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SPECIAL EDITION

Eye On Insomnia

Re-evaluating Definitions and Treatment

CME-Certified Activity

PANELISTS

Sonia Ancoli-Israel, PhD
University of California San Diego
School of Medicine
San Diego, California

David Neubauer, MD
Johns Hopkins University School of Medicine
Baltimore, Maryland

Andrew D. Krystal, MD
Duke University Medical Center
Durham, North Carolina

Thomas Roth, PhD
Henry Ford Hospital
Detroit, Michigan

MODERATOR

Peter L. Salgo, MD
National Television Medical Correspondent;
Columbia University College of Physicians and Surgeons
New York, New York

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Eye On Insomnia

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Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network.



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Educational Overview

Insomnia is the most common sleep disorder in adults, and for millions, the problem is chronic. Whether it is the primary disorder or, as is often the case, secondary to some other condition, chronic insomnia has adverse repercussions for patients. Recent guidelines are redefining how insomnia is defined and managed. At the same time, a number of new medications for insomnia have been approved, many of these with labeling for longer term use. This presents an opportunity to discuss issues surrounding the proper diagnosis and management of insomnia with both behavioral and pharmacologic therapy. Are clinical practices in alignment with the current guidelines? What is the impact of comorbid conditions on insomnia and its management? How do new therapies fit into the treatment paradigm? What can the practitioner do to integrate behavioral as well as pharmacologic therapy to improve sleep disorders?

Through debate and authoritative peer exchange, this *Medical Crossfire*[®] program, conducted in conjunction with UMDNJ, will examine issues related to integrating clinical evidence and guidelines in the definition and management of chronic insomnia.

Target Audience

This educational activity is designed for primary-care physicians and other clinicians interested in or involved with the treatment of patients with insomnia.

Learning Objectives

- Define chronic insomnia and its prevalence as either a stand-alone condition or one that presents with specific comorbidities.
- Consider the implications of the recent NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults.
- Describe the characteristics of the available sleep medications (i.e., their effects on induction and maintenance of sleep as well as duration of action), and their relevance to clinical practice.
- Appraise the role of cognitive behavioral therapy alone and in combination with pharmacotherapy for chronic insomnia.

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions. The activity is complemented with references that contain the rationale for the correct answer to each question as well as a description identifying the section in the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding AMA/PRA category 1 credit three to four weeks after receipt of the registration and evaluation materials. Estimated time to complete this activity as designed is one (1) hour.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ—Center for Continuing and Outreach Education and *Medical Crossfire*/Liberty Communications Network. UMDNJ—Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ—Center for Continuing and Outreach Education designates this educational activity for a maximum of one (1) category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Kristin G. Fless, MD; Syed Hasan, MD; Kinshasa Morton, MD; and Adam Palance, MD.

CME Academic Advisor

Kristin G Fless, MD

Clinical Division Director Pulmonary and Critical Care

Assistant Professor of Medicine

University of Medicine and Dentistry of New Jersey—New Jersey Medical School

Newark, New Jersey

Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

Faculty Disclosure Declarations

Dr. Ancoli-Israel has been a consultant for and has been a member of the scientific advisory boards of Cephalon, King Pharmaceuticals, Merck & Co., Neurocrine Biosciences, Neurogen, Pfizer Labs, sanofi-aventis, Sepracor, Somaxon, and Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of Cephalon, King Pharmaceuticals, Neurocrine Biosciences, sanofi-aventis, Sepracor, Somaxon, and Takeda Pharmaceuticals North America.

Dr. Krystal has received grant/research support from Cephalon, Cyberonics, GlaxoSmith Kline Pharmaceuticals, Merck & Co., Neurocrine Biosciences, Neuronetics, National Institutes of Health, Organon, Pfizer Labs, Respiroics, Sepracor, sanofi-aventis, and Somaxon; has been a consultant for Cephalon, Johnson & Johnson, King Pharmaceuticals, Neurocrine Biosciences, Neurogen, Organon, Pfizer Labs, Research Triangle Institute, Respiroics, sanofi-aventis, Somaxon, Sepracor, Takeda Pharmaceuticals North America, and TransOral; and has served on the speakers' bureaus of Cephalon, Cyberonics, GlaxoSmithKline Pharmaceuticals, Mecta Corporation, sanofi-aventis, and Sepracor.

Dr. Neubauer has been a consultant for Neurocrine Biosciences, Pfizer Labs, sanofi-aventis, and Takeda Pharmaceuticals North America; and has served on the speakers' bureaus of sanofi-aventis and Takeda Pharmaceuticals North America.

Dr. Roth has received grant/research support from Cephalon, GlaxoSmithKline, Neurocrine, Pfizer Labs, sanofi-aventis, Sepracor, Somaxon, Syrex, and Takeda Pharmaceuticals North America; has been a consultant for AstraZeneca Pharmaceuticals, Avera, Cephalon, Cypres, Eli Lilly and Co., GlaxoSmithKline Pharmaceuticals, Hypnion, Jazz, King Pharmaceuticals, Lundbeck, Mini Meter, McNeil Consumer & Specialty Pharmaceuticals, Merck & Co., Neurocrine Biosciences, Organon, Orginer, Pfizer Labs, Roche Laboratories, sanofi-aventis, Sepracor, Somaxon, Syrex, Takeda Pharmaceuticals North America, Transoral, Vivometrics, and Wyeth Pharmaceuticals; and has served on the speakers' bureaus of Cephalon, sanofi-aventis, Sepracor, and Takeda Pharmaceuticals North America.

Dr. Salgo has no financial arrangements or affiliations to disclose.

Dr. Fless, Dr. Hasan, Dr. Morton, and Dr. Palance have no financial arrangements or affiliations to disclose.

