

Attached is detailed information on the various treatments for insomnia. Since sleep should make up about a 1/3 of our day, not sleeping becomes critical to our well being. The following information details the types of problems people with insomnia often encounter and various ways they are currently being treated for insomnia including behavioral and medication approaches. You may find this information good to keep on hand since lack of sleep is often both a contributor to and an indicator of additional problems.

### **Helping Hearts Heal**

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## **Clinical Update - Management of Insomnia in the Primary Care Practice**

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*In part 1 of this review in the last edition of Current Perspectives in Insomnia, Volume 1, we introduced 2 patients who were having trouble sleeping and discussed the approach to diagnosis in the primary care setting. Part 2 addresses management strategies.*

### **Stepwise Treatment for Insomnia**

*The first patient is a 35-year-old woman who works as a corporate attorney. She doesn't smoke, has about 2 or 3 drinks a week, and is recently engaged to be married. She reports difficulty concentrating and daytime fatigue. These symptoms worsen during times of stress, such as when she is faced with deadlines. She goes to bed at about 11 pm but reports that she lies awake for hours staring at her alarm clock. She finally falls asleep at about 2 am.*

*The second patient is a 45-year-old man who is as an emergency department nurse. He works 12-hour shifts -- from 8 to 8, rotating from night to day on a 3-week schedule. He has osteoarthritis in his right shoulder from an old sports injury. He says he treats the shoulder pain with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), as needed. He also said he uses antacid medication for frequent heartburn. He reports having difficulty falling asleep when he is working the night shift and notes that his reflux also worsens when he works nights. Generally, he reports good sleep quality when working the day shift, except when his shoulder pain worsens.*

*Treatment of insomnia should, insofar as possible, be directed at identifiable causes or those factors that perpetuate the disorders, such as temperament and lifestyle, ineffective coping and defense mechanisms, inappropriate use of alcohol or other substances, maladaptive sleep-wake schedules, and excessive worry about poor sleep. The harder these individuals try to sleep, the worse the problem becomes. Typically, these patients keep themselves awake wrestling with their apprehensions: "If I don't get to sleep right now, I'll make a bad impression tomorrow."<sup>[1]</sup>*

*Many patients may benefit from an initial trial of behavioral therapy for insomnia.*

### **Treatments for Psychophysiologic Insomnia**

*The 3 main, contemporary behavioral treatments of insomnia are:*

- *Sleep-hygiene techniques;*
- *Stimulus control instructions; and*
- *Sleep-restriction therapy.*

*All 3 approaches attempt to correct sleep-preventing associations and to provide education about sleep to the patient.*

## **Sleep-Hygiene Techniques**

*In 1977, Dr. Peter Hauri<sup>[2]</sup> reviewed the existing sleep literature and translated the findings into a basic set of sleep-promoting rules. Since that time, these "rules" have formed the basis for sleep-hygiene techniques, which, in turn, are incorporated in both stimulus control instructions and sleep-restriction therapy:*

- *Rule 1: Limit time in bed, which leads to decreased sleep-onset latency.*
- *Rule 2: Never try to sleep, because actively pursuing sleep increases arousal, which decreases the likelihood of sleep. Rather than trying to sleep, patients are told to engage in a relatively monotonous activity, such as reading or watching television.*
- *Rule 3: Remove time pressure by moving the alarm clock to another room.*
- *Rule 4: Exercise in the late afternoon or early evening. The timing of the exercise is crucial because it relates to circadian rhythms. People sleep better when the body's core temperature decreases as part of the circadian rhythm. Exercise causes the body's core temperature to rise, which is then followed by a temperature drop about 5-6 hours after exercise. The goal of the late afternoon-early evening exercise is to create an artificial temperature trough at bedtime to aid sleep.*
- *Rule 5: Avoid all stimulants and alcohol.*
- *Rule 6: Regularize bedtime and wake-up time.*
- *Rule 7: Eat a light bedtime snack. There are 2 possible mechanisms by which the bedtime snack may be useful: Digestive hormones may have a sedative effect and/or the conversion of tryptophan into serotonin may promote sleep.*

*One difference in Hauri's approach is the recommendation to experiment with napping. Although many sleep researchers caution that daytime napping is counterproductive when attempting to entrain sleep patterns, Hauri<sup>[2]</sup> suggests that elderly patients may actually benefit from daytime napping. He notes, however, that napping should be carefully monitored with sleep diaries and suggests that a 1-week trial is sufficient to determine whether naps will benefit overall sleep quality.<sup>[2]</sup>*

## **Stimulus Control Instructions**

*Stimulus control, which was first proposed by Dr. Richard Bootzin<sup>[3]</sup> in 1972, uses a set of 6 tools that provide a logical basis for good sleep. Patients are first instructed to attempt sleep only when sleepy, rather than following a strict timetable for sleep. This first rule is aimed at eliminating frustration that comes from unsuccessful sleep attempts while*

*sensitizing the patient to his/her internal cues of sleepiness, such as head nods or droopy eyes.*

*The second instruction requires that the bedroom and bed be restricted to sleep alone -- no television, radio, music, or discussions of daily events.*

