This *Postgraduate Medicine* Special Report, “Insomnia in Primary Care: Overcoming Diagnostic and Treatment Barriers,” was sponsored by a grant from Sepracor Inc and prepared for publication by Fusion Medical Education.

Published by Healthcare Information Programs, McGraw-Hill Healthcare Information Group, Minneapolis.

Copyright ©2004, by The McGraw-Hill Companies, Inc. All rights reserved.

The articles in this publication have been independently peer reviewed.

The views and opinions expressed in this Special Report are those of the participants and authors and do not necessarily reflect the views of the publisher, editor, or editorial board of *Postgraduate Medicine*, Sepracor Inc, or Fusion Medical Education.

All reasonable precautions have been taken by the authors and publishers to verify drug names and doses. Clinical judgment must guide each physician in weighing the benefits of treatment against the risk of toxicity. Dosages, indications, and methods of use referred to in the articles may reflect the clinical experience of the authors or may reflect the professional literature or other clinical sources. Please see the full prescribing information on any products mentioned in this publication.
<table>
<thead>
<tr>
<th>Page</th>
<th>Author(s)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Sonia Ancoli-Israel, PhD, Joseph A. Lieberman III, MD, MPH</td>
<td>4 INTRODUCTION</td>
</tr>
<tr>
<td>7</td>
<td>Andrew G. Israel, MD, Joseph A. Lieberman III, MD, MPH</td>
<td>7 TACKLING INSOMNIA: DIAGNOSTIC AND TREATMENT ISSUES IN PRIMARY CARE</td>
</tr>
<tr>
<td>14</td>
<td>Paul P. Doghramji, MD</td>
<td>14 PRACTICAL DIAGNOSTIC STRATEGIES AND TOOLS FOR INSOMNIA</td>
</tr>
<tr>
<td>23</td>
<td>Ruth M. Benca, MD, PhD</td>
<td>23 BEHAVIORAL AND PHARMACOLOGIC MANAGEMENT OPTIONS FOR INSOMNIA</td>
</tr>
<tr>
<td>33</td>
<td>Sonia Ancoli-Israel, PhD, Cláudio N. Soares, MD, PhD, Raymond Gaeta, MD, Ruth M. Benca, MD, PhD</td>
<td>33 INSOMNIA IN SPECIAL POPULATIONS: EFFECTS OF AGING, MENOPAUSE, CHRONIC PAIN, AND DEPRESSION</td>
</tr>
<tr>
<td>48</td>
<td>Special Issues Board Panel</td>
<td>48 INSOMNIA IN PRIMARY CARE: PANEL DISCUSSION</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td>51 CME SELF-STUDY EXAMINATION</td>
</tr>
</tbody>
</table>
A SPECIAL REPORT

CME

Accreditation statement
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Interstate Postgraduate Medical Association and The McGraw-Hill Companies, Inc. Interstate Postgraduate Medical Association is accredited by the ACCME to provide continuing medical education for physicians.

Designation of credit
Interstate Postgraduate Medical Association designates this educational activity for a maximum of 3 category 1 credits toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

Intended audience
Primary care physicians.

Learning objectives
1. Be able to identify barriers to recognition, diagnosis, and appropriate management of insomnia in the primary care setting.
2. Be familiar with practical diagnostic and management strategies for insomnia that can be readily implemented in primary care.
3. Review commonly used behavioral and pharmacologic therapies for insomnia.
4. Understand the special considerations in management of sleep disturbances in patients with an underlying medical condition.

Faculty disclosures
Dr Ancoli-Israel is professor of psychiatry, University of California, San Diego, School of Medicine. She serves on speakers’ bureaus and scientific advisory boards for Neurocrine/Pfizer, Sepracor Inc, Takeda Pharmaceuticals America Inc, Sanofi-Aventis, and King Pharmaceuticals Inc. She has also received a grant from Janssen Pharmaceutica Products LP.


Dr Israel is clinical professor of medicine, University of California, San Diego, School of Medicine, and director, Hillcrest Internal Medicine, San Diego. He is a consultant for Sepracor Inc and Wyeth-Ayerst Laboratories.

Dr Doghramji is attending physician, Brookside Family Practice & Pediatrics, Pottstown, Pennsylvania. He serves on speakers’ bureaus for Sepracor Inc, Sanofi-Aventis, King Pharmaceuticals Inc, Cephalon Inc, and Wyeth Pharmaceuticals.

Dr Benca is professor, department of psychiatry, University of Wisconsin Medical School, Madison. She is a consultant or on the speakers’ bureau for King Pharmaceuticals Inc, Pfizer/Neurocrine, Sanofi-Synthelabo Inc, Sepracor Inc, Wyeth Pharmaceuticals, and Takeda Pharmaceuticals America Inc.

Dr Soares is associate director for research, Massachusetts General Hospital Center for Women’s Mental Health, Harvard Medical School, Boston. He is a consultant and is on the speakers’ bureau for GlaxoSmithKline, Wyeth Pharmaceuticals, Pfizer Inc, and Forest Pharmaceuticals, Inc. He is also a consultant for Sepracor Inc.

Dr Gaeta is associate professor of anesthesiology and director of pain management services, Stanford University Medical Center, Stanford, California. He is an investigator for XenoPort.

Method of participation
Physician learners will participate in this educational activity by reading articles and answering learning assessment questions. Questions can be photocopied from this report or obtained from www.ipmameded.org. A minimum score of 75% is required to receive credit for this activity. This activity should take 3 hours to complete.

Release date: December 2004. Termination date: December 2007 or earlier pending annual review. Please turn to page 51 for the CME Self-Study Examination.
Introduction

Sonia Ancoli-Israel, PhD
Joseph A. Lieberman III, MD, MPH

This Special Report is a collection of presentations and a summary of a panel discussion from a symposium convened to discuss and evaluate special issues related to diagnosis and management of insomnia in the primary care setting. The symposium was held in Boca Raton, Fla, on March 4 and 5, 2004. The panel consisted of primary care physicians and sleep experts from across the United States. Members of the primary care groups ranged from policy makers to those with a special interest in sleep medicine, all of whom contributed to an understanding of the unique circumstances and concerns encountered in primary care.

Although studies have indicated that insomnia is common among patients in primary care clinics and coexists with numerous other medical and psychiatric conditions often encountered in primary care, insomnia is poorly recognized and inadequately treated. The goals of this meeting were to identify and discuss barriers and limitations to diagnosis and treatment of chronic insomnia in primary care practice and to formulate suggestions for improving recognition and management of insomnia among primary care physicians.

The article by Drs Israel and Lieberman explores obstacles to diagnosis and treatment of insomnia in the primary care setting, including time constraints, reimbursement limitations, the paucity of sleep medicine education, and misconceptions about the use and safety of hypnotic medication. Other challenges faced by primary care physicians include outdated treatment guidelines, US Food and Drug Administration restrictions on medication prescriptions, lack of outcomes data showing the benefits of treating insomnia, and the paucity of longer-term studies that evaluate the safety and efficacy of any hypnotic in the treatment of insomnia.

Drs Israel and Lieberman present current developments in the understanding of insomnia, including results from recent longer-term medication studies that suggest that newer hypnotics are safe and are likely to be efficacious in longer-term use.

In the second article, Dr Doghramji focuses on diagnostic criteria for insomnia and practical diagnostic strategies that can be incorporated into primary care practice with minimum time burden. Heightened awareness of the possibility of insomnia can contribute to its increased recognition, and because primary care physicians represent the first point of contact for many patients, they are in a prime position to diagnose the problem. Many primary sleep disorders, such as periodic limb movements during sleep, require urgent attention and can present with the same symptoms as insomnia. Various mechanisms for distinguishing these disorders may be applied in the office environment.

Numerous medical and psychiatric illnesses, as well as the agents used to treat them, can also either cause or exacerbate insomnia. Dr Doghramji discusses diagnostic questions and tools that can be easily incorporated into the office visit.

The multiple treatment strategies, both nonpharmacologic and pharmacologic, available for insomnia are discussed in Dr Benca’s article on treatment options in the context of current understanding of sleep and wake mechanisms and neurocircuitry. Management of insomnia should focus on all of the elements of insomnia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised, and should thus address sleep initiation, sleep maintenance, and improved next-day function.

In addition, pharmacologic agents should be well tolerated and have no next-day residual effects. With these goals in mind, the relative strengths and limitations of FDA-approved hypnotics, commonly used sedating antidepressants, and
behavioral therapies are presented. Longer-term studies are needed to evaluate the use of medications in longer-term treatment of insomnia. Dr Benca briefly mentions recent developments in the field of insomnia management with an eye to future treatment of this common condition.

Insomnia is common in patients with chronic medical and psychiatric conditions, women presenting with perimenopausal symptoms, and elderly patients. Mechanisms for development of insomnia in these patient populations are elucidated in the article by Drs Ancoli-Israel, Soares, Gaeta, and Benca. The chronic nature of insomnia in such patients and the complexity of the presenting symptoms among them represent unique treatment challenges and, as the authors show, often require a multimodal and multidisciplinary approach. There is some evidence that insomnia may worsen outcomes in chronic medical and psychiatric conditions and that symptoms of insomnia are not always alleviated by treatment of the primary condition. Insomnia may actually predispose patients to recurrence of depression; therefore, treating insomnia may represent a crucial element in management of this disorder.

Finally, the panel discussion article summarizes the opinions and recommendations of the panel members that were presented in the debates that took place during the meeting and represents the thoughts and attitudes of meeting attendees. A proposed management algorithm for chronic insomnia is presented.

In conclusion, although insomnia is common among primary care patients, little attention is paid to its recognition, diagnosis, and treatment, despite evidence of the high personal and socioeconomic burden associated with it. Recognition and management of insomnia in primary care are hindered by a number of factors inherent in, but not restricted to, the constraints of primary care training and practice, which have yet to be addressed on a national level. However, other factors, such as the emergence of newer agents for treating insomnia and a better understanding of existing agents, may address some of the hesitancy surrounding appropriate treatment of insomnia. These new developments may ultimately influence the compilation of more up-to-date management guidelines and the revision of prescribing restrictions. Evidence that treating insomnia improves outcomes in patients with both primary and secondary insomnia has yet to surface; however, preliminary evidence suggests a benefit from treatment of insomnia, and as research emphasis shifts to outcomes measures, such data may become available. In the meantime, it is crucial that primary care physicians consider incorporating simple diagnostic strategies aimed at recognizing insomnia into routine office visits and, when indicated, institute insomnia treatment in order to promote the overall well-being of their patients.

Sonia Ancoli-Israel, PhD
Dr Ancoli-Israel is professor of psychiatry, University of California, San Diego, School of Medicine. She serves on speakers’ bureaus and scientific advisory boards for Neurocrine/Pfizer, Sepracor Inc, Takeda Pharmaceuticals America Inc, Sanofi-Aventis, and King Pharmaceuticals Inc. She has also received a grant from Janssen Pharmaceutical Products LP.

Joseph A. Lieberman III, MD, MPH
Dr Lieberman is professor of family medicine, Jefferson Medical College of Thomas Jefferson University, Philadelphia. He is a consultant for Abbott Laboratories, Bristol-Meyers Squibb Co, Cephalon Inc, Forest Pharmaceuticals Inc, Janssen Pharmaceuticals Corporation, Organon USA Inc, Ortho-McNeil Pharmaceutical Inc, Pfizer Inc, Sanofi-Aventis, Sepracor Inc, and Wyeth Pharmaceuticals.

Address for correspondence:
Sonia Ancoli-Israel, PhD
Department of Psychiatry 116A
VASDHs
3359 La Jolla Village Dr
San Diego, CA 92161

E-mail address: sancoliisrael@ucsd.edu

References
5. Roth T. New developments for treating

NOTES
Tackling insomnia
Diagnostic and treatment issues in primary care

Andrew G. Israel, MD
Joseph A. Lieberman III, MD, MPH

Preview
Primary care physicians are often the first healthcare providers to encounter insomnia in their patients. However, they face many obstacles to diagnosis and treatment of insomnia that stem from patient- and physician-related factors. During consultations, most patients do not mention their sleep difficulties because they believe that insomnia is a trivial concern that does not have serious health consequences. Physicians also face diagnostic obstacles related to conflicting or vague diagnostic definitions, office-based time constraints, and a lack of training in sleep medicine in medical school and residency programs. Once a diagnosis is made, initiating appropriate treatment is also complicated because of outdated treatment guidelines and US Food and Drug Administration prescribing constraints. These factors may have contributed to the perception that there are no good treatment options for insomnia and that all available medications have a poor risk-benefit ratio.

For example, benzodiazepines are known to carry a risk of tolerance and abuse. Until recently, few long-term data were available on the safety and efficacy of current agents, which may have contributed to reticence to treat chronic insomnia. Furthermore, there is limited evidence that treating insomnia is associated with improved patient outcomes, and this may have discouraged active treatment programs for insomnia. Increased awareness that insomnia can precede and exacerbate coexisting illnesses, including depression and chronic pain syndromes, is needed. As data emerge from recent clinical trials with newer, promising nonbenzodiazepine medications, it should become easier for primary care physicians to take a proactive role in diagnosing and treating insomnia and thus improve patient functioning.

Insomnia is a common problem in the United States and is most likely to be encountered in a primary care setting. In fact, almost 75% of patients with insomnia receive treatment from their primary care physician. More than 80% of prescriptions for hypnotic medications are written by primary care physicians rather than mental health or sleep specialists. Despite its ubiquity, insomnia is far from a trivial concern because it is often associated with psychologic and medical morbidity. Üstün and Sartorius found that 50% of primary care patients with sleep problems have associated psychologic stress that may lead to social instability, and 75% have chronic illness (eg, diabetes, osteoarthritis). Furthermore, the average duration of insomnia symptoms was 7 to 14 years, which suggests that insomnia is often a chronic condition. Given the proven chronicity of insomnia complaints, treatment needs to be refocused from acute intervention to long-term management.

Roughly two thirds of patients who have trouble sleeping do not tell their doctors about it, and doctors generally do not ask about the nature of their patients’ sleep. Moreover, once the topic of insomnia is broached and a diagnosis is made, a number of challenges remain to the initiation of appropriate treatment. As a result, insomnia is both underrecognized and undertreated.

Patient self-reporting
The number of patients who talk with their doctors about sleep problems is disturbingly low. In a survey of 286 primary
care patients, only one third of those who reported having insomnia had ever spoken to their doctor about it, although treatment-seeking behavior increased with severity of symptoms. Factors associated with discussing insomnia with the physician (in order of priority) were (1) feeling worse physically, (2) more years of insomnia, (3) older age, and (4) higher income. The other two thirds of patients, who had unidentified sleep complaints, were typically younger adults without concomitant health problems who had had sleep problems for a shorter time. It is important that these patients are identified and their sleep difficulties addressed because the longer insomnia persists, the more likely it is to cause decrements in daytime functioning, which can have an impact on work productivity as well as personal well-being.

In another study involving 3,284 primary care patients in Italy who were randomly selected to receive questionnaires at an office visit, the overall prevalence of insomnia was 64%. Although more than 90% of the patients with insomnia reported having 2 or more of the hallmark symptoms (ie, difficulty falling asleep, difficulty staying asleep, or waking too early), most did not mention their sleep difficulties to their doctors because they did not consider the insomnia to be a serious problem. Rather, they viewed their sleep disturbance as merely an inconvenience.

Physician-related diagnostic barriers
Patients are not the only ones who refrain from discussing insomnia. Physicians rarely introduce the question of whether their patients are sleeping well. Many doctors may view insomnia as a complaint, rather than a disease, and feel that it has little medical significance. Because insomnia is rarely the primary reason for a patient’s office visit, it is often an “add-on” complaint; it is usually brought up, if at all, as the visit is drawing to a close, at a time when detailed discussion is likely to throw the physician off schedule. Physicians may be reluctant to unnecessarily add to an already overloaded visit agenda by giving attention to what they perceive as a nonmedical problem. However, this perception of insomnia is based on a limited awareness of prevalence and impact data, rather than on clinical reality. Consequently, physicians may not consider or have time to consider that sleep hygiene, phase shifting, medical disease, medications, and pain syndromes may all underlie insomnia complaints. The current paucity of evidence-based studies showing that insomnia treatment improves outcomes further contributes to physicians’ reluctance.