Off-Label Usage Disclosure

This activity contains discussion of unlabeled and non-FDA-approved uses of commercial products. Antipsychotic and antidepressant agents are not approved for the treatment of insomnia.

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It should be noted that the recommendations made herein, with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelists. The drug selection and dosage information provided in this activity are believed to be accurate. However, the participants are urged to consult the full prescribing information on any drug mentioned in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

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Eye on Insomnia

Re-evaluating Definitions and Treatment

PANELISTS



Sonia Ancoli-Israel, PhD
Professor of Psychiatry
Co-director, Laboratory of Sleep and Chronobiology
University of California San Diego School of Medicine;
Director, Sleep Disorders Clinic
Veterans Affairs San Diego Healthcare System
San Diego, California



David Neubauer, MD
Assistant Professor of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine;
Associate Director, Johns Hopkins Sleep Disorders Center
Baltimore, Maryland



Andrew D. Krystal, MD
Associate Professor of Psychiatry
Duke University Medical Center
Durham, North Carolina



Thomas Roth, PhD
Chief, Division Head
Sleep Disorders and Research Center
Henry Ford Hospital
Detroit, Michigan

MODERATOR



Peter L. Salgo, MD
National Television Medical Correspondent;
Clinical Professor of Medicine and Anesthesiology
Columbia University College of Physicians and Surgeons;
Associate Director, Surgical Intensive Care Units
New York Presbyterian Hospital
New York, New York

Insomnia is the most common sleep problem among adults, affecting 35% of Americans; however, the majority of cases remain undiagnosed and untreated.^{1,2} The recent National Institutes of Health State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults² noted that many promising behavioral and pharmacologic approaches to the treatment of chronic insomnia are available but that “there has been limited guidance for clinicians in choosing the best treatment for chronic insomnia due to the paucity of randomized clinical trials (RCTs) for many widely-used treatments.” In this **Medical Crossfire**, a panel of national experts discusses the evolving clinical view of insomnia and the role of pharmacologic and nonpharmacologic therapies for the management of this disorder in the clinical setting.

Defining and Quantifying Chronic Insomnia: Implications of the Recent National Institutes of Health Consensus Statement on Sleep Disorders

Sonia Ancoli-Israel, PhD opened this *Medical Crossfire* by stating that “We know that about 35% of Americans report sleep difficulties.”¹ The official diagnosis of insomnia includes difficulty falling asleep, difficulty staying asleep, or non-restorative sleep, resulting in daytime consequences.²

“The problem is that although insomnia is very common, it is not well recognized within any particular practice setting,” she noted, pointing out that most physicians do not ask about it, and patients do not talk about it. “There are data showing that only about 5% of patients with insomnia will see their physician about their sleep problem.³ Approximately one quarter of patients may mention it to their physician if they happen to be seeing the physician for another reason, but that leaves about 75% who never talk about their sleep problems.³”

Andrew D. Krystal, MD confirmed that insomnia is more prevalent in practice than population estimates suggest. A study by Hohagen and colleagues on chronic insomnia showed a prevalence of about 45% in primary-care practices, which is significantly higher than the prevalence reported in epidemiologic studies of the general population.⁴ “In this group, insomnia was very long-lasting,” said Dr. Krystal. “A total of 77% of patients with severe insomnia reported a duration of longer than one year.” Insomnia persisted even longer in a group of elderly patients studied by the same researchers; 57% of elderly patients in primary-care practices had insomnia, and 80% of those reported a duration of longer than one year.⁵

Addressing a persistent myth regarding sleep patterns and aging, Dr. Ancoli-Israeli added that age, per se, does not cause difficulty sleeping. “Medical conditions, psychiatric conditions, the medications used to treat those conditions, as well as stress such as a result of bereavement, are factors that contribute to poor sleep as we get older. The

need for sleep does not change with age; rather it is the ability to sleep that changes.”

Thomas Roth, PhD pointed out that the National Institutes of Health (NIH) State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults noted that most cases of insomnia are comorbid with another condition,² so primary insomnia (insomnia in the absence of another condition) is relatively rare. Noting that the NIH State-of-the-Science Panel stressed use of the term ‘comorbid’ as opposed to ‘secondary to,’ Dr. Roth hypothesized that “the latter is why most physicians do not inquire about insomnia; the view has been, and continues to be, that insomnia is a reflection of an underlying disorder such as rheumatoid arthritis or an anxiety disorder, and that treatment of the underlying condition alone will resolve sleep problems, which may not be true.”

While it is recognized that comorbidities increase the risk of insomnia, treatment of both the medical or psychiatric condition and the insomnia is an opportunity to optimize care for patients. “For example, in patients with depression, the ability to sleep will in fact improve with appropriate treatment of the depression,” remarked David Neubauer, MD. “There may be other complicating issues with the particular medications, and there may be other residual insomnia, but nevertheless the physician should make sure that the underlying psychiatric issue is addressed.”

“Is insomnia a nighttime problem only, or should there be concern about what happens the day after a poor night’s sleep?” asked moderator Peter L. Salgo, MD.

“It is easy to think about insomnia as nighttime lack of sleep, but the daytime consequences are what drive patients to seek help,” answered Dr. Neubauer. “Patients will say that their insomnia has been going on for years, but it is only when their daytime functioning seems to be impaired that they will see their physician about it.” Daytime conse-

quences of insomnia include extreme fatigue during the day, difficulty concentrating, irritability, and lack of productivity at work.⁶

Dr. Ancoli-Israel remarked that patients often do not realize that such symptoms may be related to their sleep. “They may be irritable or are having a hard time at work, but they do not relate these effects to their lack of sleep at night.”

Correlative findings, including greater absenteeism from work or school, increased risk of depression, increased risk of anxiety and substance abuse, and greater risk of some medical problems, may suggest an association with insomnia, noted Dr. Krystal.^{7,8} “We do not really know if these findings are in fact adverse effects of the insomnia itself.”

