widespread inhibitory neurotransmitter in the central nervous system.

The widely dispersed GABA neurons reinforce sleep on a global level within the central nervous system, but it is clear that there is a specific GABA action in the hypothalamus that plays a central role in promoting sleep. Consequently, GABA is considered one of the key neurotransmitters in the VLPO.

Sleep seems to be generated primarily within the preoptic hypothalamus and the adjacent basal forebrain region. In addition to GABA, some neurotransmitters may play a role (e.g., galanin). Aside from neurotransmitters, there are other substances involved. There is evidence that the accumulation of adenosine during wakefulness may promote sleepiness. Perhaps not surprisingly, we commonly use adenosine antagonists such as caffeine to promote wakefulness.

On the other side of the equation are multiple pathways and redundant neurotransmitters that promote wakefulness. There are ascending pathways arising from nuclei in the brainstem that produce acetylcholine, serotonin, norepinephrine, and dopamine. These neurotransmitters, along with histamine, which is produced in the hypothalamus, all have a stimulating effect. Some of these pathways pass through the thalamus, and others are wired directly into the hypothalamus.

Current evidence suggests that the orexin system, which is housed in the hypothalamus, ultimately coordinates these stimulatory activities via its widespread projections into other wake-promoting regions.

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– Dr. Neubauer

STEPHEN H. SHELDON, DO, FAAP: What is the role of melatonin?

DAVID NEUBAUER, MD: We have already discussed the role of the homeostatic and circadian systems and how they regulate the ability to be active 16 hours of the day and then able to sleep at night. Most people do not become progressively sleepy from the moment they awake until they go to sleep at night, despite the fact that there is an increase in the homeostatic process.

The homeostatic process is offset by the increasing stimulation caused by circadian arousal. As bedtime approaches, the melatonin level gradually increases and the circadian arousal simultaneously decreases, leaving the homeostatic drive for sleepiness unopposed. This explains why we can get into bed and fall asleep pretty easily at bedtime.
Melatonin facilitates sleep onset; through its circadian fluctuation, melatonin levels are very low throughout the daytime, gradually rise in the evening, plateau through the nighttime, and then decrease in the morning around the time we awake.

STEPHEN H. SHELDON, DO, FAAP: We all hear about patients who have a hard time unwinding at night and have difficulty falling asleep. Is this a state of hyperarousal, or is there such a state of hyperarousal that relates to insomnia?

DAVID NEUBAUER, MD: There are several reasons why people may feel like they cannot sleep because their mind is racing. Perhaps they had too much coffee after dinner, or they may have a delayed circadian pattern. In this situation, their programmed biological sleep onset time might be 3:00 am but, despite that, they go to bed at 11 pm. Many patients with chronic insomnia, however, have evolved into a pattern of hyperarousal that interferes with their ability to fall asleep.

STEPHEN H. SHELDON, DO, FAAP: Dr. Blaivas, what are the clinical implications for a patient like this?

“GABA is believed to be the primary inhibitory neurotransmitter, whereas orexin is implicated in the stimulation of the wake-promoting systems and the stabilization of the sleep-wake cycle. It has been suggested that GABA is primarily driven by the homeostatic process and orexins may be more driven by the circadian process.”

– Dr. Blaivas

ALLEN J. BLAIVAS, DO: As described earlier, the sleep-wake cycle is regulated by 2 processes: process S and process C. Process S is the homeostatic process, and process C is the circadian process. The imbalance between these 2 competing processes tips the balance from sleep to wakefulness.

Throughout the course of the day, the longer a person has been awake, the homeostatic drive promotes the release of neuromodulators that activate sleep-promoting systems and inhibit wake-promoting systems. This is counteracted by the circadian process, which has the tendency to keep us awake at particular times of the day. The point at which process S dominates process C has been described as a “switch,” but a seesaw analogy might be more appropriate if the balance eventually is tipped one way or the other.

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There are data suggesting that GABA release is diminished while orexin is activated in patients with insomnia. We know that orexin activity is compromised in people with narcolepsy; and it is therefore logical to target the orexin system for treatment of narcolepsy, but it may also make sense to target these neurons for treatment of insomnia. In fact, there are data suggesting that blockade of the orexin receptors promotes sleep in animal models and in humans.

Treatment of Insomnia

STEPHEN H. SHELDON, DO, FAAP: Advances in our understanding of the neurobiology of sleep have been accompanied by the development of novel therapies and treatment interventions for insomnia. Dr. Ancoli-Israel, could you discuss the primary nonpharmacological interventions used and how they might elicit their clinical effects?