*The third instruction or rule requires that the patient get out of bed if he/ she is unable to sleep. Again, this short-circuits frustration and arousal caused by unsuccessful attempts at sleep. Rather than tossing and turning, patients are told to leave the bedroom and engage in relatively unstimulating tasks. They are instructed to return to the bedroom only when they feel sleepy again. This instruction is often the most difficult to carry out because many insomniacs have developed a pattern of clinging to the bed at all costs.*

*The fourth rule is simply a repeat of the third instruction. If the sleep attempt is not successful following step 3, the patient is told to again leave the bed, engage in nonstimulating activities, and return to bed only when sleepy. This process, according to Bootzin,<sup>[3]</sup> may be repeated several times during the night.*

*The fifth instruction is to get up at the same time every morning regardless of the quality of sleep during the night. This avoids a common practice among insomniacs -- seeking to make up for a lack of nighttime sleep by sleeping later in the morning, a practice that worsens sleep latency the following night. The sixth and final rule is to avoid all daytime napping. These last 2 instructions are designed to help regulate the body's sleep rhythm and deprive the patient of sleep. Sleep deprivation, in turn, is likely to decrease sleep latency while strengthening the association of sleep with the sleep environment, ie, the bedroom at night.*

### **Sleep-Restriction Therapy**

*Spielman and coworkers<sup>[4]</sup> expand on the concept of sleep deprivation as a means of decreasing sleep-onset latency, increasing periods of deep sleep, and reducing awakenings. In their sleep-restriction therapy approach, the first step is determination of the maximum allowable time in bed, which is determined by averaging the patient's estimated total nightly sleep time over a 1-week period. Note, however, that the total allowable sleep time is never set below 4.5 hours. The wake-up time is predetermined on the basis of the time the patient normally awakens to start the day. Bedtime is determined by subtracting the total allowable sleep time from the wake-up time. Thus, for example, if a patient's wake-up time is 7 am and his/her maximum allowable sleep time is 5 hours, then bedtime is 2 am.*

*The patient is put on this restricted sleep schedule for 5 days, during which time the patient is told to keep a careful log of time spent in bed and time spent awake in bed. Using the log data, the patient's mean estimate of sleep efficiency (mean total sleep time/mean total time in bed) is calculated. If the mean sleep efficiency is 90% or more, bedtime is adjusted to add 15 minutes to the total allowable sleep time. However, if sleep efficiency is less than 85%, bedtime is adjusted to reduce the total allowable sleep time by 15 minutes. The new schedule is then followed for 5 days, again with close monitoring of time in bed and total sleep time. This schedule is followed -- making adjustments every 5 days -- until the patient achieves a sleep efficiency of more than 90% for 7 hours a night.*

*Throughout the sleep-manipulation period, daytime napping, lying down, or (in some cases) monotonous sleep-inducing activities are avoided.*

## Pharmacologic Interventions

Although behavioral approaches are effective for many patients, they do not work for all. Thus, for patients with transient insomnia, a trial of brief pharmacologic therapy is recommended (Table 1).

**Table 1. Pharmacotherapy for Treatment of Transient Insomnia**

Condition	Type of Drug	Drug	Comments
Non-anxiety-related insomnia	Benzodiazepines	Temazepam ( <i>Restoril</i> )	Intermediate-acting and may be useful for patients with sleep-continuity problems
Anxiety-related insomnia	Benzodiazepines	Triazolam ( <i>Halcion</i> )	Shorter-acting; increased risk for tolerance and rebound insomnia
Anxiety-related insomnia	Benzodiazepines	Flurazepam ( <i>Dalmane</i> )	Longer-acting; may be useful for patients with daytime anxiety
Anxiety-related insomnia	Benzodiazepines	Clonazepam ( <i>Klonopin</i> )	Longer-acting
Anxiety-related insomnia	Nonbenzodiazepines	Zolpidem ( <i>Ambien</i> )	Short-acting
Anxiety-related insomnia	Nonbenzodiazepines	Buspirone ( <i>Buspar</i> )	Antianxiety effect takes at least 4 weeks
Anxiety-related insomnia	Sedative antidepressants	Nortriptyline ( <i>Aventyl</i> )	Sedating; may help with generalized anxiety disorder
Anxiety-related insomnia	Sedative antidepressants	Doxepine ( <i>Sinequan</i> )	Sedating
Anxiety-related insomnia	Sedative antidepressants	Trazodone ( <i>Desyrel</i> )	Side effects, including daytime sedation, orthostatic hypotension, and possible priapism

*Adapted from Weilburg JB. Approach to the patient with insomnia. In: Goroll AH, Lawrence A, eds. Primary Care Medicine: Office Evaluation and Management of the Adult Patient. 3rd ed. JB Lippincott Co; 1995*

*After behavioral interventions have been exhausted, the 35-year-old lawyer with insomnia who experienced daytime fatigue and difficulty concentrating is likely to benefit from a pharmacologic approach, if depression is ruled out as a comorbid condition. Generally, we rely on the newer agents -- the nonbenzodiazepines, such as zolpidem or zaleplon -- because they appear to be less likely to lead to tolerance, which is a problem with some of the older agents.*