Dr. Salgo asked the panel if there is a difference between acute and chronic primary insomnia, terms which have been used in the existing medical literature.

“If we take a consensus conference at face value, we have to stop the discussion of primary and secondary insomnia and primary and comorbid insomnia,” interjected Dr. Roth. “There is no reason to believe that there is any difference between a patient with insomnia alone and a patient with insomnia that is comorbid with rheumatoid arthritis. There is no such thing as ‘primary insomnia.’ There is simply insomnia, and a patient could either have that alone or have it with something else.”

“The point is that physicians need to treat the insomnia, no matter what other disorder might be present,” remarked Dr. Ancoli-Israel.

“Exactly,” agreed Dr. Roth. “Insomnia is a disorder in and of itself. It tends to occur with other conditions, but it is a chronic disorder and has to be treated on a chronic basis. The fact that it is comorbid with another disease in no way changes the need for treatment.”

“This is a big change from what clinicians have been taught in the past,” Dr. Ancoli-Israel offered. “We used to treat the comorbid condition first and see if the insomnia went away. Now, it is fairly clear that insomnia

“Insomnia is a disorder in and of itself. It tends to occur with other conditions, but it is a chronic disorder and has to be treated on a chronic basis. The fact that it is comorbid with another disease in no way changes the need for treatment.”

—Dr. Roth

and the comorbid condition need to be treated concomitantly.”

“In the past,” noted Dr. Neubauer, “many of the treatments for what were believed to be the underlying conditions were in fact sedating agents for the treatment of insomnia. Over time, in an area such as depression for example, we switched to agents that are not sedating and now see that the insomnia very frequently does not get better.”

Assessing Available Sleep Medications and Making Treatment Decisions

Antidepressants

According to Dr. Roth, “antidepressants are appropriate if a patient has insomnia comorbid with depression, but this will not resolve the patient’s insomnia. Sedating antidepressants should not be used to treat insomnia because they are reasonably toxic. If 100 mg of a sedating antidepressant improves a patient’s symptoms and 300 mg causes cardiac toxicity, then that is a bad ratio.” Sedating antidepressants are not indicated for insomnia because they lose efficacy within two weeks of use. “However, this should not necessarily prevent physicians from treating insomnia comorbid with depression with antidepressants.” Pointing out the importance of recognizing that sedating antidepressants do work but that the toxicity/efficacy ratio is unknown, Dr. Roth offered that, “Antidepressants work for depression; their safety in the management of insomnia is unknown.”

“The NIH State-of-the-Science Panel stated that ‘all antidepressants have potentially significant adverse effects, raising concerns about the risk/benefit ratio.’² Even if an antidepressant worked for three or four weeks, the NIH panel is not recommending use of antidepressants for the treatment of insomnia in a nondepressed individual,” stated Dr. Ancoli-Israel.

Dr. Krystal noted that there are not much data on the use of antidepressants in

the treatment of insomnia. He cited one of the few randomized, double-blind, placebo-controlled trials, which was conducted in Europe. Forty-seven patients with insomnia were studied and received either 25 mg or 50 mg of the tricyclic antidepressant doxepin or placebo for four weeks followed by two weeks of placebo withdrawal.⁹ In the doxepin-treated patients who completed the study, doxepin significantly increased sleep efficiency after acute and subchronic intake compared with the patients who received placebo. Doxepin caused significantly better global improvement at the first day of treatment, and patients rated sleep quality and working ability to be significantly improved by doxepin during the entire treatment period.⁹

Dr. Krystal went on to cite a two-week study of trazodone,¹⁰ which compared treatment of 300 primary insomnia patients randomized to two weeks of treatment with zolpidem 10 mg, trazodone 50 mg, or placebo. However, Dr. Krystal cautioned, “I would not draw any firm conclusions from this study. I would just say we have very few data.”

Dr. Ancoli-Israel responded to Dr. Krystal’s assertion by noting that the NIH conference concluded that “In short-term use, trazodone is sedating and improves several sleep parameters. These initial effects may not last beyond two weeks. However, there are no studies of long-term use of trazodone for treatment of insomnia. Doxepin has been found to have beneficial effects on sleep for up to four weeks for individuals with insomnia.” However, Dr. Ancoli-Israel went on, “all antidepressants have potentially significant adverse effects, raising concerns about the risk–benefit ratio. Moreover, there is a need to establish and communicate to prescribers the dose–response relationships for all of these agents.”

Antipsychotics

“There is similar thinking regarding antipsychotics when used off-label for insomnia,” began Dr. Krystal. “There is no question that

these medications have sedating effects. However, there are no studies in patients with insomnia except in those who have schizophrenia and insomnia, and insomnia was not specifically a target in any of those studies.” In addition, the ratio of efficacy to side effects is unknown for the treatment of insomnia.

The NIH State-of-the-Science Panel stated that “studies demonstrating the usefulness of these medications [antipsychotics] for either short- or long-term management of insomnia are lacking. Furthermore, all of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended.”²

“Antipsychotics may be sedating and ineffective in a patient with a psychosis, but to use them off-label for the sedating side effect in a patient with insomnia is not appropriate treatment,” remarked Dr. Ancoli-Israel.

Over-the-Counter and Herbal Agents

Turning the discussion toward over-the-counter and herbal agents, Dr. Neubauer said that use of such agents is problematic because “patients are wasting valuable time and not properly addressing their condition. We have always talked about how over-the-counter sleep agents do not work well because they are H1 antihistamines. In fact, we do not really know what H1 antihistamines do. Ninety-nine percent of over-the-counter sleep agents are diphenhydramine, which is more anticholinergic than antihistaminic and has a poor side-effect profile.”