SONIA ANCOLI-ISRAEL, PhD: As mentioned earlier, CBTI has been shown to be an effective nonpharmacological approach. CBTI reconditions people to associate the bed with sleep by using a combination of multiple behavioral therapies; the most common therapy is sleep restriction and stimulus control therapy, although relaxation therapy and possibly biofeedback may be incorporated as well. Sleep restriction limits the time a person spends in bed. Decreasing the amount of time in bed increases the sleep drive, making it easier to fall asleep and stay asleep. Stimulus control is used to stop the negative maladaptive behaviors that contribute to the inability to sleep.

Essentially, CBTI teaches patients to only go to bed when they are sleepy and to get out of bed when they begin to feel anxious and tense about not being able to sleep. In addition, CBTI trains the person to establish a very clear wakeup time because this helps stabilize sleep and the circadian rhythm.

Most patients who are compliant with behavioral changes see significant improvements in their sleep. Perhaps as important, if a patient who has undergone CBTI begins to experience sleep problems again, they already have the tools to manage their insomnia.

STEPHEN H. SHELDON, DO, FAAP: Dr. Blaivas, what are some of the more commonly used homeopathic remedies and over-the-counter (OTC) treatments for insomnia? What do we know about their efficacy and safety?

ALLEN J. BLAIVAS, DO: A recent systematic review on this topic was published in Sleep Medicine Reviews in 2011. The most widely...
studied homeopathic remedy is valerian, which is believed to target GABA neurons. Despite attempts to establish an evidence base for use of valerian both alone and in combination with other herbal remedies such as kava and hops, the data are relatively weak.

Another commonly used herbal medication is L-tryptophan, which is an exogenous amino acid that is converted in the body into serotonin. As is the case with valerian, the evidence of its efficacy is limited, although the weight of the evidence suggests that L-tryptophan may produce an increase in sleepiness and a decrease in sleep latency. Sarris and Byrne concluded that there is evidence to support nonpharmacological therapies such as acupressure, tai chi, and yoga.23

Melatonin, as discussed earlier, is a hormone secreted by the pineal gland that helps regulate circadian rhythms. Much of the evidence for melatonin is from circadian rhythm studies rather than insomnia studies. Melatonin is probably better at regulating circadian rhythm in instances such as phase delay or jet lag than it is at directly treating insomnia. A recent meta-analysis of primary sleep disorders, including insomnia, suggested that melatonin is effective in decreasing sleep onset latency, increasing sleep duration, and improving sleep quality.24 However, it was less effective compared with the effect reported for benzodiazepine and nonbenzodiazepine hypnotics. A prolonged-release formulation of melatonin has been shown to increase sleep quality, decrease sleep latency, and improve quality of life without the hangover effects sometimes seen with hypnotic agents.25

Two of the most widely used OTC sleep agents are the antihistamines diphenhydramine and doxylamine, which are commonly found in sleep agents labeled as a “PM” formulation and are approved by the Food and Drug Administration (FDA) as OTC sleep aids. These agents tend to have sedating effects, particularly in older people, and can cause significant anticholinergic actions resulting in dry mouth, constipation, urinary retention, confusion and delirium, and next-day hangover effects. Additionally, continued use of these agents can result in loss of response due to tolerance, leading to dose escalation to dangerous levels.

STEPHEN H. SHELDON, DO, FAAP: Do OTC sleep aids have other significant side effects or adverse reactions when used alone or in combination?

ALLEN J. BLAIVAS, DO: Generally, herbal remedies are relatively harmless with the exception of kava, which is no longer sold in many countries because of concerns about hepatotoxicity. None of the homeopathic remedies are well regulated; the FDA does not review and approve them, so despite what the packaging might say, there are no guarantees of purity, efficacy, or safety.

SONIA ANCOLI-ISRAEL, PhD: Because OTC sleep aids are relatively inexpensive and can be purchased in any drugstore or supermarket, many people assume that they can be used without risk of side effects. Granted, when used appropriately, these agents are safe for many patients, but confusion, dizziness, next-day grogginess, and the potential for tolerance can make these agents dangerous, particularly for elderly people.

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DAVID NEUBAUER, MD: Another issue with antihistamine-based sleep medications is the potentially harmful interaction between the anticholinergic sleep aids and cholinesterase inhibitors often prescribed to an elderly patient to limit memory loss. It makes no pharmacological sense to combine these agents in older patients.

STEPHEN H. SHELDON, DO, FAAP: Dr. Neubauer, could you talk about some of the pharamcotherapies that are approved by the FDA?