*Moreover, it is likely that more pharmacotherapy options will be available in the near future. Two new nonbenzodiazepine agents are poised to enter the market. The first of*

*these, eszopiclone is a nonbenzodiazepine that acts on the gamma-aminobutyric acid (GABA) receptor complex, the target of benzodiazepines, but at a different site.*

*In a phase 3 trial of the drug, Krystal and colleagues<sup>[5]</sup> reported that 60% of patients taking eszopiclone (n = 593) completed the 6-month treatment, whereas 56.6% of patients (n = 195) in the placebo arm completed treatment. Moreover, patients taking eszopiclone reported significant and sustained improvements in sleep latency, wake time after sleep onset, the number of awakenings, the number of nights awakened per week, total sleep time, and the quality of sleep as compared with placebo (P < .003). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo (P < .002). There was no evidence of tolerance, and the most common, adverse events were unpleasant taste and headache.<sup>[5]</sup>*

*In March 2004, the US Food and Drug Administration (FDA) issued conditional approval for eszopiclone, which is likely to be available by midsummer.*

*The second new agent expected to come to market soon is indiplon. In studies reported at the 2003 American Psychiatric Association Annual Meeting, Roth reported that indiplon improved sleep latency by polysomnography as well as self-report in a placebo-controlled trial. These were healthy young people without insomnia, however.<sup>[6]</sup> Indiplon's manufacturer is seeking FDA approval for both immediate-release and modified-release formulations and is requesting no time restrictions on the labeling of both formulations, which would differ from zolpidem (which is restricted to 7-10 days of use).<sup>[7]</sup>*

*Although these therapeutic options are often effective, a subset of patients is not helped by these available therapies. For those patients, complementary medicine may be an option (see Table 2). Often, patients are already experimenting with over-the-counter "natural" remedies, so it is helpful to become acquainted with these options.*

**Table 2. Available Complementary Medicines for Insomnia**

<b>Complementary Agent</b>	<b>Comments</b>
Valerian	Purported sedative and sleep aid used since medieval times
Skullcap, blue pimpernel, mad weed	Purported herbal remedy for insomnia, efficacy not established
Passion flower	Purported herbal remedy for restlessness and insomnia, efficacy not established
Chamomile	Purposed remedy for insomnia used by ancient Egyptians, efficacy not established
Melatonin	Hormone synthesized by pineal gland. Hypnotic and circadian effects documents. Safety and efficacy for treatment of sleep disorders not established by randomized, clinical trials.

**Adapted from Attele AS, Xie JT, Yuan CS. Treatment of insomnia: an alternative approach. *Altern Med Rev.* 2000;5:249-259**

*Of this list, melatonin is single compound for which there is some evidence of efficacy, although that evidence is not conclusive. For example, in a study of 7 totally blind individuals, administration of 10 mg of melatonin an hour before bedtime was associated with improved sleep efficiency (less waking time after initial onset of sleep) as compared with placebo. Additionally, the same researchers report that titrating down to .05 mg of melatonin daily for 3 months maintained synchronization of the circadian system.<sup>[8]</sup> These studies are typical of the intriguing, yet suggestive nature of melatonin research. Nonetheless, it is well recognized that melatonin plays a role in regulating the sleep-wake system.<sup>[1]</sup> Thus, it is not surprising that melatonin continues to be the subject of study.*

*Although the efficacy of melatonin has not been confirmed in large, placebo-controlled, randomized trials, its potential utility for regulating the circadian system has led to the development of agonists for the melatonin system. One of these, ramelteon (formerly TAK-375), is a selective melatonin ML-1 receptor agonist, which is being developed for treatment of transient and chronic insomnia. Ramelteon specifically targets the brain's ML-1 receptors, located, which are located in the suprachiasmatic nucleus (described in part 1 of this review).*

*In preclinical studies, ramelteon was found to be 15 times more potent than melatonin, with an average half-life of 1-2 hours.<sup>[9]</sup>*

*Roth and Walsh<sup>[10]</sup> studied ramelteon in 400 normal sleepers ages 35-60. Volunteers were randomized to 16 mg of ramelteon, 64 mg of ramelteon, or placebo 30 minutes before bedtime. Latency to sleep onset was reduced by 50% in both groups that received the active study drug. Moreover, both doses increased sleep time by an average of 15 minutes as compared with placebo. There was no psychomotor impairment 30-60 minutes after waking among the placebo patients or patients who received 16 mg of the study drug, but patients receiving 64 mg, while having no functional impairment, did have a small, but statistically significant impairment in perception of function. Patients receiving high-dose ramelteon claimed they were less alert and had difficulty concentrating in the morning.<sup>10</sup>*

*A recent, double-blind, placebo-controlled, crossover study<sup>[11]</sup> enrolled 107 volunteers who met the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) definition of primary insomnia, meaning insomnia not secondary to medical or psychiatric illness and not a primary sleep disorder. Most patients had experienced insomnia for more than a year. Participants were treated in the sleep laboratory for 2 consecutive nights. Patients were required to have a latency to sleep onset of 20 minutes or longer and to have at least 60 minutes of wake time during an 8-hour recording period. Ramelteon was studied at 4 mg, 6 mg, 16 mg, and 32 mg.*