“That is correct,” seconded Dr. Krystal, “and it is very confusing for consumers who see something over the counter and assume that somehow this must be safer than a prescription medication. Clearly, the exact opposite is true with regard to the comparison with the approved hypnotics.”

Benzodiazepines

Benzodiazepines have also been used to treat patients with insomnia.¹¹ “These agents

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clearly help people with insomnia,” noted Dr. Krystal. “There is a large body of literature supporting their efficacy, although in some ways the literature is limited compared with the literature on new agents which includes studies of longer-term treatment, treatment of comorbid insomnia, and effects of treatment on daytime function,” he said, offering that some benzodiazepines have very long half-lives and are therefore prone to causing daytime impairment.

In a meta-analysis of eight studies involving 889 patients, benzodiazepines were more likely than placebo to be associated with daytime drowsiness.¹¹ However, the shorter-duration benzodiazepines are less likely to cause such effects. Higher dosages are also associated with more side effects. “There was once the assumption that the benzodiazepines, when used in their recommended dosages for treatment of insomnia, caused long-term adverse effects although no long-term studies were performed. The data reviewed by the NIH State-of-the-Science Panel suggest that the safety profile of the newer agents, the nonbenzodiazepines, is better, most likely because of their shorter half-lives,”² explained Dr. Krystal.

Zaleplon

Dr. Salgo then asked the panel about the newer agents available for the treatment of insomnia.

Dr. Ancoli-Israel began with zaleplon, and stated that this drug is a controlled substance approved for short-term treatment of insomnia.¹² “Zaleplon has been shown to be safe and effective in helping people fall asleep faster but does not add to total sleep time. Because of its short half-life of one hour, as long as a patient has four hours left in bed, it can be taken in the middle of the night without any daytime consequences.”¹³⁻¹⁶ The recommended dose is 10 mg for adults and the recommended starting dose for the elderly is 5 mg.

Dr. Krystal clarified that longer-term treatment with zaleplon is not precluded. The results of the one-year open-label extension phases of two randomized, double-blind trials of zaleplon showed that the safety profile in a population of older adults was similar to that observed in a short-term trial of an equivalent population. The data, he noted, also suggested that long-term therapy produced and maintained statistically significant improvement in time to persistent sleep onset, duration of sleep, and number of nocturnal awakenings ($P < 0.001$ for each variable) for treatment durations of up to 12 months. In addition, discontinuation was not associated with rebound insomnia.¹⁷ Dr. Krystal added that the FDA-approved label recommends patients being treated with zaleplon should be reevaluated monthly and that prescriptions should not be given in increments larger than a 30-day supply.

Zolpidem and Zolpidem CR

Zolpidem is the most commonly used sleep agent in the United States and has been shown to be safe and effective.¹⁸⁻²¹ The therapeutic dose is 10 mg in adults and 5 mg in the elderly because of slower metabolism. Zolpidem has a half-life of 2.5 hours and a time to maximum concentration of about one hour.²² There are large individual differences in kinetics, so there may be shorter or longer half-lives with this same drug in different individuals.

“The most common complaint about zolpidem has been that it did not last long enough in a subpopulation of patients, so a modified-release formulation was developed and recently approved by the FDA,” remarked Dr. Roth. “Zolpidem CR provides a longer duration of action,” explaining that approximately 60% of the drug is immediate release, with a delayed release of the remaining 40%. Modified-release formulations offer the additional benefit of improving sleep continuity throughout the night without sacrificing the rapid elimination properties that

minimize next-day residual effects.²³

“Incorporating this type of modified-release formulation into a hypnotic is a real innovation, because other agents developed before this point have followed standard pharmacokinetics,” commented Dr. Neubauer. “With the modified-release version of zolpidem, there is the same rapid increase in concentration that should help people fall asleep, but higher plasma concentrations are maintained longer and therefore can help patients sleep better, later, during the night. Because it is fundamentally the same compound, it still has that same fairly rapid decline in concentration, which helps protect against excessive sedation after patients wake up in the morning.”

Eszopiclone

Dr. Krystal then introduced a discussion of eszopiclone, which has a six-hour half-life and has been shown in a series of studies to help patients both fall asleep and stay asleep, and to improve the quality of sleep.²⁴⁻²⁶ “Eszopiclone is an agent that consistently helps patients stay asleep. It is not an extended-release formulation; it has a longer half-life so there are higher concentrations of drug later into the night. At the recommended dosage, the serum concentration remains high enough through the night to improve sleep maintenance; and it clearly helps many patients. At the same time, few patients experience residual effects the next-day.^{25,26,27} In fact, there is evidence that insomnia patients treated with eszopiclone feel that their daytime function is improved compared with patients treated with placebo.²⁶ Dr. Krystal explained that research studies have been performed in some of the important populations, such as patients with major depression. “A recent study of patients with major depression and co-morbid insomnia suggests that treatment with eszopiclone has a significantly greater therapeutic effect on sleep and depression than placebo when combined with prozac.²⁸”

“I would encourage practitioners not to think about only one way to treat. It may be necessary to try several different medications in patients.”