Because of the lack of training in sleep medicine, most primary care physicians have little expertise in differential diagnosis of sleep complaints and sleep disorders. This lack of knowledge and experience likely contributes to their reluctance to address insomnia. The foundation for unfamiliarity is laid down during medical school, where training in sleep medicine is often missing or cursory. In 1990-1991, 37% of surveyed medical schools still did not systematically present sleep medicine to their students in either

Clinical pearls: tackling insomnia

- Chronic insomnia can have numerous adverse consequences. It also may worsen the outcome of coexistent conditions, particularly in patients with depression and chronic pain disorders. Therefore, it is important to diagnose and treat insomnia.

- Benzodiazepine hypnotics have historically been associated with a number of risks, including tolerance, withdrawal phenomena, rebound effects, and the potential for abuse and dependence. Fear of these potential risks has prompted many physicians to turn to sedating antidepressants for their patients with sleep difficulties, because these agents are perceived as safer and are not associated with the same risks of abuse and dependence. However, there is limited evidence that antidepressants improve sleep.

- Newer, nonbenzodiazepine hypnotics appear to be effective and are less likely than benzodiazepines to be associated with risk of abuse, tolerance, and withdrawal phenomena.

- A steadily growing body of research indicates that patient outcomes can be improved when insomnia is adequately managed.

- Recent data about longer-term use of both older and emerging nonbenzodiazepine sleep agents suggest that long-term treatment is safe and may also be effective without the emergence of tolerance.
the classroom or the clinic; fewer than 2 hours of total teaching time, on average, were devoted to sleep and related disorders, and only 11% of medical students had clinical contact with sleep-disordered patients. A later survey found that 65.2% of members of the two largest sleep societies in the United States, the American Sleep Disorders Association (now the American Academy of Sleep Medicine) and the Sleep Research Society, were involved with sleep education and training; however, they reported that only 2.1 hours at the medical school level and 4.8 hours at the postgraduate level were devoted to the topic. Lack of time, resources, and teaching facilities was cited as a major contributor to the dearth of attention.

The effects of this lack of education and training are borne out in the findings of studies assessing practical sleep medicine knowledge. One study asked primary care physicians to self-rate their knowledge of sleep disorders and found that 10% rated their knowledge as good, 60% as fair, and 30% as poor. None rated their knowledge as excellent.

Another barrier to recognition and diagnosis of insomnia is the perception that no good treatment options are available. Longer-acting hypnotic medications are associated with such side effects as daytime drowsiness, accidents, impaired memory, and confusion; thus, there is the attendant fear that prescribing any hypnotic may do the patient harm. Hypnotics may be perceived as drugs of convenience and users of hypnotics as drug seekers. Primary care physicians may be unwilling to assume the risks involved with prescribing controlled substances for sleep. Finally, there is the “hassle factor,” such as the limitation on prescription quantities imposed by pharmacy benefit managers and the formulary restrictions imposed by health insurance carriers. Many physicians are reluctant to prescribe insomnia medications to avoid facing the bothersome logistical issues that may arise if a prescription is denied and the patient requires the physician to make a change. Together, these obstacles may prevent appropriate prescribing of hypnotics.

Treatment barriers
Aside from the perception that the available insomnia agents are suboptimal treatment choices that are cumbersome and even dangerous to prescribe, a number of other factors contribute to physicians’ reluctance to treat insomnia. These include the lack of evidence from well-designed, long-term trials that evaluate the chronicity of insomnia; the safety and efficacy of insomnia agents; and the benefit of treatment as shown by improved patient outcomes. Also included are the prescribing limitations recommended by the National Institutes of Health (NIH) and restrictions imposed by the US Food and Drug Administration (FDA).

One of the most fundamental problems is that there is no unequivocal system for classifying types of insomnia, and thus there is currently no consensus to help physicians identify which patients may require long-term treatment. The duration of chronic insomnia per se is largely undefined or inconsistently defined in the major clinical diagnostic texts (eg, Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised; International Classification of Sleep Disorders), which makes firm diagnoses and initiation of treatment difficult. Epidemiologic data suggest that sleep difficulties are often chronic, but few data from long-term trials of insomnia medications support the long-term use of these agents in insomnia management. Until recently, there were no data from randomized controlled trials lasting longer than 12 weeks to support longer-term use of any hypnotic. Furthermore, FDA prescribing restrictions, which were based on older NIH guidelines that have not been updated since 1984, impose limitations on the duration of hypnotic use beyond 1 month.

Although rarely acknowledged, chronic sleep disturbances are associated with a number of adverse consequences, including depression, poor daytime functioning, chronic pain, chronic medical conditions, and increased risk of accidents. Unfortunately, there are no prospective studies that show an improvement in these symptoms and comorbidities upon treatment of the insomnia; lack of such data may contribute to reticence among physicians to treat insomnia.

The medications currently available to treat insomnia are perceived to have an unfavorable risk-benefit ratio, which often results in the off-label use of sedating antidepressants as substitutes. Benzodiazepines have historically been associated
with numerous risks, such as tolerance, withdrawal, and rebound effects, as well as the potential for inappropriate use and dependence. As mentioned, these concerns are reflected in both NIH clinical treatment guidelines and FDA labeling. Perceptions of benzodiazepines have extended to encompass the newer, nonbenzodiazepine hypnotics. The view that patients who use or request hypnotics will exhibit drug-seeking behavior (eg, dose escalation, inappropriate use) is particularly strong, despite observations that patients with insomnia increase dosage only when their current dose is ineffective or if they have a history of substance abuse.

The fear of hypnotic abuse and dependence has prompted many physicians to turn to sedating antidepressants for their patients with sleep difficulties, because these agents are perceived as probably being safer and are not associated with the same risks of abuse and dependence.

In fact, trends in prescribing patterns have changed over time, and although overall prescriptions for hypnotics are steadily increasing, the predominance of benzodiazepine hypnotic use in the 1980s has given way to the current predominance of use of the nonbenzodiazepine zolpidem and the sedating antidepressant trazodone. However, there is limited evidence that antidepressants actually improve sleep, and few studies have been conducted in patients with primary insomnia. It is disconcerting, then, that trazodone is the second most popular prescription sleep medication, because along with the dearth of evidence for its efficacy in patients with insomnia, it carries risks of numerous side effects, including potentially serious cardiac effects.

Tricyclic antidepressants are also given for insomnia, but again, there is little evidence of their usefulness in affected patients, other than a single randomized, double-blind, placebo-controlled trial of one antidepressant, doxepin, in subjects with primary insomnia. Safety and tolerability concerns may overshadow the potential benefits of tricyclic agents, because these drugs are associated with a number of side effects and the potential for lethal overdose.

Though not intended for the treatment of insomnia, newer antidepressants such as mirtazapine and nefazodone have been studied for their efficacy in insomnia. They have been studied exclusively in patients with depression. Polysomnography has shown the benefit of these agents in controlled trials lasting as long as 12 weeks, although effects may not be sustained. These agents are also associated with high rates of daytime sedation, as well as liver failure (nefazodone) and weight gain (mirtazapine).

Why diagnose and treat insomnia?
Insomnia can be seen to be a complicated and potentially challenging condition to address in the primary care setting, and there are a number of barriers to recognition, diagnosis, and optimal treatment (table 1). However, there are compelling reasons why insomnia should not be ignored. A patient’s disturbed sleep may be an important indicator of various other health concerns, and insomnia that goes untreated increases the risk of consequences such as impaired memory and concentration, loss of productivity, and poorer quality of life. Untreated insomnia may also be a gateway to a host of other health problems.

PREVALENCE AND IMPACT—More than half (58%) of persons in the United States experience some kind of sleep disturbance, according to a 2000 Gallup poll conducted for the National Sleep Foundation. This survey showed that 24% of respondents had insomnia. Disturbed sleep is seen even more frequently in primary care.

Shochat and colleagues, in their study of 3 primary care practices in Hawaii and California, found the overall prevalence of insomnia to be 69% (50% occasional and 19% chronic). In other words, the prevalence of insomnia in the primary care population is roughly double that in the general population.

Chronic insomnia is associated with greater morbidity than occasional insomnia, as represented by both higher frequency and longer duration of symptoms. Shochat and associates found that the frequency in patients with occasional insomnia was 4.6 ± 4.5 nights of insomnia monthly. In patients with chronic insomnia, the average frequency was 15.3 ± 9.8 nights per month of disturbed sleep. Similarly, chronic insomnia typically lasts longer than occasional insomnia; average durations
Insomnia has a major impact on patients’ quality of life. One study indicated that persons with insomnia experience twice as many days of restricted activity and days in bed due to illness as persons without the condition, as well as 3 to 4 more days per year of absenteeism from work and 25% higher mean total healthcare costs. The investigators concluded that insomnia in the primary care setting is associated with functional impairment, reduced productivity, and increased healthcare utilization and that treating insomnia may greatly improve quality of life and increase productivity.

Worse outcomes in coexisting conditions—Insomnia not only carries its own burden of morbidity, it also worsens outcomes when it is concomitant with other conditions. Depression and chronic pain disorders have particularly strong links to sleep disturbance. McCracken and Iverson found that 88.9% of 287 patients seeking treatment in a pain clinic reported having at least 1 sleep disturbance, and more severe sleep disruption was associated with higher levels of pain, depression, and physical symptoms. Persistent insomnia may be a useful indicator of an increased lifetime risk for development of depression, and in patients with remitted depression, increasing levels of sleep disturbances may act as a harbinger for an impending episode several weeks before recurrence.

Improved outcomes after treating coexistent insomnia—Although insomnia is clearly associated with worsened outcomes in other

---

**Table 1. Barriers to diagnosis and treatment of insomnia**

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited physician training in insomnia</td>
<td>Incorporate insomnia programs into medical school and residency training programs, as well as into the major medical meeting programs and journals of primary care societies.</td>
</tr>
<tr>
<td>Lack of consistent definitions for insomnia and reliable diagnostic tools</td>
<td>Raise awareness in both patients and physicians that insomnia is highly prevalent, tends to be chronic, and is associated with increased morbidity and poorer outcomes, whether it is primary or coexistent with other conditions.</td>
</tr>
<tr>
<td>Perceptions of both patients and primary care physicians that sleep problems are less important than other complaints</td>
<td></td>
</tr>
<tr>
<td>Time constraints during office visits, which limit or prevent discussion about sleep</td>
<td></td>
</tr>
<tr>
<td>Perceptions of both patients and primary care physicians that sleep problems are less important than other complaints</td>
<td>Newer, nonbenzodiazepine hypnotics appear to be less likely than benzodiazepines to be associated with risk of abuse, tolerance, and withdrawal phenomena.</td>
</tr>
<tr>
<td>Time constraints during office visits, which limit or prevent discussion about sleep</td>
<td></td>
</tr>
<tr>
<td>Perception that all insomnia treatments are ineffective or are associated with risks of abuse or dependence</td>
<td></td>
</tr>
<tr>
<td>Prescribing restrictions recommended by outdated National Institutes of Health guidelines and imposed by US Food and Drug Administration labeling and by insurance coverage</td>
<td>The safety of newer, nonbenzodiazepine hypnotics has been shown in longer-term, open-label trials.</td>
</tr>
<tr>
<td>Lack of long-term, well-controlled trials of insomnia agents</td>
<td>Recent publication of the first 6-month, randomized, double-blind, placebo-controlled trial of an insomnia agent showed safe, sustained improvements in sleep and next-day functioning, with no evidence of tolerance.</td>
</tr>
<tr>
<td>Lack of outcomes data</td>
<td>A growing body of outcomes data suggests that treating insomnia does improve patient outcomes, although more data are needed.</td>
</tr>
</tbody>
</table>
Conclusions
Management of insomnia presents a challenge in the primary care setting, where insomnia is first seen in the majority of affected patients. Nevertheless, increased awareness, recognition and, ultimately, treatment of insomnia by primary care physicians is important because of the condition’s high prevalence, tendency to chronicity, and association with increased morbidity and poorer outcomes, whether the insomnia is primary or coexistent with other conditions.

Barriers to recognition of insomnia include lack of physician training in sleep medicine, time constraints during patient office visits, and reluctance to broach the subject of insomnia on the part of both patient and physician. Treatment barriers include lack of timely clinical guidelines, long-term data on available agents, and evidence that treatment really does improve outcomes.

The main barrier to effective insomnia management, however, is physician perception. Physician education could begin with incorporating insomnia into medical meeting programs and the journal contents of major primary care societies, such as the American College of Physicians, the American Academy of Family Physicians, and the American College of Obstetricians and Gynecologists. Also, a growing body of outcomes data suggests that treating insomnia does improve patient outcomes, although more data are needed. A number of new agents are under investigation. Recently, published results of the first 6-month, randomized, double-blind, placebo-controlled trial of an insomnia agent showed that eszopiclone therapy in patients with chronic insomnia safely resulted in sustained improvements in sleep and next-day functioning without evidence of the development of tolerance.

Despite the numerous obstacles to diagnosis and treatment, physicians need not be reluctant to discuss insomnia with their patients, and treating insomnia need not be a frightening proposition. By tackling these obstacles, primary care physicians can make use of their unique position and can positively affect the lives of their patients through timely recognition and management of insomnia.

Andrew G. Israel, MD
Dr Israel is clinical professor of medicine, University of California, San Diego, School of Medicine, and director, Hillcrest Internal Medicine, San Diego. He is a consultant for Sepracor Inc and Wyeth-Ayerst Laboratories.

Joseph A. Lieberman III, MD, MPH

Address for correspondence:
Joseph A. Lieberman III, MD, MPH
2 Aston Circle
Hockessin, DE 19707-2500

E-mail address:
jlieberman@jalmd.com
References
Practical diagnostic strategies and tools for insomnia

Paul P. Doghramji, MD

Preview

Despite the high prevalence of insomnia in the primary care setting, only a small proportion of patients report sleep problems to their physician. Evidence shows that treatment of insomnia can ameliorate the high socioeconomic burden associated with the disorder, as well as improve patient outcomes in coexistent diseases such as depression, bipolar disorder, rheumatoid arthritis, and fibromyalgia. The first strategy for improving diagnosis of insomnia is heightened awareness of the condition. As the first point of contact for most patients, primary care physicians are in a unique position to improve rates of detection and treatment. All patients should be screened for sleep disorders with such questions as “How is your sleep?” “Do you have trouble getting to sleep or staying asleep?” and “Do you get drowsy during the day or at inappropriate times?” Medical history and physical examination may also reveal possible coexistent psychiatric and medical illnesses that put patients at higher risk for insomnia, as well as suggest involvement of prescription and nonprescription medications and environmental factors that contribute to insomnia. Diagnostic tools such as the Epworth Sleepiness Scale and the Sleep Hygiene Self-Test can aid patients and physicians in recognizing sleep problems, assessing their severity, and measuring improvement after treatment.

■ Prevalence of insomnia in the primary care setting may be as high as 69%; therefore, it can be expected that primary care physicians see numerous patients who are experiencing insomnia symptoms. Despite this high prevalence, only 5% of primary care patients actively seek treatment for insomnia, and only one third of them even mention their sleep difficulties to their physician. Insomnia is associated with serious health consequences and substantial personal and socioeconomic costs. Sleep disorders and daytime sleepiness have been shown to impair cognitive, psychomotor, and occupational functioning. Socioeconomic costs include increased healthcare utilization, reduced productivity, increased accident risk, and lower quality of life among persons with insomnia. There is also evidence that improved diagnosis and treatment of insomnia can lead to improved patient outcomes in coexistent diseases such as depression, bipolar disorder, rheumatoid arthritis, and fibromyalgia. Given these findings, and in view of the fact that insomnia remains largely underrecognized, improved recognition of this condition is needed.