*All doses of ramelteon reduced sleep latency by about 40% as compared with placebo. The drug also increased polysomnography-measured sleep time by more than 10 minutes. Moreover, there were no adverse effects on alertness or ability to concentrate in the morning.<sup>[11]</sup>*

*However, although ramelteon appears to be a promising compound, it is not yet approved for clinical use. Moreover, the pipeline drugs eszopiclone and indiplon are also not yet available.*

## **Rational Management Approaches**

*The primary care physician is left with several, well-proven treatment strategies on the basis of these essential principles:*

- *Careful history taking, including the use of a 2-week sleep-wake log as well as assessment of sleep hygiene.*
- *Refer patients for sleep laboratory assessment when sleep apnea, narcolepsy, or periodic limb movement disorder is suspected.*
- *Assess for psychiatric problems and for medical problems, especially thyroid disorders and congestive heart failure.*
- *Consider, the 2 "patients" introduced at the outset. Both require a careful assessment of sleep hygiene, but it is unlikely that either patient will require referral for sleep laboratory assessment.*
- *After history and physical -- including a Folstein Mini-Mental State (MMS) exam to rule out depression -- the 35-year-old lawyer should be initiated on a trial of behavior therapy, starting with sleep-hygiene techniques. If, however, the behavioral approach is not effective, this patient is a good candidate for a brief pharmacologic intervention, usually with a nonbenzodiazepine agent.*
- *The 45-year-old nurse may be the more challenging patient because he may require a more intense sleep-entraining program to overcome the circadian disturbance associated with shift work. Moreover, pain is a clear contributor to this patient's sleep problems. Remember, treat the pain and the sleep disorder is likely to benefit.*

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## **Conference Report - Highlights of the Associated Professional Sleep Societies 18th Annual Meeting**

**Karl Doghramji, MD**

*A number of advances in the pathophysiology and treatment of insomnia, and other sleep disorders, were reported at the Associated Professional Sleep Societies 2004 Annual Meeting; June 5-10, 2004; Philadelphia, Pennsylvania. This conference report reviews some of the salient developments with clinical relevance.*

### **Neurobiological Correlates of Insomnia, Anxiety, and Brain Overactivity**

*Clinical observations have long indicated that primary insomniacs exhibit behavioral and psychologic evidence of anxiety and overactivity. An investigation by Nofzinger and colleagues<sup>[1]</sup> examined the neurobiological correlates of this by obtaining regional cerebral glucose metabolic assessments in 7 insomnia patients and 20 healthy subjects during both waking and nonrapid eye movement (NREM) sleep with [18F]fluoro-2-deoxy-D-glucose positron emission tomography. Subjects with insomnia showed increased cerebral glucose metabolism during sleep and wakefulness; a smaller decline in relative metabolism from wakefulness to sleep in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala, hippocampus, anterior cingulate cortex, and medial prefrontal cortex; and reduced relative metabolism in the prefrontal cortex during wakefulness. These effects suggest that subjectively disturbed sleep in insomnia patients may be associated with increased brain metabolism. The inability to fall asleep and multiple nocturnal awakenings may be related to a failure of suppression of arousal mechanisms in the thalamocortical networks during the transition from waking to sleep. Further, the related daytime fatigue may reflect decreased activity in the prefrontal cortex that results from inefficient sleep.*

*These results are of interest, inasmuch as 1 of the important neurotransmitters in the thalamocortical network is thought to be gamma-aminobutyric acid (GABA). Thus, GABA dysregulation may play an important role in the genesis of insomnia. It is also of interest that synapses of the GABA system are the sites of action of most currently available hypnotic agents marketed for sleep.*

*Trends in the patterns of usage of GABAergic agents from 1987 to 1996 continue today; a demographic survey by Compton-McBride and colleagues<sup>[2]</sup> indicates that, in 2002, an*



antidepressant was approximately 1.53 times more likely to be used for insomnia than a hypnotic agent by office-based physicians in the United States.

## **Treatments**

### **"Natural" Remedies for Insomnia**

*Insomniacs often resort to self-medication with natural and over-the-counter remedies (Ancoli-Israel and Roth<sup>[3]</sup>). One of the most popular seems to be melatonin, available as a dietary supplement. Although this agent has been used as a sleep aid and regarded as a rhythm-setting hormone for more than a decade, methodologically rigorous studies into its efficacy and safety are scant. Scheer and associates<sup>[4]</sup> conducted a randomized, double-blind, placebo-controlled, crossover trial of 16 men with untreated essential hypertension. They assessed the influence of acute (single) and repeated (3 weeks nightly) oral melatonin (2.5 mg) administration 1 hour before sleep on actigraphic estimates of nighttime sleep quality. Repeated melatonin administration improved sleep efficiency and subjective sleep duration. Sleep-onset latency decreased. However, acute melatonin application had no significant effect on any of these sleep measures. These and other pilot investigations are paving the way toward the possibility of large-scale trials with melatonin, which may one day be useful in the chronic treatment of insomnia. At this point, however, questions remain regarding its safety and efficacy.*