—Dr. Krystal

Long-term data on treatment with eszopiclone are also available. A year-long study was conducted with a six-month double-blind placebo-controlled phase followed by a six-month open-label extension phase, in which chronic primary patients treated with eszopiclone had (1) decreased sleep latency, wake time after sleep onset, and number of awakenings; (2) increased total sleep time and sleep quality; and (3) improved ratings of daytime ability to function, alertness, and sense of physical well-being compared with baseline ($P < 0.0001$).²⁹

Ramelteon

Dr. Roth continued the discussion of available pharmacologic agents for the treatment of insomnia by describing ramelteon, a melatonin receptor agonist indicated for sleep induction in patients with insomnia.³⁰ “Ramelteon is a drug that works at a different transmitter system. The half-life may not be as important with this drug as with others because it has a different mechanism of action. It is also differentiated from the agents previously discussed by the fact that it is nonsedating and has minimal abuse liability,” which, he speculated, may be related. Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

A recent randomized, multicenter, double-blind, placebo-controlled study of ramelteon for the treatment of transient insomnia showed that ramelteon-treated participants had significantly shorter latency to persistent sleep and significantly longer total sleep time relative to placebo.³¹ Another randomized, double-blind, placebo-controlled study of ramelteon in patients with chronic primary insomnia showed statistically significant reductions in latency to persistent sleep and increases in total sleep time. No next-day residual effects were seen with treatment compared with placebo, and there were no differences in the number or type of adverse events between the treatment and placebo groups.³²

Dr. Ancoli-Israel pointed out that ramelteon is non-scheduled and has only one recommended dose. “For the other agents we have discussed, a half-dose or smaller dose is prescribed for elderly patients. With ramelteon, all patients are prescribed 8 mg.”

Considerations for Treatment

Following the discussion of the available treatment agents, Dr. Krystal offered general insight regarding their use by noting that any medication can have residual effects. “That said, all of these medications are typically well tolerated. There is quite a variation in metabolism among patients, so different treatment options are needed. We have discussed a number of treatment options in this field, and I would encourage practitioners not to think about only one way to treat. It may be necessary to try several different medications in patients,” he advised.

“It is very difficult to say that any medication, with the possible exception of zaleplon, has no residual effects,” emphasized Dr. Roth. “A drug may not produce residual effects in the majority of patients, but there are some patients who are slow metabolizers. It is important to understand that there are huge individual differences in terms of sensitivity to the drugs.” He cited individual differences in metabolism of these drugs, and recommended that “physicians select the agent that is most ideal for a particular patient, rather than referring to the mean profile for a variety of patients.”

Dr. Ancoli-Israel agreed, succinctly stating that physicians should not adopt a single “favorite” sleeping aid to be used for all patients as first-line treatment, but rather match the characteristics of the drug to the patient’s complaint.

Matching the Characteristics of Treatment Agents to the Complaint of the Patient

“Physicians need to prescribe medication depending on the nature of the symptom,” noted

Dr. Roth. “For example, it may be necessary to prescribe a drug with effects that last for only a few hours if it will be taken in the middle of the night, as opposed to a drug that will last for eight hours.” Difficulty falling asleep, difficulty staying asleep, and difficulty getting up in the morning are not viewed as different disorders, although different medications may be optimally suited to treat the varying symptoms.

Dr. Roth then provided an example of a patient with an underlying condition such as rheumatoid arthritis or depression. He noted that this type of patient needs three treatments: cognitive-behavioral therapy (CBT) for perpetuating factors, treatment of the insomnia, and treatment of the depression or rheumatoid arthritis. “CBT works, but it does not result in remission of symptoms because the other two factors remain.”

“Based on the pharmacokinetic characteristics, we have seen that some of the medications have short half-lives and some have longer half-lives,” offered Dr. Neubauer. When patients complain primarily of difficulty falling asleep, one of the shorter-acting medications may be appropriate if they will be able to stay sleep on their own later in the night. In this instance, zaleplon, zolpidem, or ramelteon may be helpful. Most patients tend to have difficulty falling asleep and also awaken later during the night. For those individuals, a medication with a longer duration of action might be more appropriate. In this case, zolpidem CR or eszopiclone may be helpful.

“If insomnia is a chronic disorder, can and should therapy be prescribed for more than very short periods?” asked Dr. Salgo.

In response, Dr. Roth noted that all of the drugs that have been approved for insomnia in 2005 (eszopiclone, zolpidem CR, and ramelteon) are indicated for treatment of insomnia without recommended limitations on duration of therapy. “The FDA has changed their view of how these medications should be used. The last three drugs were

“Many physicians are afraid to prescribe medication for insomnia for fear that long-term treatment will be necessary, and in the past they have been told not to use these drugs for more than four to five weeks at a time.”
—Dr. Ancoli-Israel

approved for long-term use, but the drugs before that were not.”

“Also, these agents were approved without any additional long-term data,” interjected Dr. Krystal.

“Physicians will be well within the current medical views of insomnia if they treat patients with insomnia on a long-term basis, because it is a chronic condition,” continued Dr. Roth, noting that labeling may not reflect available clinical data or current standards of practice. “Barbiturates were a favorite drug of obstetricians/gynecologists for many years because pregnancy was not a contraindication according to the labeling at the time.”

“The NIH State-of-the-Science Panel stated that long-term use is appropriate,” added Dr. Ancoli-Israel. “We are also getting away from the thinking that all the newer medications for insomnia have the same problems that the older longer-acting benzodiazepines had. The entire view of how to treat insomnia over time has changed.”

“We clearly need longer-term studies,” stated Dr. Krystal. “I would caution practitioners against generalizing findings of a particular drug at a particular dose as a comparison to other dosages and to other drugs.” Also, there is no guidance on how to treat insomnia long-term, or for that matter, even how long it needs to be treated. “Physicians may be daunted by the idea that once they start treatment, they will never be able to stop, or they do not know when or how to stop.” The 1983 NIH Consensus Development Conference Statement *Drugs and Insomnia: The Use of Medications to Promote Sleep* suggested considering periodic tapering of medication, such as every two to three months, to see if the patient still has insomnia.³³ “Some physicians may want to taper patients off medication because they do not feel comfortable continuing to prescribe after a few years. The fact that we do not have data on when or how to discontinue treatment is a challenge for practitioners.”