Making the diagnosis

An office consultation provides an opportunity to diagnose insomnia in patients presenting with sleep complaints, those with coexistent illnesses, and even those with unrelated problems. Asking about sleep problems should be a part of every interview with patients in whom insomnia is a possibility. Simple questions may be used to open up a dialogue regarding the presence of insomnia, its consequences, and its symptoms. In addition, interviewing the patient’s bed partner may be extremely useful in detecting other symptoms that indicate coexistent illnesses or primary sleep disorders (eg, snoring in a patient with sleep apnea, limb movement in a patient with rest-
symptoms). In all cases, a carefully obtained history and a physical examination aid in identifying primary sleep disorders as well as primary conditions that may lead to insomnia.

SYMPTOMS OF INSOMNIA—The Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised, defines insomnia as difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning. Therefore, physicians should ask about the main insomnia criteria of sleep initiation, sleep maintenance, and nonrefreshing, non-restorative sleep. The last criterion is more difficult to define than the others, and physicians should be alert to its appearance.

During the patient interview, the focus should also include recognized consequences of insomnia and questions about specific symptoms. These include the following:

• Sleepiness (drowsiness) at inappropriate times (including nodding off when sedentary and rapid eye movement sleep phenomena such as hypnagogic hallucinations)
• Psychiatric symptoms (eg, irritability, moodiness, disinhibition, apathy, flattened affect)
• Compromised executive function or mistakes (eg, impaired memory, inflexible thinking and impaired planning skills, inability to be creative or multitask)
• Poor motor skills or mistakes (sometimes caused by “microsleeps” of 5 to 10 seconds, creating lapses in attention)
• Fatigue
• More frequent doctor visits, representing more illnesses

DETERMINING THE UNDERLYING CAUSE—Insomnia may coexist with other medical and psychiatric conditions that contribute to sleep disorder symptoms. It can also be a diagnostic criterion for a disease, as in the case of depression. The first several questions of the Hamilton Rating Scale for Depression specifically address the presence of sleep problems. Specific diagnostic questions can inform the physician about the coexistent condition and lead to differential diagnosis of the cause of the insomnia. For example, almost all psychiatric illnesses can have associated sleep disturbance (table 1). Mood disorders (ie, depression, bipolar disorder, and dysthymia) often cause problems with sleep initiation or waking in the night. Anxiety disorders may impact the amount and quality of sleep when the patient’s thoughts keep him or her awake. Substance abuse, another condition correlated with insomnia, has a high prevalence in certain populations (eg, college students) and can negatively affect quantity and quality of sleep.

Numerous medical conditions result in disturbed sleep

<table>
<thead>
<tr>
<th>Psychiatry causes</th>
<th>Drug or alcohol intoxication or withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood disorders (depression, bipolar disorder, dysthymia)</td>
<td></td>
</tr>
<tr>
<td>Anxiety disorders (generalized anxiety disorder, panic disorder, posttraumatic stress disorder)</td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
</tr>
<tr>
<td>Life stressors</td>
<td></td>
</tr>
<tr>
<td>Conditioning (associating the bed with wakefulness)</td>
<td></td>
</tr>
<tr>
<td>Mania or hypomania</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td>Eating disorders</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Primary sleep disorders</td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td></td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td></td>
</tr>
<tr>
<td>Periodic limb movement disorder</td>
<td></td>
</tr>
<tr>
<td>Circadian rhythm disorder</td>
<td></td>
</tr>
<tr>
<td>Parasomnias</td>
<td></td>
</tr>
<tr>
<td>Narcolepsy</td>
<td></td>
</tr>
<tr>
<td>Medical causes</td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>(congestive heart failure, angina)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted, with permission, from Benca et al, Chokroverty, and Doghramji.
patients with metabolic syndrome. Besides illnesses that cause insomnia, a multitude of nonprescription and prescription drugs used to treat these illnesses are also associated with insomnia, so a careful inquiry into the patient’s current medications is highly recommended (table 2). Some of the medications most commonly associated with insomnia are antihypertensives, such as β-blockers, α-blockers, methyldopa, and reserpine.

Finally, environmental factors may have a role in insomnia, and patients should be questioned about their sleep environment and sleep hygiene behavior (table 3). Some environmental factors lead to self-induced sleep deprivation, which is the most common cause of daytime sleepiness in the United States. Groups at risk for deprivation-induced sleepiness include night shift workers (whose sleep during the day is often cut short), physicians in training, truck drivers, parents of young children, and teenagers.

Clinical pearls: diagnosis of insomnia in primary care

- Asking patients whether they have trouble getting to sleep (sleep initiation), trouble staying asleep (sleep maintenance), waking up too early, or sleep that is nonrefreshing and nonrestorative can aid in detection of insomnia.
- Questions about consequences of insomnia—such as sleepiness at inappropriate times, psychiatric symptoms, compromised decision making, poor motor skills, fatigue, and more frequent doctor visits, representing more illnesses—may reveal hidden sleep problems.
- Patients with primary sleep disorders may be screened by primary care physicians and referred to sleep specialists. Indicators of obstructive sleep apnea, the most common primary sleep disorder, are obesity, crowded pharynx, snoring, daytime drowsiness, and hypertension.
- At visits for other acute or chronic complaints, sleep disorders can be detected through examination and a few simple questions: “How is your sleep?” “Do you have trouble getting to sleep or staying asleep?” and “Do you find you are sleepy or drowsy during the day or at inappropriate times?” These questions take little time but are invaluable in uncovering the warning signs of a sleep disorder.
- Diagnostic questionnaires, such as the Epworth Sleepiness Scale and the Sleep Hygiene Self-Test, as well as sleep diaries can aid patients in recognizing their own sleep problems, assessing severity, and measuring improvement after treatment.

An epidemiologic survey of patients presenting to a primary care clinic in Italy found that among those patients suffering from insomnia (64%), insomnia was coexistent with primarily cardiovascular, musculoskeletal, gastrointestinal, and endocrine illnesses (figure 1). This study showed a significantly higher rate of medical disease in patients with insomnia (57%) than in those without insomnia (40%) ($P<.0001$).

In addition, primary sleep disorders other than insomnia (see table 1) may mimic insomnia in terms of impaired sleep and disturbances in next-day function. One of the most prevalent primary sleep disorders is obstructive sleep apnea (OSA), which is a form of airway obstruction during sleep and causes loud snoring and frequent arousals. Although OSA is often related to obesity, almost 30% of affected patients are not overweight. Prevalence rates for OSA are estimated to be 4% in middle-aged men and 2% in women, but these numbers are viewed by many investigators to be significantly underestimated. Moreover, in spite of all its consequences in addition to sleepiness—including resistant hypertension, chronic heart failure, cor pulmonale, nocturnal angina, stroke, and arrhythmias—OSA often goes undiagnosed, and some statistics show that the disorder is diagnosed in only 15% of those affected. Primary care physicians are well placed for identifying and recommending subspecialist care for this common sleep disorder, particularly in their overweight patients with metabolic syndrome.

Important factors in systems review and medical examination

Patients usually see their primary care physician for one of three types of encounters: an acute visit, a periodic health screening examination (complete physical examination), or a follow-up visit for a chronic problem. Insomnia is rarely the primary complaint at any of these visits, and insomnia symptoms often go unreported.

MEDICAL HISTORY—During an acute visit with a patient who
presents with pain, shortness of breath, nocturnal symptoms, or the like, the physician should ask whether the symptoms disrupt sleep or result in daytime symptoms of sleepiness.

During a complete periodic health screening examination, the first item in the review of systems is the central nervous system, which can be introduced with three simple questions regarding the patient’s sleep health: “How is your sleep?” “Do you have trouble getting to sleep or staying asleep?” and “Do you find you are sleepy or drowsy during the day or at inappropriate times?” These basic questions can be included in a standard visit without extra time or effort, and they are invaluable in detecting the warning signs of a sleep disorder.

During a follow-up visit for a chronic problem that could conceivably result in disturbed sleep, the physician should specifically ask the patient for a history of sleep disturbance.

The patient may report tiredness, and the physician should attempt to clarify this symptom and distinguish fatigue (either physical or mental) from sleepiness, since the word tiredness is used colloquially to mean both sleepiness and fatigue (exhaustion).

A history of current or previous medical or psychiatric illness is helpful in determining the cause of a sleep disturbance. Aside from common causes of insomnia (ie, psychiatric and medical illnesses and the med-
ications used to treat them [see tables 1 and 2]), numerous symptoms are indicative of other illnesses that cause insomnia, and systematic inquiry regarding these symptoms is useful. For example, hypertension and metabolic syndrome are commonly associated with insomnia, and obesity can be indicative of OSA. In addition, pain is present in a multitude of illnesses, including rheumatoid arthritis and cancer, and can often be associated with disturbed sleep. Perimenopausal symptoms also commonly include insomnia. A family history is useful because certain primary sleep disorders (eg, OSA, narcolepsy) have a hereditary component. Finally, a review of systems can help determine whether the patient suffers from consequences of insomnia, such as excessive daytime sleepiness, lack of energy, trouble getting to sleep or staying asleep, or drowsiness while driving.

**PHYSICAL EXAMINATION**—The physical examination presents an opportunity to detect important signs suggesting an underlying sleep disorder or an illness leading to insomnia. A general overview should include noting whether the patient appears drowsy or alert and whether there is any source of pain, particularly in the joints, that could cause sleep problems. Specific abnormalities to look for include resistant hypertension, which can be indicative of OSA; pathologic central nervous system findings or peripheral neuropathy, which may be causing nighttime pain; edema in the extremities, which may suggest congestive heart failure; or arthropathy. Certain physical characteristics may indicate risk for sleep disorders. Pharyngeal crowding, central (truncal) obesity, and a neck circumference of >16 in. for women or >17 in. for men may indicate possible OSA. Chest auscultation may reveal evidence of congestive heart failure, chronic obstructive pulmonary disease, or asthma, all of which can cause insomnia.

**Use of diagnostic tools**
Diagnostic tools such as questionnaires can point to the possibility of insomnia and help open a dialogue about insomnia between physician and patient. For example, the Epworth Sleepiness Scale (ESS) measures how drowsy the patient is and, thus, how likely he or she is to fall asleep during daytime activities; it therefore measures excessive daytime sleepiness and the possible presence of a sleep disorder (see box at left). This scale may be used as either a screening or a diagnostic tool and can demonstrate improvement after treatment in patients with severe sleep problems. It is therefore highly beneficial to have an ESS included as a permanent part of the chart in patients with insomnia.

**Table 3. Environmental causes of insomnia**

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep deprivation</td>
</tr>
<tr>
<td>Uncomfortable bedroom temperature</td>
</tr>
<tr>
<td>Poor air circulation in bedroom</td>
</tr>
<tr>
<td>Noise</td>
</tr>
<tr>
<td>Poor sleep hygiene (eating, exercise, and/or caffeine or alcohol use before bedtime)</td>
</tr>
<tr>
<td>Jet lag</td>
</tr>
<tr>
<td>Shift work</td>
</tr>
<tr>
<td>Daytime napping</td>
</tr>
</tbody>
</table>

*Adapted, with permission, from Doghramji.*

**Epworth Sleepiness Scale**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing (0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Watching television</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting inactive in a public place (eg, in a theater or at a meeting)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>As a passenger in a car for 1 hr without a break</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Lying down to rest in the afternoon</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Sitting quietly after lunch (when you’ve had no alcohol)</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>In a car, while stopped in traffic</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

Total score*  

0 = no chance of dozing; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing

* Total score of 10 or more indicates possible excessive daytime sleepiness or sleep disorder.

*Adapted, with permission, from Johns.*

Continued on page 21
Figure 2. The Epworth Sleepiness Scale (ESS): comparison across samples.

Adapted, with permission, from Johns.32

Sample sleep diary for use by patients with insomnia

<table>
<thead>
<tr>
<th>Name:</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete in morning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedtime (date/time)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise time (date/time)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated time to fall asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated number of awakenings and total time awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated amount of sleep obtained</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete at bedtime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naps (number, time, and duration)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks (number and time)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>List stresses of the day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate how you felt today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = Very tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Somewhat tired/sleepy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Fairly alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Wide awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Some</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 = Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 = Fairly high</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 = High</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted, with permission, from reference 33.
### Sleep Hygiene Self-Test

On 3 or more occasions in the past month, have you:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stretched your muscles (eg, arms, back, legs) regularly during the day?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Drunk coffee, tea, cocoa, or colas or other caffeinated soft drinks after noon?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Eaten chocolate candies or desserts (including ice cream) after dinnertime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Taken pain relievers that contain caffeine or other stimulants?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Taken any stimulants or over-the-counter “stay alert” pills?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Walked rather than driven to work, to the store, to visit friends, and so on?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Taken any over-the-counter diet pills?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Eaten chocolate candies or desserts (including ice cream) after dinnertime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Taken pain relievers that contain caffeine or other stimulants?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Taken any stimulants or over-the-counter “stay alert” pills?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Followed a formal exercise program and exercised?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Drunk 12 oz or more of water, soda, and so on, within 1 hour before bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Drunk alcohol or alcohol-based sleep medication to help you get to sleep?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Exercised rigorously within 2 hours before bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Slept late into the morning (more than 90 minutes after usual waking time)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Gone to bed at roughly the same time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Watched television up until bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Talked on the phone for long periods within 2 hours before bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Taken naps during the day?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Eaten meals or snacks in your bed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Engaged in daily activities during which your heart rate increased significantly?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Tossed and turned for hours in your bed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Eaten spicy foods or snacks within 2 hours before bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Fallen asleep with the television, radio, or stereo turned on?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Slept in a room that was uncomfortably hot or cold?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Relaxed by reading, listening to soothing music, and so on before going to bed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Slept with the light on or a light shining into your bedroom?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Slept in a room where you were bothered by noises of some sort?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Eaten dinner within 2 hours of bedtime?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. Eaten spicy foods or snacks within 2 hours before bedtime?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total score***

* For questions 1, 6, 11, 16, 21, and 26, “yes” is scored as 0 and “no” is scored as 1. For all other questions, “yes” is scored as 1, and “no” is scored as 0. Lower total scores indicate more adaptive sleep hygiene.

Adapted, with permission, from Blake and Gomez.24
Figure 2 shows the range of scores across diagnostic groups of patients, including those without sleep problems and patients with OSA, narcolepsy, and other sleep disorders.\(^3\) Scores from the ESS have been significantly correlated with sleep latency (time taken to fall asleep) as measured by overnight polysomnography.\(^3\)

Additional diagnostic tools are the sleep diary (see box on page 19) and the Sleep Hygiene Self-Test (see box on page 20). The sleep diary is helpful in patients with apparent insomnia as a means of quantifying the severity of the sleep problem, determining whether a sleep problem truly exists, and measuring improvement.\(^3\) It is also useful in patients who are hazy about their sleep when initially questioned and can therefore use the diary to track their sleep. Patients with sleep problems keep a night-to-night account of their sleep schedule and perception of sleep. The Sleep Hygiene Self-Test, in contrast, helps patients who are resistant to treatment recognize their sleep problem by assessment and quantification of the problem.\(^3\) The questionnaire has the patient assess his or her own night behaviors and environment, and it scores the effect of these behaviors on sleep induction. Lower total scores indicate more adaptive sleep hygiene.

### Initiating treatment and referral to a sleep expert

Once the physician has confirmed the presence of a sleep disorder, options include initiation of treatment or, in patients with a complex or primary sleep disorder, referral to a sleep specialist. Referral is appropriate for chronic, resistant, unexplained insomnia. Unusual sleep behaviors that occur with or without sleepiness, such as hypnagogic hallucinations, are also cause for referral to a specialist. Finally, patients who experience drowsiness or “microsleeps” while driving should be considered a “sleep emergency” and immediately treated or referred to a sleep expert.