*Ramelteon (TAK-375), a selective melatonin (ML-1) receptor agonist, is a related chemical compound being developed for the treatment of insomnia. Pharmacokinetic studies by Hibberd and Stevenson<sup>[5]</sup> indicate that ramelteon is rapidly absorbed, with a Tmax of 0.3 hours, and rapidly eliminated, with a half-life of 1.2 hours. Safety studies with ramelteon have recently shown that it has minimal adverse interactions with other commonly prescribed drugs.<sup>[6-9]</sup> Data from efficacy studies of this investigational compound are expected to be available soon.*

*Valerian is another "natural" compound with extensive use as a hypnotic that has undergone several controlled clinical trials in nonneurologically impaired insomniac populations with some evidence of efficacy. Saunders and coworkers<sup>[10]</sup> presented preliminary, uncontrolled data on the use of this compound in 18 patients with Parkinson's disease. Baseline-to-treatment comparisons revealed a mild reduction in sleep latency (SL) and an increase in total sleep time. Research on this compound is ongoing, and questions regarding its safety are being addressed with further trials. Valerian and melatonin remain investigational.*

### **Hypnotic Agents**

*Zolpidem, a GABAA receptor agonist, remains the most commonly prescribed hypnotic agent. The most salient recent advance in this compound is the development of a modified-release (MR) formulation, which incorporates both immediate- and prolonged-release preparations. This combination provides sustained plasma zolpidem concentrations in the middle portion of the night (3-6 hours post dose) and thus improves sleep maintenance while possessing the same elimination half-life as standard zolpidem.*

*Hindmarch and colleagues<sup>[11]</sup> reported the results of a randomized, double-blind placebo or regular zolpidem 10 mg-controlled, crossover, pharmacodynamic study of 8 zolpidem MR formulations. Two particular formulations, including the 12.5-mg "E" compound, significantly reduced the total night number of awakenings when compared with placebo and standard zolpidem. The MR formulation promises to be a superior preparation than*

*zolpidem for the treatment of sleep-maintenance insomnia, with no additional negative effects on daytime performance.*

### **How Long Is Too Long to Safely Use Hypnotics?**

*Despite their extensive safety record, a major challenge to clinicians in the treatment of insomnia is the question of how long hypnotics can be safely used in patients with chronic insomnia. To address this concern, Perlis and colleagues<sup>[12]</sup> reported on an investigation of 199 patients with primary insomnia who received either zolpidem 10 mg nonnightly or placebo for a period of 12 weeks. The medication demonstrated significant improvements in subjective sleep latency (SL), the number of awakenings, wake after sleep onset (WASO), and total sleep time (TST) as compared with placebo. The maintenance of clinical gains over the 3-month study interval suggests that, in the absence of dose escalation, habituation and tolerance do not occur with chronic, intermittent use of zolpidem.*

*Another analysis of the same data<sup>[13]</sup> indicated that patients did not increase zolpidem medication intake as compared with the placebo group. Participants using zolpidem voluntarily limited use to 80% of available medication. Increases in use represented only 20% of the possible dose escalation, and this trend did not differ from that of the patients taking placebo. These data suggest that concerns regarding dose escalation, tolerance, and rebound may be exaggerated. The results also may be helpful in allowing some chronic insomniacs, who clearly benefit from the use of these medications for long periods of time, to continue to benefit without the threat that an effective remedy may be discontinued. Such studies also raise interesting questions regarding the existing guidelines for length of use of hypnotic agents. Nevertheless, zolpidem and other hypnotic medications should be only used for as long as needed, and physicians are urged to follow patients closely for signs of dose escalation and misuse.*

*Another investigational GABAA receptor agonist, eszopiclone, has been developed for the treatment of insomnia and is nearing release for clinical use. This medication has also been found effective according to sleep-maintenance and sleep-onset measures for extended periods of time. Buysse and associates<sup>[14]</sup> reported on a placebo-controlled 6-month study with this compound and concluded that "6 months of nightly eszopiclone treatment is associated with rapid and sustained response and no evidence of tolerance, even among different patient subgroups." Krystal and colleagues<sup>[15]</sup> also concluded that eszopiclone provided sustained improvement in maintenance insomnia throughout the 6 months of treatment. These are the first reported controlled studies that demonstrate the continuing hypnotic benefit of any agent for such an extended period of time. From a clinical standpoint, they raise the possibility of long-term use of hypnotics in populations, such as the elderly, who have chronic insomnia conditions that are unlikely to improve.*

### **Treating Insomnia in the Elderly**

*The prevalence of insomnia increases with age. More than 50% of the elderly complain of difficulty staying asleep or falling asleep as compared with about 30% of the general population. In this age group, insomnia also tends to be chronic, lasting more than 3 months. Erman and others<sup>[16]</sup> reported these observations and evaluated 264 patients 65-85 years of age with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of primary insomnia in a randomized, double-blind, placebo-controlled study. Participants received eszopiclone 2 mg (n = 136) or placebo (n = 128) nightly for 2 weeks. Compared with placebo, eszopiclone 2 mg significantly reduced polysomnographic latency to persistent sleep, WASO, sleep efficiency, and number of*

awakenings during the treatment period. Subjective changes were also reported in SL, WASO, TST, and number of awakenings.