DAVID NEUBAUER, MD: There are 3 broad categories of medications approved by the FDA for treating insomnia: the benzodiazepine and nonbenzodiazepine receptor agonist hypnotics, the melatonin receptor agonists, and the selective histamine receptor antagonists. The first agents in the class of benzodiazepine receptor agonist hypnotics were approved in the early 1970s and had a benzodiazepine structure. More recent generations of these agents have a different structure but similar pharmacodynamic activity. These are typically referred to as the nonbenzodiazepine hypnotics.

Both the benzodiazepines and the nonbenzodiazepines are positive allosteric modulators of GABA. Normally, when GABA attaches to the GABA-A receptor, there is a central chloride channel that allows negative chloride ions to enter the cell, stabilizing the membrane and decreasing the likelihood of an action potential occurring. These medications enhance the normal action of GABA. They are allosteric because they have a separate attachment site on the larger GABA-A receptor complex. When a benzodiazepine-type agonist is attached to the GABA-A receptor complex, it allows more negative chloride ions into the cell than when GABA alone attaches. This is referred to a positive allosteric modulation of GABA-A activity.
“...benzodiazepines and the nonbenzodiazepines are positive allosteric modulators of GABA. Normally, when GABA attaches to the GABA-A receptor, there is a central chloride channel that allows negative chloride ions to enter the cell, stabilizing the membrane and decreasing the likelihood of an action potential occurring.”

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There were 5 original benzodiazepines, some of which are still available. Three newer-generation compounds, including zaleplon, zolpidem, and eszopiclone, are currently available in the United States. These agents are differentiated by the pharmacokinetics of their formulations; zaleplon has a very short half-life, zolpidem has a relatively short to intermediate half-life, and the half-life is eszopiclone is somewhat longer.

Compared with the older agents, the half-life of the nonbenzodiazepines is moderately short. However, zolpidem is available in an extended-release formulation, and alternate delivery formulations include a dissolving formulation that can be used at bedtime. There is also middle of the night dissolvable dosing for people with middle of the night awakenings and an oral spray version as well.

The efficacy of the benzodiazepines and nonbenzodiazepines depends on the individual patient and the nature of the underlying sleep problems. The basic activity of these agents is to promote sedation. Several safety concerns of these medications should also be mentioned. Agents with longer half-lives pose a greater risk of promoting excessive sleepiness or impairment lingering into the daytime.

The FDA has highlighted that concern and in 2013 recommended a reduction in the initial dose of zolpidem in women because they tend to metabolize it more slowly. In May 2014, the FDA decreased the recommended starting dose of eszopiclone from 2 mg to 1 mg for both men and women. The 1-mg dose can be increased to 2 mg or 3 mg if needed, but the higher doses are more likely to result in next-day impairment of driving and other activities that require full alertness.

The second category consists of the melatonin receptor agonists. There is only one approved agent in this category, ramelteon, which is indicated for the treatment of insomnia characterized by difficulty with sleep onset. People who have difficulty falling asleep or staying asleep in the early part of the night may benefit from treatment with ramelteon.

The third category contains the selective histamine receptor antagonist doxepin. Doxepin was initially approved for the treatment of depression in 1969, and now low-dose doxepin is labeled for the treatment of insomnia characterized by difficulty maintaining sleep. The exact mechanism by which the medication exerts its sleep maintenance effect is unknown, but it is thought to be highly selective for the histamine H₁ receptors. This high degree of selectivity, combined with a low dose, can help to minimize the adverse events frequently experienced with OTC antihistamine-based sleep aids.

The approved dosing of doxepin for insomnia is 3 to 6 mg at bedtime, whereas the prescribing guidelines for major depression are as high as 300 mg daily.

STEPHEN H. SHELDON, DO, FAAP: You mentioned the sedating effect of these classes of medications. Does this result in normal sleep, or is there an effect on sleep structure architecture that is different from normal sleep?

DAVID NEUBAUER, MD: In most cases, these agents do not alter the key indicators tracked in a polysomnographic study. There may be small changes in slow wave sleep with the benzodiazepine types of medications, but at the recommended doses, either with ramelteon or with low-dose doxepin, these are not significant changes.

STEPHEN H. SHELDON, DO, FAAP: Are these medications appropriate for long-term use?

DAVID NEUBAUER, MD: The label for each product clearly indicates how long these agents can be used. For example, the labels of the benzodiazepines and the nonbenzodiazepines zolpidem and zaleplon all say that they are indicated for the short-term treatment of insomnia.