### Conclusion

Insomnia is highly prevalent in primary care and is associated with a high physical and social burden. Although time constraints may limit physicians’ capacity to ask patients about insomnia, a few simple questions can elicit information about sleep problems and highlight the need for further inquiries. A small increase in detection of sleep problems by primary care physicians may result in substantial benefit to patients. During the physical examination, it is important to note any signs that suggest an underlying sleep disorder or an illness leading to insomnia. Diagnostic questionnaires administered in the office setting can also help to raise the index of suspicion for a sleep problem. Referral to a sleep medicine physician or expert should always be considered in complex cases or those in which a primary sleep disorder is suspected.

---

**References**


---

**Address for correspondence:**

Paul P. Doghramji, MD
Brookside Family Practice & Pediatrics
Pottstown Medical Specialists
1555 Medical Dr
Pottstown, PA 19464

**E-mail address:**

hyedoc@pol.net
in severe and mild insomniacs compared with good sleepers. Psychosom Med 2001;63(1):49-55
25. Richardson GS, Miner JD, Czeisler CA. Impaired driving performance in shiftworkers: the role of the circadian system in a multifactorial model. Alcohol Drugs Driving 1989-90;5(6-4-1):265-73
34. Blake DD, Gomez MH. A scale for assessing sleep hygiene: preliminary data. Psychol Rep 1998;83(3 Pt 2):1175-8

NOTES
Behavioral and pharmacologic management options for insomnia

Ruth M. Benca, MD, PhD

Preview
Sleep and wakefulness are both active processes regulated by complex neural networks, the precise mechanisms of which are not yet fully understood. Patients with insomnia, particularly primary insomnia, often exhibit hyperarousal and may receive therapies to reduce wakefulness and promote sleep. Apart from standard sleep hygiene measures, physicians can offer patients behavioral therapy (if available) or pharmacologic therapy, or both. Both provide relief for insomnia symptoms; however, that relief appears durable on cessation of behavioral therapy only. Practice parameters for the treatment of insomnia are available for the use of behavioral therapy, but those for pharmacologic therapy are dated and do not reflect the current state of clinical practice. Hypnotic agents currently approved for use by the US Food and Drug Administration may be used for only 4 weeks and are limited by variable efficacy and concerns about safety profiles. This situation has prompted many physicians to prescribe antidepressants and other agents for their sedating properties, despite a paucity of efficacy and safety data in patients with insomnia. Of the hypnotic agents currently under clinical investigation, so far only eszopiclone has been studied in regard to efficacy over a prolonged period (6 months) with no evidence of significant tolerance. Although reports suggest that other hypnotics may also provide longer-term benefits, further research is needed to determine the optimal duration of treatment in chronic insomnia.

Updated clinical guidelines that encompass both behavioral therapy and pharmacologic treatment of primary insomnia are yet to be developed. Although practice recommendations for the evaluation and behavioral treatment of chronic insomnia were made about 5 years ago, the last official guidelines for the pharmacologic treatment of insomnia were developed 20 years ago at the Drugs and Insomnia Consensus Conference, convened by the National Institutes of Health (NIH). The development of new practice parameters has been hindered, in part, by a lack of well-conducted efficacy studies. In recent years, however, important advances have been made in this area. Successful attempts have been made to integrate behavioral therapies into the primary care setting; however, their general availability is limited, and because of this, pharmacotherapy remains the cornerstone of treatment. Over the short term, hypnotic therapy resolves symptoms of insomnia, but only one randomized, placebo-controlled, double-blind study has examined the long-term effects of treatment. Given the lack of long-term data and on the basis of the 1984 NIH consensus conference guidelines, the US Food and Drug Administration (FDA) has approved only short-term use (4 weeks) of currently available hypnotic agents.
The paucity of long-term outcomes data has created several misconceptions about hypnotic use. For example, the association of benzodiazepines with next-day dysfunction, dependence, abuse, and tolerance has had a ripple effect on the way all hypnotics have been perceived. This may partly explain why patients with insomnia are not always offered the full range of potentially effective treatment strategies. Pathophysiologic mechanisms

Both sleep and wakefulness are active processes that are mediated by separate but interacting neural systems. There is strong evidence to suggest that a complex sleep-switch mechanism, located within the hypothalamus, mediates sleep and arousal. Results from various studies, although not conclusive, indicate that patients with primary insomnia show evidence of hyperarousal. However, they often report tiredness and impairments in memory, concentration, attention, and reasoning. Patients with objectively defined chronic insomnia were also shown to have a significantly higher metabolic rate than that in age-, sex-, and weight-matched subjects with normal sleep. Findings from another small cohort study (n=14) revealed that young patients with insomnia (mean age, 31 years) had significantly greater activation of the hypothalamic-pituitary-adrenal (HPA) axis than matched controls over a 24-hour assessment period. In this study, plasma levels of corticotropin and cortisol were used as an index for HPA-axis activation. These data complement findings that patients with insomnia have higher core body temperatures, a higher metabolic rate, and a tendency to secrete higher quantities of cortisol and excrete higher quantities of adrenaline.

Data from cohort studies using quantitative electroencephalographic techniques indicate heightened arousal of the central nervous system; compared with controls who have good sleep, patients with insomnia display increased high-frequency electroencephalographic wave activity in the beta range during non–rapid eye movement sleep. This type of electrical activity is usually representative of the normal waking rhythm of the brain, which is associated with active thinking, attention, focus on the outside world, and problem solving. Thus, evidence to date suggests a persistent increase in activity of arousal systems in patients with primary insomnia.

Treatment goals

The aims of behavioral and pharmacologic therapy, either alone or in combination, are to decrease arousal level and promote sleep, thereby restoring normal daytime function. The
optimum duration of treatment that would achieve these aims is not yet known.21 Until recently, there was also limited direct evidence to indicate which measures of improved sleep (eg, sleep maintenance, more rapid sleep onset) are correlated with daytime function benefits.23 Nevertheless, some daytime function domains that were self-reported in cohort studies as being impaired have shown subjective improvement after treatment in clinical trials.

Insomnia is a heterogeneous complaint, characterized by shifting patterns of symptoms.24 It is not unusual for a patient with sleep-onset insomnia to later have problems maintaining sleep (staying asleep at night), or vice versa. Because the symptoms of insomnia may change over time, it may be useful that therapy for chronic insomnia reduces the amount of time required to fall asleep (sleep-onset latency), as well as the number and duration of awakenings from sleep (sleep maintenance).25 It is generally assumed that parameters such as number of awakenings and wake time after sleep onset are relevant markers for sleep maintenance. Unfortunately, objective and subjective responses to treatment in clinical trials have not always been consistent.21

**Behavioral therapy**

Behavioral therapy is aimed at reducing autonomic and cognitive hyperarousal, as well as resultant maladaptive behaviors (eg, irregular sleep times, napping).26 A meta-analysis comparing cognitive-behavioral and pharmacologic therapies27 found that after termination of acute treatment, the two were equally efficacious, although there was some indication that cognitive-behavioral therapy may be superior for sleep-onset problems. Patients with primary insomnia can derive benefit from a range of behavioral interventions, including sleep hygiene measures, stimulus control, sleep restriction, cognitive therapy, progressive muscle relaxation, paradoxical intention, biofeedback, relaxation training, and imagery training28 (table 1). Education about the practice of good sleep hygiene is crucial. Although sleep hygiene practice may not be as effective as stimulus control or sleep restriction,26 it does ensure that patients will not engage in activities that may compromise their sleep.

About 70% to 80% of patients with chronic insomnia benefit from behavioral therapy.29 In those who respond, a normalization of sleep-onset latency to ≤30 minutes generally occurs, and increases in total sleep duration (about 30 minutes) are also reported. Sleep quality and patient’s satisfaction with sleep patterns are also significantly improved. One of the advantages of behavioral treatments is that the improvements appear to be sustained for at least 6 months after therapy has stopped.26 Clinical data supporting the efficacy of behavioral therapy are strongest for stimulus control, progressive muscle relaxation, and paradoxical intention. Data pertaining to the efficacy of sleep restriction, biofeedback, and multifaceted cognitive-behavioral therapy so far are less convincing. Of note, no behavioral therapies have been shown to lead to improvement in day-time function.28

Although behavioral therapy is highly acceptable to patients,29 it has several limitations. For instance, its implementation into the primary care setting requires considerable resources, because a trained healthcare professional is required to deliver this therapy. Given the high prevalence of insomnia among the adult population, behavioral therapy is unlikely to be available for all patients in the immediate future. In addition, patients must also be motivated to comply with this treatment.

**Pharmacotherapy**

All hypnotic agents currently approved for use in the treatment of primary insomnia (table 2) act at γ-aminobutyric acid A (GABA_A) receptor sites, which mediate the fast inhibitory synaptic response produced by activity in GABAergic neurons. Hypnotic agents facilitate the opening of GABA-activated chloride channels and, therefore, enhance the response to GABA. Their overall effect is probably to inhibit activity in arousal centers as well as to promote sleep.

Although not FDA-approved for this indication, a variety of agents, including sedating antidepressants and antihistamines, are also used as treatments for insomnia. Sedative effects of antidepressants and antihistamines are exerted by means of histaminergic blockade on either H_1 or H_2 receptors, or both.

**DRUGS ACTING AT THE GABA_A RECEPTOR**—These hypnotics include the benzodiazepines and the structurally
unrelated nonbenzodiazepines. The latter exhibit differential binding affinities for subunits on the GABA<sub>A</sub> receptor complex, which may partly explain their diverse clinical profiles. With the exception of flurazepam, currently available benzodiazepines have consistent-ly demonstrated subjective reductions in sleep latency.\textsuperscript{30-36} The subjective sleep-onset efficacy data for flurazepam are equivocal\textsuperscript{30-32,37,38} although this hypnotic has shown short-term objective efficacy for this parameter.\textsuperscript{39} Only the longer-acting benzodiazepines (eg, flurazepam, quazepam, estazolam) have demonstrated objective and self-reported reductions in wake time after sleep onset and number of awakenings, and thus improved sleep maintenance,\textsuperscript{30-32,38-41} although the longest period of active drug administration in studies of benzodiazepine

| Table 1. Summary of common behavioral therapies for primary insomnia |
|--------------------------|----------------------------------------------------------------------------------|
| **Type**                 | **Principle and practice**                                                       |
| **Sleep hygiene measures** | To normalize sleep patterns by reducing or eliminating maladaptive behaviors           |
|                          | The patient should:                                                               |
|                          | • Go to bed only when tired                                                        |
|                          | • Get up at the same time each morning, including weekends                         |
|                          | • Reduce or eliminate use of alcohol; avoid alcohol 4 hr before bedtime             |
|                          | • Reduce or eliminate use of caffeine; avoid caffeine 6 hr before bedtime           |
|                          | • Reduce or eliminate use of nicotine; avoid nicotine 6 hr before bedtime           |
|                          | • Exercise regularly, but avoid strenuous exercise 2-4 hr before bedtime            |
|                          | • Engage in only relaxing activities before bedtime                                 |
|                          | • Make sure the bedroom and the temperature of the bedroom are comfortable         |
| **Stimulus control**     | To remove negative conditioning for sleep by avoidance of waking time in bed       |
|                          | The patient should:                                                               |
|                          | • Retire only when sleepy and after set bedtime                                     |
|                          | • Leave the bed after 20 min if unable to sleep or worried                         |
|                          | • Return to bed when feeling sleepy                                                |
|                          | • Arise at a set wake-up time                                                      |
|                          | • Avoid daytime napping                                                            |
| **Sleep restriction**    | To limit the amount of time spent in bed to only time spent asleep                  |
|                          | The patient should:                                                               |
|                          | • Restrict the time spent in bed to amount of time actually spent sleeping (ie, if the patient spends 8 hr in bed but only 4 hr sleeping, the following night he or she should stay in bed for only 4 hr) |
|                          | • Increase time spent in bed only as sleep improves and time asleep increases      |
| **Cognitive therapy**    | To remove patients’ sleep misperceptions                                           |
|                          | The physician should:                                                             |
|                          | • Correct dysfunctional beliefs or opinions about sleep                             |
|                          | • Remove patients’ unrealistic expectations of sleep                               |
|                          | • De-emphasize the importance of sleep                                             |
| **Progressive muscle relaxation** | To remove symptoms of insomnia by practicing a deep relaxation technique         |
|                          | In a specific order, the patient should tense (or tighten) one muscle group at a time, then release the tension |
| **Paradoxical intention** | To reduce the performance anxiety caused by trying to fall asleep, which is thought to prevent adequate quantity and/or quality of sleep |
|                          | The patient is persuaded to engage in the most feared behavior that makes him or her stay awake. As the patient stops trying to fall asleep, the performance anxiety arising from trying to fall asleep gradually dissipates |
hypnotics was only 2 weeks. Of note, the reductions in wake time after sleep onset associated with flurazepam use were observed only over the first 2 nights of administration and were absent by study night 7.38

Similar to that of other benzodiazepines, the long-term clinical efficacy of temazepam has yet to be characterized. In short-term studies (≤5 weeks), the objective hypnotic efficacy of temazepam has been variable. Of the 3 placebo-controlled trials of temazepam that used polysomnography to measure sleep,4,42,43 2 reported reductions in sleep latency,5,42 but the other study failed to detect this effect.43 In addition, in one of the studies,8 there were no significant differences between temazepam and placebo regarding number of awakenings and waking time after sleep onset, whereas the others reported mixed effects.42,43 The shorter-acting agent triazolam has shown efficacy with sleep onset more often than sleep maintenance,44,45 although some studies35,45 have shown that triazolam reduced the number of awakenings as well.

Finally, a meta-analysis of benzodiazepine use in insomnia,46 which pooled data from 45 placebo-controlled studies (total N=2,672), indicated that benzodiazepines were not associated with a statistically significant reduction in sleep latency. However, total sleep time was increased by about 1 hour, which suggests that when data for all benzodiazepines are combined, there is an effect on sleep-maintenance measures.

Benzodiazepine use may be limited by adverse effects that are partly related to their elimination half-lives (see table 2). Whereas the intermediate duration of temazepam’s half-life enables a reasonable level of alertness on awakening,34 longer-acting estazolam and flurazepam may be associated with next-day residual effects.32 Triazolam10,35 and, to a lesser extent, temazepam4 have a tendency to induce rebound insomnia. Triazolam has also been associated with pharmacologic tolerance.10

The nonbenzodiazepine hypnotic agents zolpidem47-50 and zaleplon51-53 may have less tendency to induce rebound insomnia, tolerance, or next-day residual and adverse effects when given at recommended therapeutic doses. The efficacy data for zolpidem are an example of when subjective and objective sleep outcomes are not always in agreement. In placebo-controlled trials of up to 5 weeks’ duration, zolpidem improved all self-reported measures of sleep; however, objective data indicated that zolpidem reduced sleep latency but not necessarily sleep maintenance in patients with insomnia.47-50 The sleep improvements produced by zolpidem have not been shown to enhance daytime function, as assessed by the Sheehan Disability Scale,54 although no evidence of impaired daytime function has been reported in placebo-controlled trials.55,56

Zaleplon improved objective and self-reported measures of sleep latency, as evidenced by dose-dependent (range, 5-20 mg per night) improvements in this parameter over a 4-week period.51,52 Polysomnographic recordings and subjective assessments revealed that the initially-recommended dosage of zaleplon (5 or 10 mg per night) did not improve total sleep time or number of awakenings relative to placebo, likely because of its short half-life (1 hour).52 The absence of next-day residual effects associated with zolpidem and zaleplon and their low risks for producing rebound insomnia have made these agents useful options for patients with sleep-onset insomnia.