*These data provide evidence that this medication is effective for the treatment of insomnia in the elderly. Of particular interest was that eszopiclone also reduced the cumulative number of naps and duration of naps among patients who napped. Eszopiclone also produced improvements in the patients' Insomnia Severity Index total scores and quality of sleep, and in the SF-36 domains of physical functioning. These data provide preliminary evidence regarding the potential benefit of treatments on daytime function in insomniacs. Patients experienced no rebound insomnia after treatment withdrawal. The most common adverse event was unpleasant taste.*

### **Immediate-Release, Short-Acting Agents**

*Indiplon is another investigational GABAA receptor modulator for insomnia and is formulated in an immediate-release (IR) preparation; this is rapidly absorbed and has an elimination half-life of 1.0-1.5 hours. Walsh and colleagues<sup>[17]</sup> conducted a randomized, placebo-controlled study with 194 adult outpatients with primary insomnia who were randomized to 5 weeks of double-blind treatment with either 10- or 20-mg doses of indiplon-IR, or placebo. This polysomnographic study demonstrated that both doses of indiplon-IR significantly reduced latency to persistent sleep during the 5 weeks of study with comparable findings for SL. There was no evidence of next-day residual effects, and no evidence of withdrawal or rebound upon abrupt discontinuation. The ultrashort half-life of this compound also offers the possibility of middle-of-the-night dosing for patients who awaken in the middle of the night.*

*Garber and associates<sup>[18]</sup> compared middle-of-the-night dosing of indiplon-IR, zolpidem, and the investigational agent zopiclone, and noted that neither 10- nor 20-mg doses of indiplon-IR resulted in next-day residual effects. By contrast, middle-of-the-night treatments with zolpidem and zopiclone were associated with significant residual sedation. These data suggest that indiplon may have a suitable profile for middle-of-the-night administration. Like zaleplon, another ultrashort half-life agent, indiplon offers the possibility of minimal daytime residual sedation for shift workers and long-distance jet travelers who may require short periods of sleep on an intermittent basis.*

### **Other Strategies for Insomnia**

*Anticonvulsants have also seen a rise in use for sleep-related difficulties. One such compound, tiagabine, is a GABA reuptake inhibitor and has been shown in a pilot study to improve sleep efficiency and levels of delta sleep in aging adults. Randazzo and colleagues<sup>[19]</sup> performed a more extensive investigation with 26 subjects, 24 of whom completed the study. Bedtime administration of 4 mg of tiagabine produced a significantly greater amount of TST (407.7 min) than placebo (396.0 min) and less WASO (64.9 min) as compared with placebo (77.2 min). Minutes of slow-wave sleep increased (59.7) relative to placebo (44.5). Bedtime administration of 8 mg of tiagabine provided significantly more slow-wave sleep (87.0 vs 60.0 min), less stage I sleep (62.4 vs 81.3 min), and less REM sleep (58.4 vs 68.3 min). No differences on subjective sleep measures or measures of morning sedation were noted among treatment and placebo groups. These results, collectively, suggest that tiagabine 4 and 8 mg has positive effects on sleep, particularly sleep-maintenance variables, with infrequent adverse effects. Thus far, however, tiagabine is not approved for treating insomnia.*

*Behavioral strategies play an integral role in the management of insomnia. Unlike pharmacologic therapies, the efficacy of behavioral techniques lasts well beyond the*

*discontinuation of treatment. Edinger and associates<sup>[20]</sup> reported on a series of 86 patients, age 40-75 years, with sleep-maintenance insomnia, who were randomized to a waiting list control or to variable periods of treatment (1-8 weeks) with therapist-guided cognitive behavioral therapy sessions. They concluded that the 4-session intervention, with sessions scheduled 2 weeks apart, was most effective overall. Of the patients receiving 4 sessions, 58.3% achieved at least a 50% reduction in WASO through treatment.*

## **Other Sleep Disorders**

### **Restless Legs Syndrome**

*In addition to primary insomnia, the differential diagnosis of insomnia includes a variety of conditions, such as restless legs syndrome (RLS). Patients complain of a "creeping" sensation in the lower extremities upon reclining. They resort to moving the affected extremity by stretching, kicking, or walking to relieve symptoms. Most exhibit periodic limb movements during sleep studies. Whereas RLS was originally thought to be no more than a rare, independent disorder in children, an investigation by Sayed and colleagues<sup>[21]</sup> revealed that, of 207 children with a mean age of  $8 \pm 6$  years presenting to a sleep disorders program, 5% had RLS independent of attention-deficit/hyperactivity disorder. Treatments for the condition include dopaminergic agents, benzodiazepines, anticonvulsants, and (in refractory cases) opioids. Because iron-deficiency states and anemia can underlie the condition, a thorough search for causal entities should be conducted before symptomatic management.*