“Many physicians are afraid to prescribe medication for insomnia for fear that long-term treatment will be necessary, and in the past they have been told not to use these drugs for more than four to five weeks at a time,” added Dr. Ancoli-Israel. “Physicians need to understand that insomnia is a chronic problem, and these patients may need to be treated on a long-term basis. Clinical practice, long-term studies,^{17,26,29} and studies in progress suggest that, when used appropriately, these drugs are likely safe, even on a long-term basis. Physicians should not be afraid to treat these patients for the long-term if necessary.”

“What should physicians tell patients who say they are afraid of becoming dependent on these drugs?” asked Dr. Salgo.

“We need to educate the patient the same way we educate the physician,” replied Dr. Ancoli-Israel. “Physicians should explain that the problem is chronic and that these drugs tend to be safe. If medication will help them sleep in the long-term, that is actually much safer for them than not sleeping night after night.”

In the absence of long-term data, noted Dr. Roth, “We do not really know whether we will treat these patients for the rest of their lives or whether they will remit if they are treated for six months or a year.” He pointed out that in the open-label studies, patients always showed improvement after one year from baseline. “There is no placebo to find out whether it is a therapeutic response, but perhaps we do not need to treat these patients for life. We know we are going to treat them for more than five weeks, because after five weeks they go back to baseline. But after six months, they may not. We do not know if this condition remits, because we have never studied that question.”

Dr. Roth pointed out that “insomnia has many consequences, and we cannot fix consequences with two weeks of treatment. The NIH wants us to study more long-term data, but also more nonsleep endpoints.” For exam-

ple, a study of nursing home residents showed that, contrary to popular belief, insomnia—but not hypnotic use—is associated with a greater risk of subsequent falls.³⁴ “This shows that data are critically important to study these conditions and their consequences.”

“In the future, we will also see more studies focusing on measures of daytime function,” added Dr. Neubauer. “In regard to pharmacology, we will see new mechanisms of action, which is another important development. The more ways we can approach this problem, the better we will be able to help our patients.”

“That is a very important point from many different views,” concurred Dr. Roth. The management of insomnia has always involved a drug; for many years it was triazolam, and for many years it was zolpidem. There were not many drugs available to treat insomnia. “Now, we are going to have several different drugs that have different kinetic parameters and, more importantly, work at several different transmitting systems. For example, it would not make sense to give triazolam and zolpidem in combination because they fundamentally work at the same site of action. Drugs that work on cholecystokinin, 5-HT receptors, and melatonin receptors might augment the effect. The combination of a benzodiazepine receptor agonist and a melatonin receptor agonist has additive effects because they work on different mechanisms, while 5-HT_{2A} augments the effect of a benzodiazepine receptor agonist. We are not simply giving higher doses now,” he speculated.

Role of Cognitive Behavioral Therapy

Dr. Krystal cited the importance of discussing CBT in the treatment of insomnia, noting that there is clear evidence that CBT can work in the treatment of primary insomnia.^{35,36} For example, a 2001 randomized, double-blind, placebo-controlled trial in 75

patients examined the effectiveness of CBT for treating insomnia, and found that CBT represents a viable treatment intervention.³⁵ Additionally, meta-analysis of 59 treatment outcome studies involving a total of 2,102 patients demonstrated that “nonpharmacological interventions produce reliable and durable changes in the sleep patterns of patients with chronic insomnia.”³⁶ With regard to combination therapy with CBT and medication, Dr. Krystal pointed to a clinical trial, “which reported a trend for patients treated with CBT plus temazepam (7.5 mg to 30 mg) to experience greater improvement in sleep than those treated only with placebo, only temazepam, or CBT plus placebo after eight weeks of treatment, though the sleep improvement in those receiving CBT was better sustained in the two years following treatment discontinuation.”³⁷

Dr. Krystal added that in the setting of comorbid conditions, while there is evidence of clear efficacy of CBT in conditions such as cancer, chronic pain, human immunodeficiency virus, depression, posttraumatic stress disorder, alcoholism, bipolar disorder, eating disorders, generalized anxiety, and obsessive-compulsive disorder,³⁸ there is also evidence that CBT is not often utilized in the primary-care setting.³⁹ Some primary-care physicians discuss sleep hygiene with their patients, which involves avoidance of practices such as cigarette smoking near bedtime, alcohol use, caffeine use, excessive napping, excessive time in bed, and sleeping in on weekends,⁴⁰ but sleep hygiene may not work on its own as well as the other nonpharmacologic therapies do.³⁶

“These therapies are underused in primary care because they require a lot of time and training,” Dr. Krystal stated. A study conducted by Edinger and Sampson attempted to create a primary-care “friendly” CBT for insomnia.³⁹ In this study, patients were randomized to either two sessions of brief CBT for insomnia or a similarly-brief intervention that included only generic recommendations on sleep hygiene. Statistical analyses showed that the abbreviated CBT for insomnia pro-

duced significantly larger improvements across a majority of outcome measures than did the similarly-brief sleep hygiene intervention. Approximately 52% of those receiving the abbreviated CBT for insomnia reported at least a 50% reduction in their wake time after sleep onset, and 55.6% of those receiving the abbreviated CBT for insomnia who entered the study with pathologic scores on an insomnia symptom questionnaire achieved normal scores by their final outcome assessment.³⁹

“There really is a question about CBT and efficacious treatment,” stated Dr. Roth. “CBT has many components, but three of the behavioral aspects—sleep hygiene, sleep restriction, and stimulus control—should be used by every primary-care physician. There are more-sophisticated CBTs, such as relaxation training and cognitive therapy, which require more time and more effort. To combine all CBTs into one group is unfortunate, because I believe every primary-care physician can have a piece of paper in his or her office that describes sleep hygiene rules, sleep restriction, and stimulus control.”

Dr. Ancoli-Israel added that the cognitive factors of CBT should also be integrated into the practice of primary-care physicians, although it is time consuming and requires training. “However, it does not need to be done by a physician, or even a nurse. Primary-care physicians could have a staff member trained in CBT or find someone in their community who is trained in CBT.”