ANTIDEPRESSANTS—The sedating properties of some antidepressants are commonly exploited to treat comorbid

### Table 2. Hypnotic agents approved by the US Food and Drug Administration for use in primary insomnia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nightly dose (mg)</th>
<th>Elimination half-life (hr)</th>
<th>Active metabolite</th>
<th>Type of metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25</td>
<td>2-4</td>
<td>No</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15-30</td>
<td>8-20</td>
<td>No</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Estazolam</td>
<td>1-2</td>
<td>10-24</td>
<td>No</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Quazepam</td>
<td>15</td>
<td>25-41</td>
<td>Yes</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15-30</td>
<td>24-100</td>
<td>Yes</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Nonbenzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaleplon</td>
<td>10</td>
<td>1</td>
<td>No</td>
<td>Oxidation</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5-10</td>
<td>1.5-2.5</td>
<td>No</td>
<td>Oxidation</td>
</tr>
</tbody>
</table>
depression and insomnia (table 3). Their prolonged, continuous use in depressive illness, coupled with a lack of long-term clinical data for standard hypnotic agents, appears to have resulted in their widespread use for primary insomnia as well. 

The efficacy and safety of antidepressants in primary insomnia have been evaluated in only two randomized, placebo-controlled studies to date, however.\textsuperscript{54,55} The results from one study involving 40 patients with primary insomnia\textsuperscript{54} showed that low-dose doxepin (25-50 mg) over the short term (1 night) and medium term (28 nights) improved objective measures of sleep efficiency, total sleep time, wake time after sleep onset, and stage 2 sleep percentages. Although doxepin did not produce an overall rebound effect on the basis of these parameters, patients with severe rebound insomnia were more likely to have received doxepin than placebo. Importantly, patients’ self-ratings documented improved sleep quality and next-day working ability with doxepin use.

Findings from the other study (N=188)\textsuperscript{55} indicated that self-reported measures of sleep onset and total sleep time improved with trazodone (50 mg per night) during the first week, but not the second week of therapy. Trazodone has largely been investigated in depressed or dysthymic patients with insomnia or in patients who have insomnia related to treatment with stimulant antidepressants. Studies conducted in depressed patients\textsuperscript{56-59} generally showed improved time to sleep onset and improved patient-perceived sleep quality. The studies conducted in patients with iatrogenic insomnia\textsuperscript{60,61} revealed improvement on measures of total sleep time and number of awakenings in only one study.\textsuperscript{60}

In general, trazodone and doxepin should not be discontinued abruptly, because serious withdrawal effects (eg, rebound insomnia, tachycardia) may occur. This phenomenon makes occasional use of tricyclics, in particular, difficult. Tricyclic antidepressants and, to a lesser extent, trazodone are also associated with anticholinergic side effects (eg, development of arrhythmias, orthostatic hypotension, dry mouth, constipation, urinary retention, sweating, cognitive deficits). In addition, priapism\textsuperscript{62} is a rare but serious side effect of trazodone therapy. Because the antidepressants are all extensively metabolized by oxidative reactions in the liver, interactions with drugs that are also metabolized by this route need to be considered.

In the only other study of antidepressant use in patients with primary insomnia (N=15),\textsuperscript{63} open-label paroxetine produced change-from-baseline improvements in self-reported sleep quality that were not accompanied by increased sleep quantity.

**ANTIHISTAMINES**—Sedating antihistamines (eg, diphenhydramine, hydroxyzine) are often used by patients to induce sleep because of their availability and relatively low cost. However, these agents have shown minimal efficacy in placebo-controlled studies and are associated with next-day residual sedation, psychomotor impairment, anticholinergic side effects, and pharmacologic tolerance.\textsuperscript{64-67}

**OTHER AGENTS**—Several other drugs have been used in the treatment of insomnia despite a paucity of efficacy and safety data. γ-Hydroxybutyrate,

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Elimination half-life (hr)</th>
<th>Active metabolite</th>
<th>Type of metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>50-150</td>
<td>5-9</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25-100</td>
<td>24</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Doxepin</td>
<td>25-50</td>
<td>8</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>400-600</td>
<td>2-4</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5-15</td>
<td>24-48</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-30</td>
<td>19-26</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100-300</td>
<td>15-19</td>
<td>Yes</td>
<td>Oxidation and conjugation</td>
</tr>
</tbody>
</table>
a metabolite of GABA used for treating narcolepsy, increases the proportion of slow-wave and rapid eye movement sleep and may provide sleep consolidation; however, this agent has a low therapeutic index, thus rendering it unsuitable for widespread use.

Melatonin has been used as an over-the-counter alternative medicine for primary insomnia. It has been reported to induce sleep in healthy volunteers, as well as elderly patients and medically ill patients with insomnia, by an action unrelated to its hypothermic effects. Data pertaining to its effect on other measures of sleep are variable. In a study involving monitoring of sleep-wake patterns with actigraphy, 7-day regimens of immediate-release or sustained-release melatonin (2 mg) were associated with reduced sleep latency and increased sleep efficiency, respectively. Sleep latency and efficiency improved further when 1 mg of sustained-release melatonin was administered over a 2-month period, which is indicative of a lack of tolerance. Objective and self-reported findings from another study in elderly patients with sleep-maintenance insomnia also indicated that melatonin reduced sleep latency but did not improve total sleep time, sleep efficiency, or wakefulness time after sleep onset. Indeed, even patients with low melatonin production did not respond to treatment. In contrast, melatonin in doses of 0.1 mg, 0.3 mg, and 3.0 mg improved sleep efficiency in 15 elderly patients with insomnia but not in 15 elderly patients with good sleep. No well-controlled safety data on melatonin use are available at present.

Valerian, an herbal product from the plant Valeriana officinalis, is widely used as a sleep aid in Europe. Because its active ingredient has yet to be identified, its hypnotic mechanism of action is not yet known. According to self-reported measures of hypnotic efficacy in small, poorly designed trials, valerian is associated with reduced sleep latency as well as increased total sleep time and sleep quality. On the basis of case reports, valerian is also associated with hepatotoxicity, residual next-day sedation, and withdrawal effects. There are insufficient data on its hypnotic efficacy and safety to recommend its use in primary insomnia.

**NEWER AGENTS**—Several novel anti-insomnia agents are currently in clinical development. In one randomized, placebo-controlled study of 308 patients with chronic insomnia, eszopiclone (2 or 3 mg) resulted in objective and self-reported improvements in sleep latency, sleep efficiency, total sleep time, and quality and depth of sleep over the entire 44-night treatment period. The results of another randomized study (N=788) showed that eszopiclone (3 mg per night) was effective over a 6-month continuous treatment period; there were subjective improvements in sleep latency, sleep maintenance, and sleep quality compared with placebo. Importantly, next-day measures of daytime alertness and daytime ability to function were also significantly improved. There was no evidence of pharmacologic tolerance or next-day residual effects in either study.

Indiplon is another nonbenzodiazepine hypnotic in phase 3 clinical development. An immediate-release formulation of this agent was shown to have efficacy for polysomnographic and patient-reported sleep-onset measures as well as total sleep time in 194 adult patients over a 5-week period. Sleep quality was also improved, and the drug was well tolerated. In another 2-week study, the modified-release formulation of indiplon improved time to sleep onset, total sleep time, and wake time after sleep onset on subjective measures in adult outpatients with insomnia.

Other drugs that are being evaluated for chronic insomnia include GABA agonists (eg, gabapentin, gabitril), and atypical antipsychotics. Their sleep-promoting effects have not yet been evaluated in randomized placebo-controlled studies of patients with primary insomnia, however.

**Combination therapy**

Limited evidence suggests that concomitant behavioral and pharmacologic treatment induces rapid improvements in sleep that are maintained when treatment is discontinued. Data from a small, randomized placebo-controlled trial suggested greater improvements in sleep with use of cognitive-behavioral therapy in combination with temazepam (≤30 mg per night) than with either therapy alone. However, during 24 months of follow-up, the
sleep improvements from cognitive-behavioral therapy alone appeared more durable than either combination therapy or temazepam therapy. More research is needed to clarify the effects and long-term outcomes of behavioral therapy, pharmacotherapy, and their combination in the treatment of chronic insomnia.

**Future directions in insomnia management**

Currently available pharmacologic agents used to treat insomnia are not necessarily ideal for all patients, and decisions about management should be made on a case-by-case basis. All patients should receive information about sleep hygiene practice. Adjunctive behavioral therapy (if available) or hypnotic therapy may be prescribed if sleep hygiene measures prove inadequate.

Further studies are needed to fill specific gaps in the knowledge on insomnia and its treatment. A greater understanding of the role that neuromodulators play in insomnia would enable the development of new treatments. For example, it has been postulated that increased central release of corticotropin-releasing factor is associated with depression and that antagonists of this peptide may reduce depressive symptoms, including insomnia. There are preliminary indications that hypnotic therapy for secondary insomnia may improve the outcome of underlying diseases such as depression and bipolar disorder, as well as improve the quality of life in patients with dementia, Parkinson’s disease, and rheumatoid arthritis. However, more studies are required to evaluate whether treatment of insomnia reduces comorbidities, especially psychiatric disorders. Finally, clinical trials, based on those designed for depressive illness, are needed to clarify the optimal duration of hypnotic therapy and identify those patients who are most likely to respond to treatment.

**References**

3. Consensus conference. Drugs and insomnia: the use of medications to promote sleep. JAMA 1984;251(18):2410-4
58. Moon CA, Davey A. The efficacy and residual effects of trazodone (150 mg nocte) and mianserin in the treatment of depressed general practice patients. Psychopharmacology (Berl) 1988-95 Suppl:S57-19
71. Hughes RJ, Sack RL, Lewy AJ. The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: assessment in a clinical trial of melatonin replacement. Sleep 1998;21(1):52-68
Insomnia in special populations
Effects of aging, menopause, chronic pain, and depression

Sonia Ancoli-Israel, PhD, Cláudio N. Soares, MD, PhD, Raymond Gaeta, MD, and Ruth M. Benca, MD, PhD

Preview
Chronic insomnia is highly common in adults, and certain population groups are particularly prone to sleep disturbances, including the elderly, women in menopausal transition, persons with chronic pain, and those with depression. Diagnosis and treatment of insomnia in such patients may be problematic because of (1) the presence of one or more comorbid medical illnesses, as in the elderly or patients with a chronic pain syndrome, (2) the presence of depressive symptoms, or (3) the patient’s underlying physiologic status (eg, hormone fluctuations due to perimenopause). Effective management of sleep disturbances in these special populations requires an integrative approach to evaluation in the context of the underlying condition and to concurrent treatment of the sleep disturbance and any coexisting medical condition or associated symptom. The contributors to this article discuss insomnia as it is experienced by each of these populations and present representative case examples and proposed treatment plans for each.

Insomnia in the elderly: lessons from the data
Sonia Ancoli-Israel, PhD

SDI is a 72-year-old woman (body mass index, 24 kg/m²) who has been widowed for 10 years. Her chief insomnia complaints include difficulty falling asleep (typical sleep onset at midnight), frequent awakenings during the night, early-morning waking (4:30 AM), and daytime sleepiness. Her sleep and bedtime rituals include falling asleep on the couch while watching evening television, then awakening at 10 PM to retire to bed. Current medications include hydrochlorothiazide (12.5 mg once daily in the evening), atenolol (50 mg once daily in the evening) for hypertension, and valdecoxib (20 mg) for arthritis.

Consequences of sleep disturbances in the elderly—It has long been recognized that complaints of sleep problems increase with age. Recent epidemiologic data show that the prevalence of chronic insomnia increases from about 25% in the adult population to about 50% in the elderly. Sleep maintenance problems predominate in elderly patients; the most common complaints are frequent nocturnal awakenings and waking up too early in the morning.

In the past, sleep disturbances in the elderly were hypothesized to reflect a decreased need for sleep. Although sleep architecture does change with age, with
older adults having less slow-wave sleep, it is less clear whether the need for sleep decreases. Older adults may have more subjective complaints of insomnia but do not always exhibit objective characteristics of poorer sleep to account for their sleep complaints. For example, in a study that compared community-dwelling older elderly adults (≥75 years) with a younger elderly group (65-74 years), the frequency of sleep complaints was higher in the older group (42% versus 23%, respectively). However, time to sleep onset (sleep latency) was increased by only 10 minutes in the older group, and total sleep time was only 8 minutes longer.6

These findings are also supported by survey data obtained by the National Sleep Foundation showing that duration of nighttime sleep does not differ between older adults (55-84 years) (mean, 7.0 hours per night) and younger adults (18-54 years) (mean, 6.7 hours per night).4 Similarly, Ohayon7 reported that insomnia symptoms, but not diagnoses of insomnia, increase with age. Thus, although the number of persons with sleep complaints increases with age, aging per se does not appear to cause sleep problems, and sleep does not necessarily become poorer with increasing age.

Although sleep difficulties may have detrimental consequences in persons of all ages, these consequences can be particularly deleterious in the elderly and may be confused with dementia. Sleep difficulties and their consequences can increase the risk of accident-related injuries and likelihood of nursing home placement.

The five most common causes of insomnia in the elderly are circadian rhythm sleep disorders (eg, advanced sleep phase syndrome), a primary sleep disorder (eg, periodic limb movements in sleep), medical or psychiatric illness, dementia, and use of concomitant medications.

Clinical pearls: insomnia in the elderly
- The prevalence of chronic insomnia increases from 15% to 25% in the adult population to about 50% in the elderly. Although the number of persons with sleep complaints increases with age, aging per se does not appear to cause sleep problems, and sleep does not necessarily become poorer with increasing age.
- The increased prevalence of sleep complaints in the elderly may simply reflect their poorer overall medical and psychologic health rather than the direct effects of aging.
- The consequences of insomnia—cognitive impairment, memory difficulties, and psychomotor impairment—can be particularly deleterious in the elderly and may be confused with dementia. Sleep difficulties and their consequences can increase the risk of accident-related injuries and likelihood of nursing home placement.
- The five most common causes of insomnia in the elderly are circadian rhythm sleep disorders (eg, advanced sleep phase syndrome), a primary sleep disorder (eg, periodic limb movements in sleep), medical or psychiatric illness, dementia, and use of concomitant medications.

In a study of 6,444 adults aged ≥65 years, chronic insomnia (as distinguished from transient disturbed sleep) was a significant independent predictor of cognitive decline in elderly men but not women. Depression was also an independent risk factor for cognitive decline. In another study, chronic insomnia was associated with evidence of attention deficits in older adults (≥260 years), although the elderly patients’ subjective assessment of their own cognitive and psychomotor performance was worse than objectively measured functional impairment.10 It has been hypothesized that alterations in slow-wave sleep may account for some of the daytime cognitive deficits seen in elderly patients with insomnia.11

CONTRIBUTING FACTORS IN THE ELDERLY—Whether or not the need for sleep changes with age, it is clear that the ability to sleep decreases, and the factors contributing to this disability need to be identified. Various factors in the elderly, including circadian rhythm disturbances, diagnosis of a primary sleep disorder, medical and psychiatric illness, concomitant medications, and dementia, may all lead to complaints of insomnia.

