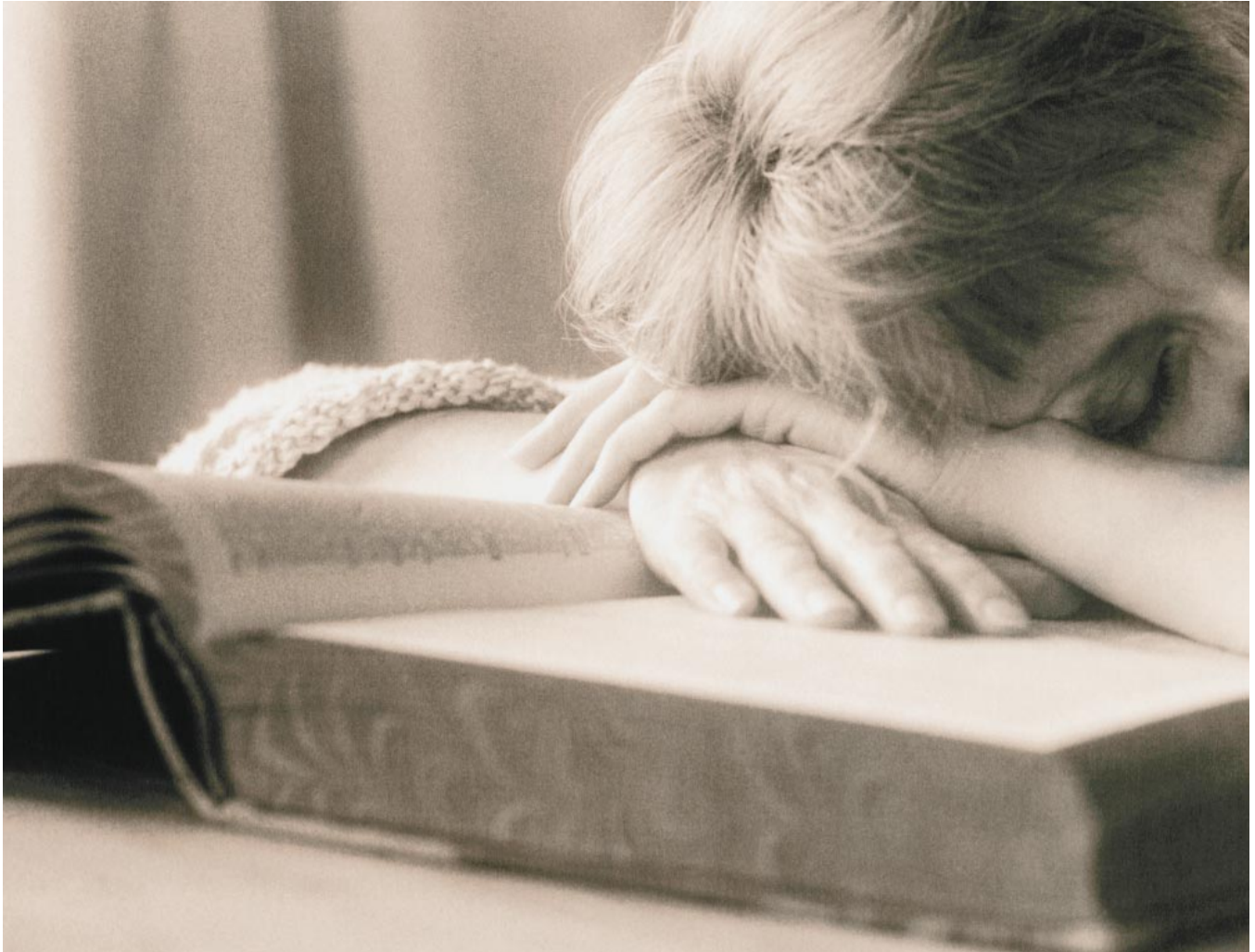

Evaluating and Treating Menopausal Sleep Problems

by Philip S. Eichling, MD, MPH



Postmenopausal women are twice as likely as their premenopausal peers to report sleep disturbances. The clinician must differentiate between true insomnia and sleepiness that results from multiple nighttime arousals. Various physical and medical causes may be involved, including hot flashes, depression and anxiety. Treatment with medication and/or behavioral therapy can have a profound effect on the quality of life of postmenopausal women.