With greater clinical experience and the recognition that many patients have benefited from continued treatment without an increased number of adverse events, the FDA changed its approach to labeling some of the newer agents. For example, the label for eszopiclone does not contain wording about short-term use. It was simply approved for the treatment of insomnia, and there is no implied limitation on the duration of use. This is also true for ramelteon and low-dose doxepin.

The one exception to this trend seems to be for the newer formulations of zolpidem, including the oral spray and the bedtime dissolvable formulation. These formulations still carry the duration limitations in their labels because the approval of these new formulations was based on earlier efficacy studies.

STEPHEN H. SHELDON, DO, FAAP: Are there other prescription medications with sedating effects that are used for the treatment of insomnia in an off-label manner?

DAVID NEUBAUER, MD: Many agents are used off-label for the treatment of insomnia, including sedating antidepressants, other benzodiazepines, mood stabilizers, and sedating antipsychotics. Perhaps the best time to use these sedating agents is when a patient has the...
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appropriate comorbid condition such as a depressive or psychotic disorder. However, there are only limited efficacy and safety data on the off-label use of these products as sleep-promoting agents in patients who do not present with an appropriate comorbidity.

STEPHEN H. SHELDON, DO, FAAP: Is there potential value of an agent targeting orexins for the treatment of insomnia?

DAVID NEUBAUER, MD: Because the orexin system plays a central role in the regulation of sleep and waking, it is an appealing therapeutic target. As we discussed earlier, there are data suggesting that the orexin system may drive the excessive arousal seen in many patients with chronic insomnia. Thus, it is appealing to consider if interventions designed to reduce orexin activity will have a positive effect on sleep.

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— Dr. Neubauer

STEPHEN H. SHELDON, DO, FAAP: Dr. Ancoli-Israel, are there any robust clinical data on the efficacy and safety of agents that target the orexin system?

SONIA ANCOLI-ISRAEL, PhD: Several phase 3 studies enrolling more than 300 patients have been conducted to investigate the long-term safety and efficacy of antiorexin therapies. Specifically, these studies were designed to determine the effects of orexin-targeted agents on sleep induction and sleep maintenance assessed at various time points, including 1 week, 1 month, 3 months, and 1 year.29-32

The results of these trials indicated that these agents are efficacious for sleep onset and sleep maintenance in both elderly and nonelderly populations. The effect is observed as early as the first night the drug is taken and lasts for up to 1 year. These agents are generally safe and well tolerated on both a short-term and long-term basis.

STEPHEN H. SHELDON, DO, FAAP: Dr. Blaivas, based on these data, how do these agents compare with currently approved insomnia therapy?

ALLEN J. BLAIVAS, DO: Orexin antagonists allow patients to sleep by inhibiting the excitatory input to the arousal system rather than imposing a sedative-like effect, like the GABAergic drugs do. This is a unique mechanism of action. Orexin antagonists may selectively promote sleep without the side effects seen with the sedating agents such as a hangover effect, balance problems, parasomnias, and tolerance with prolonged use.

“Orexin antagonists may selectively promote sleep without the side effects seen with the sedating agents such as a hangover effect, balance problems, parasomnias, and tolerance with prolonged use.”

— Dr. Blaivas

It may be that many patients with treatment-resistant insomnia are actually overaroused and that treatment of these patients with GABA-targeted agents will continue to fail because they do not address the root cause of the insomnia. In theory, treatment of these patients with arousal system antagonists should help.

Summary

STEPHEN H. SHELDON, DO, FAAP: This has been a fascinating discussion. Summarizing briefly, 7 to 8 hours of sleep each night is recommended for adults, but this is an often unattainable goal in people with insomnia. Although sleeplessness is one of the most common symptoms voiced by patients during a primary care office visit, insomnia is often underdiagnosed. There are a number of consequences of undiagnosed and untreated insomnia, and those who sleep less are more likely to have chronic illness and a low quality of life. There are several nonpharmacological and pharmacological approaches to the treatment of insomnia, including cognitive behavioral interventions, homeopathic and herbal remedies, OTC agents, FDA-approved prescription drugs indicated for the treatment of insomnia, and approved drugs used off-label for the treatment of the condition. Targeting the arousal system is an exciting and novel new direction in the treatment of insomnia. We all look forward to gaining clinical experience with these novel medications and more guidance about appropriate dosing and possible adverse effects.

The FDA approved BELSOMRA® (suvorexant) for adults with insomnia who have difficulty falling asleep and/or staying asleep in August 2014.33
“Targeting the arousal system is an exciting and novel new direction in the treatment of insomnia.”

— Dr. Sheldon

References

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