Circadian rhythms are 24-hour physiologic cycles that include cycles of melatonin and cortisol, fluctuations of core body temperature, and the sleep-wake cycle. At different ages, the circadian rhythm shifts either forward (delayed rhythm) or backward (advanced rhythm) such that the timing of sleep is misaligned with the normal environmental...
light-dark cycle. Advanced sleep phase syndrome is common in the elderly. In this disorder, the person gets sleepy early in the evening and wakes up in the early morning hours. This often manifests as a complaint of early-morning awakening. Other older adults with advanced sleep phase syndrome might fall asleep early in the evening while reading or watching television, get up an hour or more later to go to sleep, and then have trouble falling asleep. Thus, while the patient with advanced sleep phase syndrome may present with insomnia symptoms, the complaints are actually secondary to the phase shift. Patients with advanced sleep phase syndrome may benefit from attempts to align their physiologic sleep-wake cycle with the normal environment.\textsuperscript{3} Evening bright-light therapy, which acts to shift the sleepy phase forward to a more appropriate bedtime hour and thereby normalizes the wake-up time, is an effective treatment for advanced sleep phase syndrome.\textsuperscript{12-14}

Primary sleep disorders can also contribute to insomnia. Sleep-disordered breathing\textsuperscript{13} and periodic limb movements in sleep\textsuperscript{15} are very prevalent in the elderly and may present as symptoms of insomnia. In patients with periodic limb movements in sleep, leg kicks and jerks occur every 20 to 40 seconds throughout the night and cause frequent arousals and disturbed sleep.\textsuperscript{16} This disorder is best treated with an L-dopa agonist, such as pergolide, pramipexole, or ropinirole.\textsuperscript{17}

The elderly may be particularly prone to sleep problems associated with medical and psychiatric disorders, in part, because of the increased number of comorbidities and somatic complaints in this subpopulation and to the increased frequency of chronic diseases that are characteristically associated with sleep fragmentation, such as dementia and Parkinson’s disease\textsuperscript{18} (table 1). Depression and insomnia are also correlated (see discussion later in this article), and depression coincident with insomnia is highly prevalent in the elderly.\textsuperscript{19}

In the 2003 National Sleep Foundation survey of sleep in the elderly,\textsuperscript{4,21} the incidence of insomnia in community-dwelling individuals aged 55 to 84 years was higher in those with heart disease (57%), lung disease (64%), stroke (63%), and depression (70%) than in each of the comparator groups without disease (46%-47%). Excessive daytime sleepiness was also more common in patients with these diseases (22%, 24%, and 25%, respectively) than in the respective control groups (13%-14%). As the number of medical conditions increased to 4 or more, patients were more likely to report waking frequently during the night (51% versus 19% with no medical illnesses) and having at least 1 symptom of insomnia (67% versus 35% with no medical illnesses). In addition, 19% of older adults reported sleep disturbances attributed to physical pain or discomfort.\textsuperscript{4,21}

Thus, medical illnesses common in the elderly contribute to sleep disturbances. Because the number of diagnosed medical illnesses in individual patients increases with age, it is not surprising that older persons are at greater risk for sleep problems secondary to medical illness. In fact, epidemiologic studies in the elderly show that healthy older people report few or no insomnia symptoms and that they sleep as well as younger subjects.\textsuperscript{7,21}

Dementia, including Alzheimer’s disease, is also strongly associated with sleep disruption in the elderly. Patients with dementia experience extremely fragmented sleep, often not being able to

---

**Table 1. Medical illnesses that contribute to insomnia**

* Excluding primary sleep disorders.

- Pain (from any cause)
- Dyspnea (from any cause)
- Rheumatic disorders (rheumatoid arthritis, osteoarthritis, fibromyalgia syndrome)
- Neurologic disorders
  - Neurodegenerative disorders (Alzheimer’s disease, Parkinson’s disease)
  - Neuromuscular disorders
  - Headache syndromes
  - Stroke, traumatic brain injury, brain tumors
- Organ-system failure
  - Respiratory (chronic obstructive pulmonary disease, asthma)
  - Cardiovascular (angina, congestive heart failure, ischemic heart disease)
  - Gastrointestinal (gastroesophageal reflux disease, peptic ulcer disease)
- Other conditions
  - Cancer
  - AIDS
  - Dermatologic disorders
  - Chronic fatigue syndrome
  - Incontinence
  - Benign prostatic hyperplasia

Adapted from Chokroverty.\textsuperscript{19}
Table 2. Lifestyle and sleep hygiene measures for improving sleep

<table>
<thead>
<tr>
<th>Lifestyle measures</th>
<th>Cognitive measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior modification</td>
<td>• Stimulus control (practice relaxation techniques, change negative behaviors and stress associated with sleep)</td>
</tr>
<tr>
<td>• Sleep restriction (limit time in bed to actual sleep time)</td>
<td>• Change faulty attitudes/unrealistic expectations toward sleep that may exacerbate insomnia</td>
</tr>
<tr>
<td>• Institute good sleep hygiene measures (see below)</td>
<td></td>
</tr>
<tr>
<td>Educational measures</td>
<td>• Examine dietary habits contributing to insomnia (caffeine and alcohol intake, timing of meals, fluid intake)</td>
</tr>
<tr>
<td>• Examine environmental factors contributing to insomnia (see below)</td>
<td>• Examine dietary habits contributing to insomnia (caffeine and alcohol intake, timing of meals, fluid intake)</td>
</tr>
<tr>
<td>• Engage in daily exercise, but not late in day</td>
<td>• Examine environmental factors contributing to insomnia (see below)</td>
</tr>
</tbody>
</table>

Sleep hygiene measures
Rise at same time every day of the week
Avoid or limit daytime naps
Create comfortable sleep environment (optimize temperature, darken room, eliminate noise)
Maximize bright light exposure in the early evening, but once in bed, keep the bedroom dark
Institute regular sleep routine with relaxing activities
Try to minimize time awake in bed
Avoid use of caffeine and other stimulants
Avoid use of alcohol before bedtime

stay asleep or awake for a full hour throughout the day and night.3,8,22

Disturbed sleep can also be a side effect of concomitant medications. Prescription medications (eg, β-blockers, calcium channel blockers, corticosteroids, stimulating antidepressants, thyroid hormones), over-the-counter agents (eg, stimulants, bronchodilators, decongestants), alcohol, caffeine, and nicotine can all contribute to insomnia.3 Older patients often have multiple illnesses that may each be managed by separate therapeutic agents, and polypharmacy may exacerbate insomnia in the elderly.

MANAGEMENT OF INSOMNIA IN ELDERLY PATIENTS—Because of the number of interrelated factors that affect sleep in the elderly, management of insomnia in this population requires an integrative approach to optimize sleep. Patient management should include the following steps:
• Evaluate the patient for any underlying medical illness, and treat accordingly.
• Explore with the patient the presence of depressive symptoms that may be disturbing his or her sleep, and if present, consider antidepressant treatment, particularly a sedating antidepressant taken at night.
• Explore with the patient and, if possible, the patient’s bed partner whether there are symptoms suggestive of sleep-disordered breathing or periodic limb movements in sleep.
• Evaluate the patient’s current medication use and administration schedules, which may contribute to specific insomnia symptoms.
• Consider nonpharmaceutical approaches, such as educating the patient about lifestyle and habits associated with sleep disturbances and about the benefits of regular exercise and good sleep hygiene (table 2). Changing sleep habits and lifestyle may be difficult, however, in very old patients.
• Evaluate for circadian rhythm disorders, and consider use of evening bright-light therapy to delay the circadian rhythm (ie, shift the biologic sleep cycle forward).
• If sleep problems persist, consider pharmacotherapy with a hypnotic agent; however, longer-acting sedative-hypnotics must be used with caution in the elderly, who may have changes in metabolism and may be particularly sensitive to residual effects, such as daytime sedation.

PROPOSED MANAGEMENT STRATEGY FOR PATIENT SDI—The following steps may help balance her sleep-wake cycle and relieve her insomnia:
• Switch administration of antihypertensive medications from evening to morning dosing to avoid nighttime awakenings due to nocturia.
• Institute evening bright-light therapy to shift sleep-wake cycle to more appropriate times for falling asleep and waking up.
• Advise lifestyle changes (not napping in front of the television set, going to bed when sleepy, sleeping only in the bedroom) to help prolong period of uninterrupted sleep.
• If insomnia persists, consider pharmacotherapy with a shorter-acting sedative-hypnotic.

In summary, sleep patterns and the ability to sleep do appear to change with age. Conditions often present in older persons may contribute to insomnia, such as coexisting medical and psychiatric illnesses, dementia, polypharmacy, and the presence of circadian rhythm changes and specific sleep disorders. Thus, the increased prevalence of sleep complaints in the elderly may simply reflect their poorer overall medical and psychologic health status rather than the direct effects of aging. These can be addressed by the primary care physician and managed appropriately.

**Menopausal transition: mood disturbances and sleep**

Cláudio N. Soares, MD, PhD

KN is a 49-year-old woman with a 10-year history of treatment with antidepressants for obsessive-compulsive disorder, with positive results. Three weeks following a hysterectomy with bilateral oophorectomy, KN reported falling into a deep depression and being unable to sleep. She feels that the depression and sleeplessness are having a severe negative impact on her daytime functioning and quality of life.

**RISK OF MOOD DISTURBANCES DURING PERIMENOPAUSE—**
Mood changes and depressive symptoms are frequent complaints in women experiencing the transition to menopause (perimenopause). Various studies have attempted to identify risk factors associated with the occurrence of depressive symptoms during this transition. Results have been mixed, in part, because of the methodologic limitations of the studies. For example, studies have been conducted in different population types (eg, clinic- versus community-based), have employed varying definitions of and criteria for menopausal status (eg, status defined primarily by age rather than menstrual cycle changes or characteristics; lack of differentiation between natural and surgically induced menopause), and may not have included systematic psychiatric assessments for the determination of current or past history of depression and confirmation of mood symptoms (eg, use of screening instruments or scales versus standardized psychiatric interviews).

Variations in data collection and study methodology may also have contributed to reported differences among menopause studies. For example, clinic-based studies report high prevalences of physical symptoms (up to 96%) and psychologic symptoms (up to 73%) among women seeking treatment for perimenopause-related complaints. However, women seeking treatment at a clinic for relief of menopausal symptoms may not necessarily be representative of menopausal women in the general population. In community-based studies, although findings are also inconsistent among studies, predominant risk factors for mood disturbances appear to be family and life stressors, perimenopausal status, menstrual history characteristics, and vasomotor symptoms.

Phases of intense hormone fluctuations appear to be associated with increased risk for depressive symptoms among some, but not all, women. In examining the mechanism by which hormone changes affect mood in women who are premenstrual, Schmidt and associates evaluated women with and

---

**Clinical pearls: insomnia in perimenopausal women**

- Female reproductive hormones play a critical role in sleep regulation through their central nervous system actions. Therefore, sleep disturbances during periods of intense hormone fluctuations (eg, those occurring during perimenopause) are not unexpected.
- Sleep disturbances are primarily seen in women who experience vasomotor symptoms during perimenopause, which commonly manifest as frequent awakenings. These effects may result from the dual action of reproductive hormones on the temperature-regulating and sleep-regulating centers in the brain.
- Hormone therapy may alleviate sleep disturbances that are part of the overall perimenopausal symptom complex, which can include vasomotor symptoms, insomnia, and depression. Consultation with an obstetrician-gynecologist is recommended when hormone therapy is being considered.
without a history of severe premenstrual syndrome (PMS) who had undergone ovarian suppression with 8-week leuprolide therapy, then had been treated with 8-week hormone therapy (estradiol plus leuprolide for 4 weeks, followed by progesterone plus leuprolide for 4 weeks). Women with no history of PMS showed little or nonsignificant variations in mood, irritability, or anxiety after the reexposure to estrogen and progesterone that followed the use of leuprolide alone; in contrast, women with a history of PMS showed marked recurrence of mood symptoms once reexposed to estrogen and progesterone. These results suggest that the occurrence of premenstrual mood disturbances may be indicative of an abnormal response to normal hormonal changes, which would explain the presence of such symptoms only in a subgroup of women. A similar mood response to relatively abrupt changes in reproductive hormones was reported in a study of women with a history of postpartum depression.31

The recently completed Harvard Study of Moods and Cycles,27 a large community-based study that evaluated 976 women aged 36 to 44 years, determined the relationship between mood changes and changes in reproductive endocrine function. Women with a history of depression were more likely to enter the menopausal transition earlier (hazard ratio, 1.2; confidence interval, 0.9-1.6) compared with women with no such history. While experiencing the clinical and hormonal changes of perimenopause, women appear to have a significantly higher risk of depression (3.2 times greater likelihood), even in the absence of a previous history of depression, compared with those who remained premenopausal. The risk of depression is also considerably higher (6.4 times) in the presence of severe vasomotor symptoms.29

SLEEP DISTURBANCES DURING PERIMENOPAUSE—Female reproductive hormones play a critical role in sleep regulation through central nervous system actions. Therefore, it is not unexpected that sleep disturbances would manifest during phases of hormonal fluctuation. Temperature-regulating and sleep-regulating centers in the brain may be disturbed concurrently by changes in hypothalamic-pituitary-ovarian hormone levels that occur during menopause, resulting in not only vasomotor symptoms but also sleep disturbances.32 Reports of sleep problems and reduction in sleep quality are quite common among women transitioning to menopause,33 even though reduced sleep quality may not always be captured by objective measures. Epidemiologic data indicate that between one fourth and one half of perimenopause-aged women experience some sleep problems.54 Sleep disruption is common in women with nocturnal hot flashes.55 Perimenopausal women who have vasomotor symptoms report more frequent awakenings, reduced sleep efficiency, and changes in sleep stages compared with women who do not report vasomotor symptoms.54,55

CLINICAL STRATEGIES FOR MANAGING MENOPAUSE-RELATED INSOMNIA—Sleep disturbances, vasomotor symptoms, mood changes, cognitive impairment, and sexual dysfunction comprise the most commonly reported menopause-related symptoms.23 Treatment strategies, therefore, may address these symptoms individually or in different combinations. Numerous studies have evaluated the benefits and risks of hormone therapies (either as estrogen therapy or as combination estrogen-progestin) for mood symptoms and depression during the perimenopausal and postmenopausal years. Positive findings have been demonstrated with estrogen therapy for depression during perimenopause36-39 but not for postmenopausal depression.36,40,41 Evaluations of hormone therapy for sleep disturbances during menopause have also shown mixed results. Estrogen has been reported to improve sleep in women with hot flashes by reducing the number of awakenings and total nighttime wakefulness and improving sleep efficiency.42-44 However, some studies have failed to demonstrate a significant impact of estrogen therapy on sleep characteristics.45 The use of sedative-hypnotic agents for sleep disturbances during menopause has also been explored (table 3). The ultimate goal of the therapy for managing sleep disturbances in women during menopause remains the same as that in other patients, specifically, to improve sleep while minimizing the risk of next-day sedation and impaired function. Benzodiazepines, although effective hypnotic agents, have been associated with next-day sedation and decline in cognitive
The sleep benefits of trazodone have been described in patients primarily suffering from depression with comorbid insomnia; however, most data are limited to short-term trials. The nonbenzodiazepine agents zolpidem and zaleplon have shown efficacy in initiating sleep (sleep onset), but results for maintaining sleep without awakenings (sleep maintenance) have not been consistent. Novel hypnotic agents in clinical development for treatment of insomnia, such as eszopiclone and indiplon, appear to be promising options; positive results for sleep onset and sleep maintenance have already been demonstrated in clinical trials involving patients with insomnia (although not specifically selected for menopausal symptoms).

In summary, the management of perimenopausal patients with insomnia should include the following steps:

- Evaluate the patient for any underlying medical illness that would require treatment.
- Evaluate the patient for full range of menopausal symptoms (eg, hot flashes, insomnia, sexual dysfunction, depression), and consider pharmacotherapy options to address insomnia coincident with other symptoms (eg, in consultation with an obstetrician-gynecologist, weigh risks and benefits of hormone therapy for hot flashes accompanied by insomnia; consider antidepressant therapy for depression with concomitant sleep disturbances).
- Consider nonpharmacologic approaches, such as educating the patient about lifestyle and habits associated with sleep disturbances and about the benefits of good sleep hygiene (see table 2).
- If insomnia persists, consider pharmacotherapy with a sedative-hypnotic agent.

**PROPOSED MANAGEMENT STRATEGY FOR PATIENT KN—** The following steps may help relieve her insomnia:

- Consider adjusting, augmenting, or switching the patient’s current antidepressant to better manage her obsessive-compulsive symptoms, as well as alleviate her depression and concomitant insomnia.
- In consultation with an obstetrician-gynecologist, evaluate the benefits and risks of recommending the use of hormone therapy.
- Recommend lifestyle changes (eg, increased exposure to natural light, exercise) that may improve both depressive symptoms and nighttime sleep.
- If insomnia persists, consider pharmacotherapy with a sedative-hypnotic agent.

In summary, insomnia can significantly affect women’s physical and social functioning and quality of life during menopausal transition, a process known to be associated with the occurrence of intense hormone fluctuations and vasomotor symptoms. Insomnia should be investigated and properly treated as part of a patient’s overall menopausal symptom profile.