Among women seeking healthcare, sleep difficulty is one hallmark of menopause. Both sleep-onset insomnia and sleep-maintenance insomnia are characteristically increased during perimenopause and menopause in some women. Insomnia itself is approximately twice as prevalent in women as in men and the general population, although the National Sleep Foundation says some evidence exists that many more women than men may seek medical care for the problem. In studies of various populations, approximately 10 to 15% consider themselves to have frequent significant to severe insomnia.^{1,2}

Twice as many postmenopausal women as premenopausal women report sleep disturbances.^{3,4} Thus, sleep disorders and insomnia are major features of the medical care of women during menopause and should be appropriately addressed by physicians who treat these women. This article intends to outline some common sleep disorders and their physiologic basis. It also discusses a practical approach to the evaluation and treatment of sleep disorders in menopausal women.

Two major sleep disorders occur with increased frequency at the time of menopause: sleep apnea and insomnia. Mood disorders, considered by many to be associated with perimenopause and menopause, may be intertwined with sleep disorders.

Both sleep apnea and insomnia are affected by biologic changes that occur perimenopausally. Thus, a review of the sleep effects of the hormonal shifts associated with menopause is in order.

Normal Sleep Stages and Architecture

There are two basic types of sleep: rapid eye movement (REM) and non-REM (NREM). Normally, humans cycle through NREM to REM about every hour and a half during the night. NREM is divided into two types of sleep. The first type is stage 1 (a transitional stage) and stage 2 ("true sleep"). The second type is comprised of stages 3 and 4 ("slow-wave sleep"). Most of the night is spent in stage

2 sleep. Stage 2 and slow-wave sleep are very restorative. One purpose of sleep is to reduce the build-up of adenosine, the "sleepiness" chemical, in the brain. Because this chemical builds up during the course of the day, sleep researchers commonly refer to the concept of a "sleep debt" that can only be "paid off," or reduced, with sleep. Slow-wave sleep (stages 3 and 4) is the most effective for reducing the levels of adenosine in the brain.

The REM cycles increase in duration as the night progresses. In general, the NREM slow-wave sleep phase is the deepest sleep, in that individuals are least arousable during that time. Individuals are most arousable during REM sleep, which is accompanied by faster EEG activity. Increased "fast activity" on the EEG is associated with poorer sleep. The body also goes through temperature changes during normal sleep, such that there is a nadir in the middle of the nighttime sleep cycle.

Effect of Hormonal Changes on Sleep

Progesterone. While estrogen is a common focus of perimenopause discussions, progesterone has very profound effects on sleep and is somewhat more straightforward in its effects on sleep than estrogen. Progesterone, when given intravenously, has direct sedative qualities, stimulating benzodiazepine receptors that in turn stimulate the production of γ -aminobutyric acid (GABA) receptors.⁵ GABA is the neurochemical responsible for NREM sleep. It is the same receptor stimulated by benzodiazepines and standard sleeping medications. As a GABA agonist, progesterone is anxiolytic, although the exact mechanism is unclear, as it seems not to be helpful in attempts to taper patients off benzodiazepines.⁶ During a normal menstrual cycle, there is a rapid peak during the mid-luteal phase and a drop-off premenstrually, which are associated with sleep difficulties and increased arousals.

A second impact of progesterone is its effect on breathing. Progesterone is a respiratory stimulant and has been used to treat mild obstructive sleep apnea.⁷

During pregnancy, there is remarkably little obstructive sleep apnea, given the amount of weight gain that typically occurs, and it is felt that the high progesterone levels characteristic of pregnancy function as a respiratory stimulant. Similarly, prior to menopause, when there are naturally occurring higher progesterone levels, less sleep apnea is seen.

Estrogen. The effect of estrogen on sleep is more complicated than that of progesterone. In animals, estrogen suppresses REM sleep, but in humans it increases REM cycles. Estrogen is involved in norepinephrine, serotonin and acetylcholine metabolism.⁸ Estrogen has been shown to decrease sleep latency, decrease the number of awakenings after sleep occurs, increase total sleep time and decrease the number of cyclic spontaneous arousals.⁹ During the luteal (low estrogen) phase in premenopausal women, a two-fold increase in the number of arousals occurs, particularly when both estrogen and progesterone levels are low.⁵

Estrogen is also related to temperature regulation in the body. An obvious effect of low estrogen levels is the classic hot flash characterized by increases in both peripheral and central temperature. Hot flashes also are characterized by bursts of catecholamines and surges in luteinizing hormone (LH).¹⁰ A wide range of symptomatic hot flashes is seen at menopause. Obviously, hot flashes can be associated with increased arousals.