“There is an assumption that there is only one form of behavioral therapy—sleep hygiene—in primary care,” said Dr. Krystal. “This is a complicated issue, and the biggest challenge is follow-up. It is like trying to get patients to lose weight or stop smoking. Physicians working with patients in an attempt to achieve a major change in behavior often fail. The key is helping patients if they are initially unsuccessful or if they have setbacks.”

“It is very difficult for patients to adhere to a sleep restriction or stimulus control therapy,” added Dr. Ancoli-Israel, “but physicians can use CBT effectively if they

have the time. Time is the problem. Primary-care physicians spend seven to 10 minutes with each patient, and that is not enough time for CBT. However, CBT could be integrated if primary-care physicians have a trained staff member on hand.”

“The fundamentals of sleep hygiene or sleep physiology relating to sleep restriction, stimulus control, and sleep hygiene practices should be a component of all primary care,” reiterated Dr. Roth. “It has to be a part of all practices.”

“I agree,” concurred Dr. Neubauer, “and informing physicians about all of the behavioral options available is a first necessary step.”

Dr. Ancoli-Israel stressed the importance of follow-up, noting that physicians may focus on comorbid conditions instead of insomnia.

One way in which primary-care physicians can follow up on patients with insomnia is to have patients keep a sleep diary, remarked Dr. Neubauer. “Quickly looking at the sleep diary during a follow-up visit may provide a more realistic assessment than a description from the patient. However, all of the ideas we have discussed during this *Medical Crossfire* require that physicians believe insomnia is an important issue and take the time to assess insomnia in their patients.”

Final Thoughts

“We have learned over the past several years—and this was clearly enunciated by the NIH State-of-the-Science Panel—that insomnia is a chronic disorder,” remarked Dr. Roth in offering a final thought to conclude this

Medical Crossfire. “It is not a symptom of other disorders, but it is often comorbid with other disorders. As a result, it requires a multi-dimensional approach to its management.”

“There is evidence that insomnia is an important disorder and that it affects patient’s lives,” offered Dr. Krystal. “My hope is to raise the consciousness of practitioners to look for insomnia and to treat it appropriately. I believe that management of insomnia enhances the management of comorbid conditions.”

“This is an exciting time in terms of the treatment of insomnia, because we have so many more options available as well as others that are in the pipeline,” stated Dr. Neubauer. “There have always been therapies available to get patients to sleep, but the real history of insomnia treatment with medications has been improving safety. There have been great improvements in terms of the pharmacokinetic characteristics and decreased side effects of medications while maintaining good efficacy. New medications may target special populations of patients who could benefit from particular neurotransmitter systems being addressed.”

“Primary-care physicians should not be afraid to ask about insomnia,” noted Dr. Ancoli-Israel to close this *Medical Crossfire*. “Ask patients how they are sleeping, and do not be afraid of the answer. There are so many treatment options available. Listen to what patients tell you about their sleep and then use the armamentarium of treatment agents and behavioral therapies available to provide the most appropriate care for that patient.” ■

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University of Medicine & Dentistry of New Jersey
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Eye On Insomnia

Re-evaluating Definitions and Treatment

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In order to obtain AMA/PRA category 1 credit(s), participants are required to:

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Circle the best answer for each question on the CME test.

- | | | | | | | | | | |
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| 2. | A | B | C | D | 7. | A | B | C | D |
| 3. | A | B | C | D | 8. | A | B | C | D |
| 4. | A | B | C | D | 9. | A | B | C | D |
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Eye On Insomnia

Re-evaluating Definitions and Treatment

Activity Evaluation Form

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Please note: CME credit letters will be issued only upon receipt of a completed evaluation form. Thank you for your cooperation!

Program Objectives

Having completed this activity, are you better able to:

	Strongly Agree				Strongly Disagree
Define chronic insomnia and its prevalence as either a stand-alone condition or one that presents with specific comorbidities.	5	4	3	2	1
Consider the implications of the recent NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults.	5	4	3	2	1
Describe the characteristics of the available sleep medications (ie., their effects on induction and maintenance of sleep as well as duration of action), and their relevance to clinical practice.	5	4	3	2	1
Appraise the role of cognitive behavioral therapy alone and in combination with pharmacotherapy for chronic insomnia.	5	4	3	2	1

Overall Evaluation

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The activity was educationally sound and scientifically balanced.	5	4	3	2	1
The activity avoided commercial bias or influence.	5	4	3	2	1
Overall, the activity met my expectations.	5	4	3	2	1
I would recommend this activity to my colleagues.	5	4	3	2	1

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.