### Table 3. Agents for managing sleep disturbances during menopause

<table>
<thead>
<tr>
<th>Estrogen therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves sleep by reducing number of awakenings and nighttime wakefulness and improving sleep efficiency</td>
</tr>
<tr>
<td>May not impact sleep characteristics</td>
</tr>
<tr>
<td>Risk-benefit ratio for use of estrogen therapy should be evaluated in consultation with an obstetrician-gynecologist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Over-the-counter agents*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxylamine preparations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective hypnotic agents</td>
</tr>
<tr>
<td>Associated with next-day sedation, rebound insomnia, risk of abuse and dependence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical studies limited to short-term studies and to depressed patients with secondary insomnia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonbenzodiazepines (zolpidem, zaleplon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset efficacy</td>
</tr>
<tr>
<td>Some demonstrated sleep maintenance efficacy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Novel hypnotics in development (eszopiclone, indiplon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated sleep onset and sleep maintenance efficacy</td>
</tr>
</tbody>
</table>

* Preferably for intermittent use only.
Insomnia in chronic pain syndromes
Raymond Gaeta, MD

VS, a 52-year-old man, has had lower back pain for 4 years. The pain did not resolve after a laminectomy and treatment with high-dose opioids, and he has been unable to be rehabilitated. The patient has been referred to the inpatient pain management center for observation and optimization of a comprehensive treatment plan. At presentation, he appeared to be depressed, and questioning about sleep habits revealed that he has poor sleep hygiene.

COMORBIDITY OF MEDICAL ILLNESS, PAIN, AND INSOMNIA—There is a strong correlation between insomnia and comorbid medical conditions.\(^7,58-60\) Persons with insomnia have significantly higher rates of medical illness and overall poorer health than those without sleep problems. Conversely, individuals with somatic complaints and medical illnesses are more likely to experience insomnia symptoms.\(^5,7,60,61\)

Insomnia has been shown to be associated with a higher risk of cardiovascular diseases (eg, myocardial infarction, congestive heart failure, angina, hypertension), pulmonary disease (eg, chronic obstructive pulmonary disease), back and hip pain, arthritis, and other systemic diseases (eg, peptic ulcer disease, diabetes, prostate disorders).\(^59,61\)

Many comorbid medical disorders can cause or contribute to insomnia\(^59\) (see table 1). Specifically, medical conditions involving chronic pain are associated with disturbed sleep,\(^62,64\) including rheumatic diseases,\(^64\) conditions that cause musculoskeletal pain,\(^65\) and cancer.\(^66\) Sleep maintenance problems (frequent nocturnal awakenings, sleep fragmentation) are more often associated with medical complaints\(^1\) and are the most common complaints in patients experiencing pain and dyspnea, such as arthritis, hypertension, and chronic obstructive pulmonary disease.\(^65,67\) Pain has been shown to cause sleep maintenance problems in patients with cancer,\(^68\) Parkinson’s disease,\(^69-71\) nonorganic pain syndromes,\(^72\) and chronic fatigue syndrome.\(^71\) Pain and discomfort associated with medical illness are common causes of insomnia in the elderly and are often associated with fragmented sleep due to frequent nocturnal awakenings.\(^71\)

The relationship between pain and insomnia is complex. In patients with chronic pain, greater severity of sleep disturbance correlates with more severe pain, more physical and psychosocial disability, and more physical symptoms.\(^63,74\) Insomnia coexistent with chronic illness is also associated with reduced health-related and overall quality of life.\(^60,75\)

The relationship between pain and insomnia is also complicated by comorbid depression. In addition to the strong correlation between insomnia and depression (discussed later in this article), depression is also correlated with pain and disability and is prevalent in many chronic medical disorders, including chronic pain syndromes, asthma, back pain, and disorders of the gastrointestinal, endocrine, vascular, and metabolic systems.\(^74,76-78\)

This phenomenon is not surprising given that pain pathways comprise both sensory (nociceptive, neuropathic, inflammatory) and affective pathways. The interdependence of these systems allows for an understanding of how physical events can affect mental state and, conversely, how affective disorders (depression, anxiety, anger) can have a tremendous effect on the perception and experience of pain.\(^79\) The combination of insomnia and depressive symptoms is particularly problematic in patients with chronic pain, because patients with both of these conditions report the greatest pain severity and also have the highest levels of pain-related impairment (eg, difficulty with measures of life control and distress).\(^75\)

Disturbed sleep in patients with chronic pain is itself associated with the development of depression.\(^60,65\) The risk of severe insomnia has been reported to be higher in patients with depression in addition to insomnia and an underlying medical condition than in patients with only insomnia and an underlying medical condition.\(^59\) In a study of patients with chronic illness,\(^60\) those with severe insomnia were more likely to be clinically depressed (32% of patients) than those with mild or no insomnia (15% and 9%, respectively). In another study involving patients with chronic musculoskeletal pain,\(^60\) those who reported severe sleep-onset insomnia and high pain intensity were at the highest risk for suicidal ideation.

MANAGING PATIENTS WITH PAIN AND INSOMNIA—The complexities of pain and its
resultant behavior necessitate a multidisciplinary approach to evaluation and initiation of a treatment plan in patients with pain and insomnia. Admission to an inpatient pain program (Table 4) may be necessary for patients with complex pain syndromes. Diagnosis and treatment of insomnia in a patient with a coexistent chronic medical disorder can be challenging, especially if the disorder is also associated with depression. The goal for these patients is symptomatic control of pain, along with improvement in poor-quality sleep and any depressive symptoms. Interdisciplinary care, which requires the coordination of the multidisciplinary team, has been well proven to be the most effective mode of treatment in chronic pain.

As with all patients presenting with insomnia, the clinical team should first address any underlying medical and psychiatric disorders. Treatment of the underlying illness may help alleviate the insomnia. Also, medications used to treat an underlying medical condition should be evaluated for their potential detrimental effects on sleep. Medications commonly prescribed to patients with chronic medical illnesses that can cause or exacerbate insomnia include bronchodilators, ß-blockers, calcium channel blockers, corticosteroids, stimulating antidepressants, decongestants, and thyroid hormones.

In a patient presenting with pain and insomnia, simultaneous treatment of both disorders is a critical component in overall management. Treatment of the insomnia may improve the course and symptoms of the underlying disorder in some clinical populations and may provide more rapid relief from insomnia, alleviate its daytime consequences, and improve quality of life. For example, beneficial effects on patients’ daily activities and overall quality of life, a delay in institutionalization, and a reduction in the need for nursing care have been shown in patients with dementia and Parkinson’s disease, and improvement in symptoms (eg, decreased morning stiffness and daytime sleepiness) has been seen in patients with rheumatoid arthritis after treatment of insomnia.

Nonpharmacologic approaches to improving sleep (see Table 2) may also improve the underlying medical disorder or the patient’s ability to cope with chronic pain, or both. Various nonpharmacologic approaches, such as cognitive-behavioral therapy, have been effective for insomnia that is secondary to chronic pain and in patients experiencing cancer-related pain.

Table 4. Inpatient multidisciplinary program for comprehensive pain management

<table>
<thead>
<tr>
<th>Pain management service</th>
<th>Psychiatry service</th>
<th>Behavioral medicine</th>
<th>Physical and occupational therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication “cocktails”</td>
<td>Antidepressants</td>
<td>Goal setting</td>
<td>Emphasis on functionality</td>
</tr>
<tr>
<td>Intravenous infusions</td>
<td>Education on drug addiction, dependence, and tolerance</td>
<td>Instituting social and recreational activities</td>
<td></td>
</tr>
<tr>
<td>Neuronal blockade</td>
<td>Counseling for pseudoaddiction</td>
<td>Cognitive-behavioral therapy</td>
<td></td>
</tr>
<tr>
<td>Psychotropic medications</td>
<td>Spinal medication trials</td>
<td>Physical and occupational therapy</td>
<td></td>
</tr>
</tbody>
</table>

Clinical pearls: insomnia in patients with chronic pain

- There is a strong correlation between insomnia and comorbid medical conditions, particularly those associated with chronic pain. Sleep maintenance problems, which manifest as fragmented sleep due to frequent awakenings, are more common in patients with medical illnesses and in the elderly, who have an increased number of comorbidities and somatic complaints compared with younger adults.
- The complex relationship between pain and insomnia is further complicated by comorbid depression, which itself is strongly correlated with pain, disability, chronic medical disorders, and increased age. The combination of insomnia and depressive symptoms is particularly problematic in patients with chronic pain, leading to difficulties in diagnosis, treatment, and achievement of a positive clinical outcome.
- Caring for patients with pain and insomnia necessitates a multidisciplinary approach and may require admission to an inpatient pain management program. This type of comprehensive program can best address evaluation and treatment of the pain associated with the underlying medical disorder, psychiatric and behavioral needs, and the patient’s sleep difficulties.
Because sleep maintenance difficulties are the most common type of sleep problem in medically ill patients, treatment of secondary insomnia should focus on improving sleep continuity and decreasing sleep latency. The ideal hypnotic agent for a medically ill patient would also have little or no adverse effect (eg, reduced respiratory drive) on the patient’s underlying medical problems and would have minimal propensity for drug interactions. The need for increased monitoring of the underlying disorder and the insomnia must be stressed when the two are coexistent.

Management in patients with chronic pain and insomnia should include the following steps:

- Fully evaluate the patient for pain due to underlying medical illness and comorbid psychiatric illness. Consider admitting the patient to an inpatient medical behavior unit for observation, if necessary.
- Employ a multidisciplinary treatment approach that includes treatment of the underlying medical or psychiatric illness, pain management, behavioral therapy, and physical and occupational therapy if rehabilitation is needed.
- Initiate pharmacotherapy with a sedative-hypnotic agent for insomnia.

PROPOSED MANAGEMENT STRATEGY FOR PATIENT VS—

The following steps may help relieve his insomnia:

- Admit the patient to an inpatient program for comprehensive evaluation and treatment plan.
- Administer a methadone-containing pain “cocktail,” and begin treatment with venlafaxine for depression.
- Add a sedative-hypnotic to manage daily complaints of insomnia.
- Schedule a physical activity and exercise program, and begin low-back physical therapy.
- Monitor and adjust the sedative-hypnotic dosage, and adjust the methadone regimen until fully weaned.
- Discharge the patient from the program, and continue regular evaluations for medication management, physical therapy, and sleep assessments.

In summary, the complexities of insomnia coincident with pain-causing medical illness necessitate a multidisciplinary approach to patient management. The integration and expertise brought to bear with interdisciplinary communication and coordination form a proven method of handling these difficult cases. Simultaneously treating insomnia and pain likely will also improve the clinical condition of the patient.

Insomnia and depression
Ruth M. Benca, MD, PhD

CR is a 48-year-old woman with a 7-year history of insomnia. She had no sleep disturbances before age 41, at which time she began to experience intermittent insomnia (1 or 2 times a month). The frequency of insomnia gradually increased to a nightly occurrence for the past 4 years. Sleep symptoms include difficulty falling and staying asleep, as well as middle-of-the-night or early-morning awakenings, or both. Previous hormone replacement therapy had little effect on insomnia. Zolpidem therapy (10 to 20 mg per night, 3 to 7 nights a week) initiated 2 years ago has improved sleep onset, but total sleep time remains 5 hours or less nightly. The patient takes a middle-of-the-night zolpidem dose if she wakes before 3 AM, but this causes next-day hangover effects. The patient’s insomnia has worsened over the previous 3 months, which has led to depression and impaired daytime functioning (inability to work full-time, limited social activities). At presentation, the patient reported no other medication use, and results of physical and laboratory evaluations were normal.

COMORBIDITY OF DEPRESSION AND INSOMNIA—Sleep disturbance is strongly associated with depression and is part of the criteria for depression according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised. Polysomnographic studies have demonstrated a number of objective sleep abnormalities in patients with depression or other psychiatric disorders compared with healthy individuals (table 5). The converse is also true; that is, people with insomnia have higher rates of psychiatric disorders. Epidemiologic studies of adult populations show that about one third (34%-40%) of adults with insomnia have a psychiatric disorder (most commonly depression or an anxiety disorder) compared with 11% to 16% of those without insomnia. In clinical populations, the association between insomnia and psychiatric illness is even greater;
between 50% and more than 75% of patients with insomnia in the clinical setting (eg, primary care or sleep-disorder clinics) have a diagnosable psychiatric disorder.59,87,89

Insomnia or disturbed sleep predicts an increased risk of new-onset depression and relapse, precedes the onset of depression, often persists during periods of remission, and is a risk factor for suicide. Studies have shown that:

- In the general population, the odds of developing depression if persistent insomnia occurred during the preceding year were 39.8, whereas the odds were 1.6 if insomnia resolved during that time.86
- Persons who were not depressed but who experienced insomnia or difficulty sleeping during periods of stress had an increased risk for depression later in life.90
- Insomnia predicted depression in elderly and younger adults who were not depressed.91,92
- Insomnia increased the risk of recurrence of depression and preceded the development of other depressive symptoms in patients with a history of depression who were in clinical remission.93
- Insomnia was one of the symptoms predictive of suicidal behavior in emergency department patients.94

The strong relationship between insomnia and depression has led researchers to postulate whether these conditions share common mechanisms. In a study that examined the role of stress in primary insomnia, Morin and colleagues95 showed that persons with insomnia are more reactive to stress. Compared with persons who have no trouble sleeping, they tend to rate minor stressful life events as more severe and perceive that their lives are more stressful, despite reporting equivalent numbers of stressful events. Persons experiencing higher daytime stress levels also experienced greater pre-sleep cognitive and somatic arousal. This increased perception of stress and resultant bedtime arousal resulted in poorer sleep efficiency and sleep quality.95

Hypothalamic-pituitary-adrenal axis activation may mediate the association between sleep and depression. Leproult and colleagues96 found that sleep deprivation increases hypothalamic-pituitary-adrenal axis activity, and this elevated activity has been associated with depression.

MANAGING PATIENTS WITH DEPRESSION AND INSOMNIA—Management of insomnia and depression should include the following steps:

- Evaluate the patient for any underlying medical illness, and treat accordingly.
- Evaluate the patient’s full range of depressive symptoms, treat with an appropriate antidepressant, and recommend adjunctive psychotherapy.
- Evaluate the patient’s current medication use and administration schedules, which may contribute to the specific insomnia symptoms.

<table>
<thead>
<tr>
<th>Clinical pearls: insomnia in patients with depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There is a strong association between insomnia and psychiatric illness, particularly depression. Insomnia predicts increased risk of new-onset depression and relapse after remission, precedes the onset of depression, often persists during periods of remission, and is a risk factor for suicide.</td>
</tr>
<tr>
<td>• The overlap between sleep disturbances and symptoms of depression causes difficulties in diagnosis and confounds effective treatment of both. Improving sleep often, but not always, improves depressive symptoms and vice versa.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5. Sleep in patients with psychiatric disorders versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affective disorder</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Eating disorder</td>
</tr>
<tr>
<td>Alcoholism</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
</tbody>
</table>

REM, rapid eye movement; ↑↑, increased unequivocally; ↓↓, decreased unequivocally; •, no change; ↑, increased in some studies; ↓, decreased in some studies.

Data from Benca et al.85
Consider nonpharmaceutical approaches, such as educating the patient about lifestyle and habits associated with sleep disturbances and the benefits of good sleep hygiene (see table 2). Consider use of specific behavioral treatments for insomnia.

If insomnia persists, consider pharmacotherapy with a sedative-hypnotic agent, possibly one with a longer duration of action. Pharmacotherapy with an agent that effectively treats sleep maintenance difficulties, as well as provides rapid sleep onset, would be particularly beneficial to patients who experience sleep fragmentation and frequent awakenings.