Estrogen replacement is associated with decreasing high-frequency EEG activity in NREM sleep, which is associated with better sleep. REM sleep is associated with memory consolidation. Some symptoms of menopause, including memory difficulties, perhaps can be traced to poor sleep patterns and decreased memory consolidation associated with disturbed REM sleep.^{11,12}

In addition to its obvious prevention of hot flashes, estrogen has a significant effect on core body temperature during sleep. Estrogen in mammals is a thermoregulatory hormone that helps regulate the time of lowest body temperature dur-

ing the night. Stopping estrogen shifts this time forward and changes the depth of the temperature drop.¹ Both of these changes result in more arousability and lighter sleep. It is hypothesized that one of the reasons for deeper sleep during the follicular phase in premenopause is the temperature-regulating effect of high estrogen during this time.

Cortisol. Cortisol is a so-called “stress hormone” that increases in times of stress, including both depression and anxiety. Estrogen also affects sleep via cortisol. Normally, serum cortisol peaks in the early morning. Menopause is associated with higher cortisol levels occurring earlier in the sleep period. Menopausal women are more susceptible to nocturnal rises in cortisol associated with mild stressors.^{13,14} Estrogen helps regulate cortisol peak and therefore helps stabilize nighttime sleep. The same effect is postulated to underlie improvement of depression with estrogen replacement therapy.¹⁵

Melatonin. Melatonin and estrogen are somewhat inversely related and have a very complicated interaction. Melatonin is a reproductive hormone in animals with seasonal reproductive habits, and it functions to suppress estrus in these animals. In very high pharmacologic doses, melatonin can be used as a birth control pill. In males it can cause regression of testicular tissue. Melatonin is linked to LH production, such that disruption of melatonin will disturb LH surges and therefore cause fertility difficulties. It seems that the predominant direction in which melatonin and estrogen are related is melatonin driving reproductive hormones rather than vice versa.^{16,17}

Melatonin functions less as a sedating agent than as an anti-arousal agent. It blocks normal circadian arousal mechanisms and tends to keep humans asleep at night. In general, melatonin levels decrease with the aging process, but decreases in total melatonin levels are not necessarily associated with menopause. Waking up at night and turning on bright lights will cut off melatonin production, so anything that causes arousals or awak-

ens people might also reduce melatonin. Additionally, estrogen probably has a melatonin-supportive function. Tamoxifen, an anti-estrogen, causes a decrease in melatonin.¹ After menopause there is an initial rise in melatonin followed by an age-related decline.¹⁶ However, postmenopausal women with insomnia generally have been shown to have low melatonin levels.¹⁸

Testosterone. Testosterone has been less well studied than the other sex hormones in relation to sleep. Testosterone tends to decrease REM sleep in animals, and significant gender differences have been seen in REM sleep in animal studies.¹ Testosterone seems not to have a major effect on sleep in humans, except that testosterone is related to obstructive sleep apnea. Higher testosterone levels are associated with increased apnea, but the reason for this is unclear.¹⁹ This observation has implications regarding testosterone replacement therapy for both men and women. It has been shown that exogenous testosterone replacement can and does worsen obstructive sleep apnea.

Assessment of Sleep Disorders

One of the more simple ways to view sleep medicine is to differentiate problems that occur as a result of multiple nocturnal arousals versus difficulty initiating sleep. In general, the term “insomnia” is commonly used to refer to those disorders associated with difficulty initiating sleep, either at sleep onset or in reinitiating sleep after waking. On the other hand, sleep physicians and polysomnography studies commonly focus on arousal events that lead to daytime sleepiness instead of insomnia. Pure psychophysiologic insomnia is characterized by feeling tired, but not sleepy. Insomnia itself is a hypermetabolic state in which the brain is “wired” and overly alert. Patients with insomnia have difficulty falling asleep at any time—day or night—and may present with complaints of fatigue, fibromyalgia or depression.

“Sleepiness” or “Insomnia”?

Sleepiness. When a menopausal patient

presents with the complaint of being “tired,” this can mean either that she is “sleepy,” the way patients with sleep apnea are sleepy, or “tired,” in the way that insomniacs are tired. Since many people have lived with sleepiness for a long time, they often think of it as a normal state. When questioning them, one usually needs to ask more than simply, “Are you sleepy during the day?” Specific situations, such as dozing off while riding as a passenger in a car or airplane, falling asleep at the theater, wanting to drift off during boring meetings, etc., all are indicators of excessive sleepiness.