*One of the most significant concerns with the long-term treatment of RLS is the development of tolerance and augmentation, or the occurrence of symptoms in a more severe form at alternate times during the course of the day. Montplaisir and colleagues<sup>[22]</sup> and Karrasch and coworkers<sup>[23]</sup> reported on a 36-week investigation with ropinirole, a dopaminergic agent, during which the agent was administered in an uncontrolled, followed by a controlled fashion. At week 20, after which dose changes were not allowed, the median ropinirole dose was 2.0 mg/day. The odds of a patient relapsing while receiving placebo were 3 times greater than for a patient receiving ropinirole (32.6% with ropinirole vs 57.8% with placebo; adjusted odds ratio = 0.33; 95% confidence interval: 0.13, 0.81;  $P = .0156$ ). Furthermore, only 3 patients (1.5%) experienced augmentation (reported as hyperkinesia) during ropinirole treatment; this worsening of symptoms resolved spontaneously with continuing treatment with ropinirole. Ropinirole is not yet approved for use in RLS.*

### **Obstructive Sleep Apnea**

*Obstructive sleep apnea syndrome (OSA) also often enters into the differential diagnosis of insomnia, yet more often presents with the symptom of excessive somnolence. Although treatment with continuous positive airway pressure (CPAP) often relieves symptoms of apnea, investigations have documented a persistence of crippling levels of daytime sleepiness despite adequate treatment of the underlying disease.<sup>[24]</sup>*

*Modafinil, a medication that has been used for the treatment of excessive sleepiness in association with narcolepsy for many years, was also recently approved for the treatment of residual sleepiness in association with OSA. Because these symptoms are usually chronic and unremitting, it is important to ensure continued efficacy and safety during chronic treatment. Schwartz and Hirshkowitz<sup>[25]</sup> presented data on 744 patients (478 with narcolepsy and 266 with OSA on CPAP with residual excessive sleepiness) from multiple trials who received modafinil in open-label fashion in which dosing was flexible (200-400 mg/day). The duration of the narcolepsy studies was 40 weeks and the OSA study lasted*

12 months. Baseline excessive sleepiness, assessed by the mean ( $\pm$  standard deviation) Epworth Sleepiness Scale, was  $17.4 \pm 4.1$  in narcolepsy vs  $14.5 \pm 3.6$  in OSA ( $P \leq .001$ ). The change from baseline of the Epworth Sleepiness Scale at the end point was  $-4.5 \pm 4.7$  for OSA and  $-4.4 \pm 4.9$  for narcolepsy. These results imply a persistence of efficacy despite long-term treatment with modafinil.

In conclusion, insomnia is a multifaceted condition with a large number of associated disorders. In primary insomnia, GABA receptor agonists continue to be the primary pharmacologic method for the management of this condition, and data are emerging to reveal their efficacy and relative safety with long-term use. Newer agents with similar receptor characteristics are being developed as well as agents with other mechanisms. In the case of specific disorders, medications are now being developed for the long-term management of RLS and OSA with residual sleepiness.

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## **Expert Column - Insomnia and Menopause**

**Phyllis C. Zee, MD, PhD**

**Complaints of sleep disturbance are more prevalent among women than men across the entire life span.<sup>[1,2]</sup> Among women, the prevalence of insomnia rises sharply by approximately 40% during the period of transition to menopause and after menopause.<sup>[3,4]</sup> Therefore, it is not surprising that menopausal women are more likely to take hypnotic medications than younger women or men (National Sleep Foundation Women and Sleep Poll, 1998).**

**Although sleep quality clearly diminishes with menopause, less is known regarding the underlying pathophysiology of insomnia in this population. Alterations in the hormonal environment during various phases of a woman's life, from menstruation,<sup>[5]</sup> pregnancy,<sup>[6]</sup> to menopause,<sup>[3]</sup> likely contribute to the high prevalence of this problem. Despite the popular notion that hot flashes cause insomnia, the clinical significance of hot flashes is also an area of scientific debate. Some studies have reported an association between hot flashes and awakenings from sleep,<sup>[7,8]</sup> whereas others did not find a relationship between hot flashes and objective sleep measures of sleep quality.<sup>[9]</sup> Although the relationship between hot flashes and objective measures of sleep remains unresolved, hot flashes appear to be associated with poor subjective sleep quality.**

**In addition to hormonal changes and hot flashes, depression, anxiety, and sleep disorders (such as primary insomnia, restless legs syndrome, and sleep apnea) have been proposed as factors underlying sleep disturbances associated with menopause.<sup>[2,8]</sup> The importance of sleep-disordered breathing as an etiology of poor sleep quality in postmenopausal women has been recognized.<sup>[10]</sup> A recent analysis of the Wisconsin Sleep Cohort data showed that menopause was an independent risk factor for sleep apnea-hypopnea.<sup>[11]</sup> Consideration of the many potential causes of insomnia and specific therapeutic approaches provides an excellent opportunity to improve health and quality of life in this population at high risk for insomnia.**

### **Evaluation of Insomnia in Perimenopausal and Postmenopausal Patients**

**The recognition that the etiology of insomnia is often multifactorial rather than attributing sleep problems only to the absence of estrogen is key to the evaluation and subsequent treatment of "menopausal insomnia." Hot flashes, medical disorders, medications, mood disorders, other sleep disorders, and lifestyle factors should be considered. In addition to the patient's own sleep habits, it is important to inquire about the bed partner's snoring or**

**movements during sleep that can disturb the patient's sleep. Key questions in the history can help uncover these causes and conditions.**