Eye On Insomnia

Re-evaluating Definitions and Treatment

CME Test

1. Approximately what percentage of patients will discuss their insomnia with their physician?
 - a. one quarter
 - b. one half
 - c. two thirds
 - d. three quarters
2. According to the National Institutes of Health (NIH) State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults, most cases of insomnia are
 - a. associated with only nighttime problems.
 - b. the result of aging.
 - c. comorbid with another condition.
 - d. None of the above.
3. Which of the following classes of medications was recommended by the NIH State-of-the-Science Panel for use in treating insomnia?
 - a. antidepressants
 - b. nonbenzodiazepines
 - c. antipsychotics
 - d. All of the above.
4. According to the expert panel, one possible benefit of treatment with zaleplon is that it may offer the potential for
 - a. helping patients fall asleep faster.
 - b. improving the quality of sleep.
 - c. increasing total sleep time.
 - d. providing a higher level of sedation than other available medications.
5. Which of the following medications is available in a modified-release formulation?
 - a. eszopiclone
 - b. ramelteon
 - c. zaleplon
 - d. zolpidem
6. Which of the following medications has a long half-life, providing higher concentrations of drug later into the night?
 - a. eszopiclone
 - b. ramelteon
 - c. zaleplon
 - d. zolpidem
7. How does ramelteon differ from other available agents for the treatment of insomnia?
 - a. It works at a different transmitter system.
 - b. It has a different mechanism of action.
 - c. It is nonsedating and has minimal abuse liability.
 - d. All of the above.
8. According to the panel, what is the current medical view on the treatment of insomnia?
 - a. Patients with insomnia may be treated on a long-term basis.
 - b. Patients with insomnia should only be treated on a short-term basis.
 - c. There are not many drugs available to treat insomnia.
 - d. Treatment of the underlying condition alone will resolve a patient's insomnia.
9. Which of the following is considered a barrier to the treatment of patients with insomnia?
 - a. Long-term treatment is unsafe.
 - b. Medications used to treat insomnia are not indicated for long-term use.
 - c. Patients will become dependent on agents used to treat insomnia.
 - d. Physicians may be reluctant to prescribe treatment for insomnia because long-term treatment may be necessary.
10. According to the panel, which of the following components of CBT should be used by every primary-care physician?
 - a. sleep hygiene
 - b. sleep restriction
 - c. stimulus control
 - d. All of the above.

1. a. “The problem is that although insomnia is very common, it is not well recognized within any particular practice setting,” noted Dr. Ancoli-Israel, pointing out that most physicians do not ask about it, and patients do not talk about it. Approximately one quarter of patients may mention it to their physician if they happen to be seeing the physician for another reason, but that leaves about 75% who never talk about their sleep problems.”

Locator: Defining and Quantifying Chronic Insomnia: Implications of the Recent National Institutes of Health Consensus Statement on Sleep Disorders

2. c. Dr. Roth pointed out that the NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults noted that most cases of insomnia are comorbid with another condition. Noting that the NIH State-of-the-Science Panel stressed use of the term ‘comorbid’ as opposed to ‘secondary to,’ Dr. Roth hypothesized that “the latter is why most physicians do not inquire about insomnia; the view has been, and continues to be, that insomnia is a reflection of an underlying disorder, and that treatment of the underlying condition alone will resolve sleep problems, which may not be true.”

Locator: Defining and Quantifying Chronic Insomnia: Implications of the Recent National Institutes of Health Consensus Statement on Sleep Disorders

3. b. According to Dr. Ancoli-Israel, “Even if an antidepressant worked for three or four weeks, the NIH panel is not recommending use of antidepressants for the treatment of insomnia in a nondepressed individual.” With regard to antipsychotics, the NIH State-of-the-Science Panel states that “studies demonstrating the usefulness of these medications [antipsychotics] for either short- or long-term management of insomnia are lacking. Furthermore, all of these agents have significant risks. Thus, their use in the treatment of chronic insomnia cannot be recommended.”

Locator: Assessing Available Sleep Medications and Making Treatment Decisions

4. a. According to Dr. Ancoli-Israel, “Zaleplon has been shown to be effective in helping people fall asleep faster but does not add to total sleep time. Because of its short half-life of one hour, as long as a patient has four hours left in bed, it can be taken in the middle of the night without any daytime consequences.”

Locator: Assessing Available Sleep Medications and Making Treatment Decisions

5. d. “The most common complaint about zolpidem has been that it did not last long enough in a subpopulation of patients, so a modified-release formulation was developed and recently approved by the FDA,” remarked Dr. Roth. “Zolpidem CR provides a longer duration of action,” meaning that approximately 60% of the drug is immediate release, with a delayed release of the remaining 40%. Modified-release formulations offer the additional benefit of improving sleep continuity throughout the night without sacrificing the rapid elimination properties that minimize next-day residual effects.

Locator: Assessing Available Sleep Medications and Making Treatment Decisions

6. a. Dr. Krystal noted that eszopiclone helps patients stay asleep. “It has a longer half-life so there are higher concentrations of drug later into the night. Some patients experience next-day effects, but the majority do not.”

Locator: Assessing Available Sleep Medications and Making Treatment Decisions

7. d. Dr. Roth described ramelteon, a melatonin agonist indicated for sleep induction in patients with insomnia. “Ramelteon works at a different transmitter system. The half-life may not be as important with this drug as with others because it has a different mechanism of action. It is also differentiated from the agents previously discussed by the fact that it is nonsedating and has minimal abuse liability.” Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

Locator: Assessing Available Sleep Medications and Making Treatment Decisions

8. a. “Physicians will be well within the current medical views of insomnia if they treat patients with insomnia on a long-term basis, because it is a chronic condition,” said Dr. Roth, noting that labeling may not reflect available clinical data or current standards of practice. Dr. Ancoli-Israel added that the NIH State-of-the-Science Panel stated that long-term use is appropriate.

Locator: Matching the Characteristics of Treatment Agents to the Complaint of the Patient

9. d. “Many physicians are afraid to prescribe medication for insomnia for fear that long-term treatment will be necessary, and in the past they have been told not to use these drugs for more than four to five weeks at a time,” noted Dr. Ancoli-Israel. “Physicians need to understand that insomnia is a chronic problem, and these patients may need to be treated on a long-term basis. Clinical practice, long-term studies, and studies in progress suggest that, when used appropriately, these drugs are likely safe, even on a long-term basis. Physicians should not be afraid to treat these patients for the long-term if necessary.”

Locator: Matching the Characteristics of Treatment Agents to the Complaint of the Patient

10. d. Dr. Roth noted that, “CBT has many components, but three things—sleep hygiene, sleep restriction, and stimulus control—should be used by every primary-care physician. There are more-sophisticated CBTs, such as relaxation, training, and cognitive therapy, which require more time and more effort.”

Locator: Role of Cognitive Behavioral Therapy