The following steps may help relieve her insomnia:

- Initiate therapy with an antidepressant to improve depressive symptoms and potentially improve sleep, and recommend adjunctive psychotherapy.
- Institute cognitive-behavioral therapy to improve perceptions about sleep that may exacerbate insomnia, and educate the patient about good sleep hygiene.
- Continue once-nightly doses of zolpidem, but avoid the middle-of-the-night dose to diminish morning sleepiness.
- If insomnia persists, consider pharmacotherapy with an alternative sedative-hypnotic that has a longer half-life.

In summary, there is a strong correlation between depression and insomnia, which translates into an overlap of symptoms, difficulties in diagnosis, and confounding treatment issues. Depression can be difficult to diagnose in the presence of insomnia, because patients often attribute mood changes and depressive feelings to insomnia rather than acknowledging the possibility of a distinct mood disorder. The goal of treating insomnia and depression is to improve symptoms of both conditions. Although improvement in insomnia may accompany improvement in depression, pharmacotherapy for insomnia should also be considered, because insomnia may persist even after remission of depression. Furthermore, insomnia may be a side effect of many of the newer antidepressants, including serotonin reuptake inhibitors (eg, fluoxetine, sertraline, paroxetine), serotonin and norepinephrine reuptake inhibitors (eg, venlafaxine), and others (eg, bupropion), and thus require specific treatment.

Clinical pearls: insomnia in special populations

- Patients who are elderly, are in menopausal transition, have chronic pain, or are depressed represent populations that are particularly susceptible to developing sleep difficulties. Sleep disturbances in these populations are usually chronic and therefore more difficult to treat than transient disorders.
- Subpopulations that are particularly prone to sleep disturbances, such as the four population segments discussed in this article, will each benefit from (1) a comprehensive physical and psychologic evaluation, (2) treatment of any underlying disorders, and (3) education about the benefits of good sleep hygiene and nonpharmacologic approaches to improving sleep.
- Treatment of insomnia coincident with management of any underlying disorder may more quickly alleviate patients’ sleep disturbances, improve functionality and quality of life, and improve clinical outcome. Pharmacotherapy with an agent that effectively treats sleep maintenance difficulties, as well as provides rapid sleep onset, would be particularly beneficial to patients who experience sleep fragmentation and frequent awakenings.

Sonia Ancoli-Israel, PhD
Dr Ancoli-Israel is professor of psychiatry, University of California, San Diego, School of Medicine. She serves on speakers’ bureaus and scientific advisory boards for Neurocrine/Pfizer, Sepracor Inc, Takeda Pharmaceuticals America Inc, Sanofi-Aventis, and King Pharmaceuticals Inc. She has also received a grant from Janssen Pharmaceutica Products LP.

Cláudio N. Soares, MD, PhD
Dr Soares is associate director for research, Massachusetts General Hospital Center for Women’s Mental Health, Harvard Medical School, Boston. He is a consultant and is on the speakers’ bureau for GlaxoSmithKline, Wyeth Pharmaceuticals, Pfizer Inc, and Forest Pharmaceuticals Inc. He is also a consultant for Sepracor Inc.

Raymond Gaeta, MD
Dr Gaeta is associate professor of anesthesiology and director of pain management services, Stanford University Medical Center, Stanford, California. He is an investigator for XenoPort.

Ruth M. Benca, MD, PhD
Dr Benca is professor, department of psychiatry, University of Wisconsin Medical School, Madison. She is a consultant or on the speakers’ bureau for King Pharmaceuticals Inc, Pfizer/Neurocrine, Sanofi-Aventis, Sepracor Inc, Wyeth Pharmaceuticals, and Takeda Pharmaceuticals America Inc.

Address for correspondence:
Sonia Ancoli-Israel, PhD
Department of Psychiatry 116A VASDHS
3359 La Jolla Village Dr
San Diego, CA 92161

E-mail address: sancoliisrael@ucsd.edu


35. Saleutz-Zylahr G, Anderer P, Gruber G, et al. Insomnia related to postmenopausal syndrome and hormone replacement therapy: sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen...
modified-release in elderly patients.


Differences in objective and subjective sleep measures and public health-related quality of life in patients with chronic insomnia. J Fam Pract 2002;51(3):229-35

The diagnosis and management of insomnia in primary care. A postgraduate medicine special report.

INSOMNIA IN PRIMARY CARE • A POSTGRADUATE MEDICINE SPECIAL REPORT


Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry 2003;60(1):39-47


Shochat T, Umphress J, Israel AG, et al.

NOTES
Insomnia in primary care
Panel discussion

Special Issues Board panel: Sonia Ancoli-Israel, PhD; Ruth M. Benca, MD, PhD; Paul P. Doghramji, MD; Raymond Gaeta, MD; Andrew G. Israel, MD; Joseph A. Lieberman III, MD, MPH; Cláudio N. Soares, MD; Neil Brooks, MD, Rockville Family Physicians, Rockville, Connecticut; Larry Culpepper, MD, Boston University Medical Center; Brian Foresman, DO, University of Indiana Medical Center, Indianapolis; James Voirin, DO, Physician Associates of Florida; Charles Wells, MD, SleepMed, Inc.

The Special Issues Board panel focused on a number of issues central to the current understanding of insomnia and on obstacles to adequate recognition, diagnosis, and management of insomnia in the primary care setting.

There was general agreement that insomnia is both a symptom and a diagnosis, both of which are poorly recognized in primary care for a number of reasons unique to this setting. The practical reality of office visits is that time is a valuable commodity, and because insomnia is usually viewed as a less important concern relative to other, more serious diseases, it is rarely brought to the forefront of consultations by either patients or physicians. Primary care physicians may also be reluctant to introduce the subject of insomnia for fear that the treatments for insomnia introduce risks, such as dependence and abuse of hypnotic agents. In addition, there is currently an absence of studies showing that treatment of insomnia improves outcomes, such as quality of life, daytime functioning in primary or secondary insomnia, and prognosis of the coexistent disease when insomnia is comorbid. Thus, panel members agreed that the ideal way to encourage primary care physicians to adopt strategies for managing insomnia lies in establishing a strong evidence base of outcomes data.

However, in the absence of more robust outcomes data about the effects of insomnia treatment, the panel noted that the identification of insomnia and consideration for treatment in primary care may be encouraged in several other ways. The most strongly endorsed of these was patient education. In particular, the strong association between insomnia and poor health outcomes should be emphasized because, at the very least, insomnia is an important marker for patients at risk for depression and poorer outcomes from other medical disorders. Armed with the knowledge of insomnia’s prevalence and the potential negative impact on health, patients may be more likely to initiate discussion of the subject during a primary care visit. Tactics for providing patients with the information necessary to stimulate their involvement in their care include physician-provided brochures and other waiting-room materials. Regardless of the mode of distribution, these materials should feature symptoms and types of insomnia, the associations between insomnia and negative health outcomes, and treatment and management options. The focus of patient education initiatives should be on the patient’s level of satisfaction with his or her sleep. The panel agreed that when patients talk to and question their doctors, the physicians themselves are encouraged to increase their awareness and knowledge. Over the years there has been increased interest among consumers in conditions such as depression and chronic pain, which has encouraged improved recognition and treatment of these conditions. The hope is that the same will happen with sleep disorders.

Panel members also suggested that primary care physicians would be more likely to attempt insomnia management if they had a greater understanding of the underlying pathophysiology of insomnia and the mechanisms of action.
of medications used to treat it. It is also important to emphasize to primary care physicians that insomnia often has potentially serious consequences; that it can be treated effectively, with a good risk-benefit ratio; and that coexistent insomnia may not respond to treatment of the primary condition. Some panel members proposed that sleep medicine training be incorporated into residency programs. Possible tactics discussed for physician education were dinner meetings and other continuing medical education initiatives.

**Practical diagnostic strategies**
Panel discussions highlighted practical strategies to improve recognition and diagnosis of insomnia that may be incorporated into the office visit without being too time-consuming. There was consensus that standardized screening questionnaires or tools are too cumbersome to implement because primary care physicians already have a large volume of screening questions that they must address. Recommendations about screening would be greatly strengthened by evidence of the effectiveness of specific screening strategies to efficiently identify patients who would benefit from treatment. However, a few select questions, easily incorporated into the standard patient history, may identify those patients who need increased vigilance for sleep disturbance. Questions should address daytime function, such as tiredness or sleepiness, as well as sleep complaints.

The key questions cited by panel members as being important to incorporate into the history were the following:

1. Are you having trouble sleeping?
2. Are you having trouble falling or staying asleep?
3. Are there consequences to having this sleep difficulty?

Questions about tiredness should be open-ended, such as “Are you feeling tired? Tired in what way? Sleepy-tired? Exhausted-tired?” When taking a general history of the complaint, it is also useful to ask questions about the severity and impact of the chief complaint, such as “Is this problem interfering with your sleep?” It is especially important to ask whether the patient becomes drowsy while driving.

The panel further noted that the identification of sleep problems may signal the possibility of a new illness or deterioration in an existing chronic condition. In patients with an existing illness, it was suggested that disturbed sleep or insomnia could be useful as a kind of sedimentation rate or barometer of deterioration, much like the erythrocyte sedimentation rate is used for determining deterioration in some chronic illnesses. For example, the National Asthma Guidelines have indicated that nighttime awakening correlates directly with severity of asthma, and in congestive heart failure, nighttime apneas are associated with decompensation. More studies would be needed to support this use of insomnia as an indicator of disease status.

**Treatment issues**
Challenges to appropriate treatment of insomnia and strategies for overcoming these challenges were also a focus of the panel discussion. A fundamental difficulty for primary care physicians in initiating appropriate treatment is that most insomnia treatment guidelines are prescriptive, emphasizing what not to do, without making recommendations for what to do. It is also unclear which patients are most likely to need treatment, especially those with secondary insomnia.

As a general recommendation, the panel suggested that the primary condition be treated first and that concomitant cognitive-behavioral interventions or sleep hygiene education be instituted. If the insomnia persists, pharmacotherapy should be considered. All patients should be treated on a case-by-case basis, however, and severe insomnia may require immediate pharmacologic treatment, as may primary insomnia. Thorough history taking and physical examination should be used to rule out the possibility of contraindications for hypnotic use, such as severe congestive heart disease or a history of substance abuse. Referral to a sleep expert should be individualized on the basis of the primary care physician’s comfort level, concerns about the possibility of another primary sleep disorder (e.g., sleep apnea), or treatment resistance. The panel further agreed that drowsiness while driving is a potential sleep emergency that may necessitate immediate referral to a sleep specialist.

The panel noted that the greatest obstacle to the treatment of chronic insomnia is the inability to treat patients for an adequate length of time because
of restrictions imposed by the US Food and Drug Administration (FDA) on prescribing duration for hypnotics. Panel members agreed that even with the emergence of data from trials of insomnia agents given over extended periods, physicians would be unlikely to prescribe off-label for longer periods, and therefore, FDA labeling changes about duration of treatment would be required. Once again, the importance of outcomes data was emphasized; these data should be able to show that patient outcomes improve with longer-term treatment of insomnia, that these improvements are sustained even after medication is withdrawn, and that treatment improves patients’ quality of life by reducing the need for medications to treat the coexistent condition (eg, pain medication can be reduced in patients with chronic pain, once they have responded to insomnia treatment). The panel also suggested that more data that explore the risks of dose-escalation and drug-seeking behavior in patients with insomnia are needed to clarify the risks of abuse and dependence associated with these agents.

Finally, because treatment of chronic insomnia is particularly difficult, given current restrictions to prescribing and inadequate data regarding use of insomnia agents, the panel agreed to an algorithm that may guide physicians in management of chronic insomnia (figure 1).

Address for correspondence:
Sonia Ancoli-Israel, PhD
Department of Psychiatry 116A
VASDHS
3359 La Jolla Village Dr
San Diego, CA 92161

E-mail address:
sancoliisrael@ucsd.edu

Figure 1. Proposed management algorithm for chronic insomnia.
CME Self-Study Examination—Insomnia in Primary Care

Instructions
Circle an appropriate response to each question or incomplete statement. Only 1 answer or completion is correct.

1. All of the following are barriers to diagnosis and treatment of insomnia except
   A. Low prevalence of the disorder
   B. Limited physician training in sleep medicine
   C. Time constraints during office visits
   D. Perception that all insomnia treatments are ineffective or are associated with risks of abuse or dependence, or both

2. One 1999 study found the prevalence of insomnia in the primary care population to be roughly how much in comparison with the prevalence in the general population?
   A. One quarter
   B. One third
   C. Two thirds
   D. Double

3. Several studies have shown an association between chronic sleep disturbances and
   A. Depression
   B. Chronic pain
   C. Increased risk of accidents
   D. All of these

4. What percentage of primary care patients actively seek treatment for their insomnia?
   A. 1%
   B. 5%
   C. 10%
   D. 25%

5. Which of the following is not a criterion for insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition revised?
   A. Difficulty initiating sleep for at least 1 month
   B. Difficulty maintaining sleep for at least 1 month
   C. Sleep that is nonrestorative for 2 weeks
   D. Sleep difficulties that cause clinically significant distress or impairment in social, occupational, or other important areas of function

6. Important steps in diagnosis of insomnia in the primary care setting include
   A. Asking the patient about sleep problems
   B. Interviewing the patient’s bed partner to detect symptoms indicating coexistent illnesses or primary sleep disorders
   C. Taking a careful history and performing a physical examination
   D. All of these

7. Patients with primary insomnia exhibit all of the following features except
   A. Evidence of hyperarousal
   B. Higher core body temperature
   C. A tendency to secrete increased quantities of cortisol
   D. A tendency to excrete lower quantities of adrenaline

8. What percentage of patients with insomnia benefit from behavioral therapy?
   A. 10% to 20%
   B. 40% to 50%
   C. 70% to 80%
   D. More than 85%

9. Benzodiazepine use is limited by all of the following adverse effects except
   A. Prolonged QT interval
   B. Next-day residual effects
   C. Tendency to induce rebound insomnia
   D. Pharmacologic tolerance

10. Recent epidemiologic data demonstrate that the prevalence of chronic insomnia in the elderly is
    A. 30%
    B. 50%
    C. 70%
    D. 85%

11. According to epidemiologic data, what percentage of perimenopause-aged women experience sleep problems?
    A. 5% to 10%
    B. 15% to 20%
    C. 25% to 50%
    D. 60% to 75%

12. All of the following statements about insomnia or disturbed sleep are true except
    A. It decreases hypothalamic-pituitary-adrenal axis activity
    B. It is associated with an increased risk of new-onset depression and relapse
    C. It precedes the onset of depression
    D. It is a risk factor for suicide
CME Self-Study Examination—Insomnia in Primary Care

Obtaining CME Credit
Release date: December 2004. Termination date: December 2007 or earlier pending annual review.

To earn CME credit for this activity, circle your answers on the quiz, and complete the accompanying registration and evaluation forms. Please print clearly. This credit is available through December 31, 2007. No credit will be given after that date. This activity is certified for a maximum of 3 category 1 credits toward the AMA Physician’s Recognition Award.

Mail or fax the quiz and the registration and evaluation forms to:
Interstate Postgraduate Medical Association
PO Box 5474
Madison, WI 53705
Fax: 877-292-4489

Evaluation form

1. Please rate the content of this Special Report using the following scale:
   5 = excellent; 4 = very good;
   3 = good; 2 = fair; 1 = poor.
   Please circle your response.

   Timely, up to date
   Excellent 5 4 3 2 1 Poor
   Relevant to your practice
   Excellent 5 4 3 2 1 Poor

2. Are there any other topics you would like to have seen addressed in this activity?
   □ Yes    □ No
   If Yes, please specify.

3. Please describe any changes you plan to make in your clinical practice based on the information presented in this activity.

4. Did you detect any commercial bias in this activity?
   □ Yes    □ No
   If Yes, please specify.

5. Do you have any additional comments or suggestions for future educational programs relating to these topics?

Insomnia in Primary Care Registration Form

Please print

Name: __________________________________________

Degree: _________________________________________

Specialty: ______________________________________

Address: _______________________________________

________________________________________________

I claim _____ category 1 credits.

Signature: ______________________________________