**When obtaining a history, all patients should be asked the following questions: Do you have difficulty falling or staying asleep, and are you excessively sleepy during the day? If the answer is "yes," then a more careful history can be investigated regarding hot flashes, depression, anxiety, pain, medications, sleep environment, snoring (herself and partner), and symptoms of restless legs (such as uncomfortable sensations in the limbs at rest and/or leg kicks during sleep). For patients with hot flashes, in addition to the assessment of menopause, night sweats due to metabolic disorders, such as diabetes mellitus and thyroid dysfunction, should be considered in the differential diagnosis. A sleep diary during a 2-week period can provide a more detailed assessment of sleep and wake behavior. When sleep apnea, restless legs syndrome, or periodic leg movements of sleep are suspected, an overnight sleep study (polysomnogram) is a useful diagnostic tool.**

### **Managing Insomnia in Perimenopausal and Postmenopausal Patients**

**Successful management often requires a comprehensive approach that addresses hormonal-related changes in sleep, hot flashes, poor sleep habits, disruptive environmental factors, stress management, underlying medical and psychiatric conditions, and sleep disorders (such as primary insomnia, restless legs syndrome, and sleep apnea). For patients with restless legs syndrome, following evaluation for possible causes, such as iron deficiency, diabetes mellitus, or thyroid disease, dopamine agonist medications are effective and are preferred to the benzodiazepine medications. For patients with sleep apnea, the most commonly used medical treatment is nasal continuous positive pressure.**

**The general approach to managing primary and secondary insomnia associated with menopause includes sleep hygiene, behavioral interventions, cognitive behavioral therapy, and pharmacologic approaches. Behavioral interventions aim to correct or remove factors that perpetuate or worsen insomnia. These include dysfunctional beliefs about sleep, poor sleep hygiene, conditioned arousal, excessive napping or time in bed, and irregular sleep and wake times (for specific guidelines, see Chesson and colleagues<sup>[12]</sup>).**

**Behavioral therapy alone or combined with pharmacologic treatments has been shown to be effective for primary as well as secondary insomnia.<sup>[13,14]</sup> Although traditional behavioral therapy requires multiple sessions over a period of 6-8 weeks, an abbreviated cognitive behavioral therapy comprising two 25-minute sessions can also be effective.<sup>[15]</sup> Therefore, behavioral strategies should be an integral part of the management of insomnia. Evidence also indicates that pharmacotherapy used in combination with behavioral approaches can produce greater short-term benefits than behavioral therapy alone.<sup>[13]</sup>**

**Pharmacologic agents used in clinical practice to induce sleep or maintain sleep include hypnotics and sedating antidepressants. Sedating antidepressants, such as the tricyclics and trazodone, produce drowsiness and may help sleep, but residual sedation and interactions with other medications need to be considered in postmenopausal older women. The controversy concerning hormone replacement therapy (HRT) has increased the use of antidepressant medications, such as the selective serotonin reuptake inhibitors (SSRIs), for managing hot flashes as well as treating anxiety and depression. Of interest, 1 potential side effect of this class of antidepressants is sleeplessness.**



*The mechanism of action of the available hypnotics is via modulation of the gamma-aminobutyric acid type A (GABAA) receptor complex. Hypnotic medications fall into 2 major categories: the benzodiazepines (temazepam, flurazepam, and triazolam) and the newer nonbenzodiazepines (zaleplon and zolpidem). Good efficacy, together with improved safety and tolerability of these newer agents, have made them the first-line choices when a hypnotic medication is indicated.*

*The use of HRT for treating insomnia in postmenopausal women, particularly with regard to objective measures, is controversial, and results may depend on the specific type of hormone or hormone combination used.<sup>[2]</sup> Similarly, because of conflicting objective and subjective results, there is no consensus regarding the role of HRT for treating hot flashes and related sleep disruption.<sup>[16,17]</sup>*

*HRT (estrogen alone or in combination with progesterone) has also been investigated for the treatment of sleep apnea-hypopneas in postmenopausal women. In general, epidemiologic studies indicate a positive effect of HRT on sleep-disordered breathing.<sup>[11,18]</sup> However, small prospective trials have shown either little effect or a reduction in the severity of sleep-disordered breathing.<sup>[19]</sup> Therefore, prospective, randomized, placebo-controlled studies are needed to more definitely determine the role of HRT in the treatment of insomnia as well as sleep-disordered breathing in menopause.*

## **Conclusion**

*Insomnia complaints are common among perimenopausal and postmenopausal women. Hormonal and physiologic changes; medical, psychiatric, and sleep disorders; and lifestyle factors contribute to the high prevalence of sleep problems in this population. Underlying disorders that may contribute to insomnia should be identified and treated. Advances in behavioral therapies, as well as superior safety and tolerability of the newer hypnotic agents, have resulted in improvements in the management of "menopausal insomnia." A number of new nonbenzodiazepine hypnotics (including 1 with a modified-release formulation), GABAA modulators, corticotropin-releasing factor antagonists, and melatonin receptor agonists are currently being evaluated for the treatment of insomnia. Recognizing and appropriately treating sleep disorders represent an opportunity not only for improving the quality of life of women, but also an opportunity to prevent the development of mood and medical disorders later in life.*

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