Sleepiness tends to be an eye sensation, whereas fatigue tends to have a total body ache and drooping quality. Patients who have sleep apnea, the most prevalent model of a disorder with multiple arousals, may fall asleep in any given situation. They usually have no trouble falling asleep at night and usually wake repeatedly during the course of the night in addition to sleeping inappropriately during the day. A patient who has difficulty with multiple arousals will tend to score high on the Epworth Sleepiness Scale, which is a series of eight questions used to assess sleepiness (Figure). The Epworth Scale is standard, but it may under-represent sleepiness in women versus men. Thus, if the Epworth score is high, it may represent more severe sleepiness in women than men.²⁰

There is a normal afternoon dip in wakefulness, which is the most common time for people to report difficulty with excessive drowsiness at work or home. Naps tend to occur in this time frame. If a patient reports feeling sleepy in mid-morning or early evening, e.g., falling asleep watching television or at the theater, they are overriding a period of the day when they would be naturally more alert. Feeling sleepy at this time should be seen as a greater indicator of sleepiness than simply napping in the midafternoon.

Nocturnal arousals often can be mistaken for “bladder problems.” Patients with sleep apnea often think they are aroused by a full bladder, but nocturia should be specifically seen as a primary

0 = Would never doze	1 = Slight chance of dozing
2 = Moderate chance of dozing	3 = High chance of dozing
Situation	Chance of Dozing
• Sitting and reading	_____
• Watching television	_____
• Sitting inactive in a public place (e.g., theater)	_____
• As a car passenger for an hour without a break	_____
• Lying down to rest in the afternoon	_____
• Sitting and talking to someone	_____
• Sitting quietly after lunch without alcohol	_____
• In a car, while stopped for a few minutes in traffic	_____
Total	_____

Figure. The Epworth Sleepiness Scale. A score greater than 10 is abnormally sleepy.

sleeping disorder before it is considered a urologic problem. Following an arousal, patients often cannot go back to sleep without urinating.²¹

Insomnia. Once the primary distinctions between insomnia and sleepiness are made, evaluation and treatment approaches can be designed. Many people who have disorders that cause them to wake repeatedly during the night have secondary insomnia. Menopause is a classic example in which a woman may wake up repeatedly with hot flashes but, secondarily, she has difficulty falling back to sleep.²² This “sleep-maintenance insomnia” is perhaps a more common symptom of menopause than sleep-onset insomnia.

All insomnia has a learned quality to it, which is similar to performance anxiety (i.e., difficulty sleeping one night leads to difficulty sleeping the next night because of worry over not being able to sleep). This pattern tends to feed on itself. Hot flashes may wake a woman up one night, and on that particular night, anxiety or physical discomfort may prevent her from falling back to sleep. The next night when an arousal occurs, the patient cannot fall back to sleep because she remembers the difficulty she had getting back to sleep the previous night. Thus, secondary psychophysiological insomnia occurs.

The importance of distinguishing insomnia from simple arousals with sleepi-

ness is that behavioral therapy can be quite effective for the treatment of insomnia and should be added to treatment, whereas treatment of arousals can be specific to the cause of the arousals.

Additionally, insomnia (as opposed to simple sleep deprivation) has been shown to be a precursor to depression. Commonly, depression is temporarily preceded by insomnia.²³ One major feature of menopause is the onset of mood disorders.²⁴ Treatment of menopausal sleep disorders may medically prevent depression by way of preventing insomnia that might have been initiated by hot flashes.

It is often thought that mood disorders result from the sleep deficit associated with menopausal hot flashes, but it is more likely they stem from the development of insomnia.⁷

Other Physical and Medical Causes of Insomnia

Restless Legs. Restless Legs Syndrome (RLS) is a feeling of discomfort when lying still in bed. It is usually relieved by movement. RLS is not related specifically to menopause, but it increases in frequency with aging.²⁵ Patients with restless legs often have accompanying insomnia because it is difficult for them to get comfortable before going to sleep. Patients are seldom asked about RLS in the usual medical setting, but clinicians should inquire

about it when patients complain of being fatigued or having “insomnia.” Patients with RLS also have periodic leg movements or twitching of the legs all night, which can lead to multiple arousals and secondary sleep-maintenance insomnia.

Medications. Medications are not always considered as obvious causes of insomnia, but they should be. The most common and obvious medications that can interfere with sleep are psychiatric medications that are arousing in nature. These include many selective serotonin reuptake inhibitors (SSRIs) and all of the drugs used for attention-deficit disorder (ADD). In addition, many asthma medications are adrenergic, and steroids often have a profound effect on sleep onset. Many herbal preparations also are stimulating, including ginkgo and ginseng. Fatigued patients often take these herbals to stay alert during the day.

Cigarettes, alcohol and caffeine. The half-life of caffeine is approximately 7.5 hours. In some people, this can lead to sleep-maintenance insomnia because caffeine is still in their system in the middle of the night after the first cycle of sleep. Alcohol also classically leads to sleep-maintenance insomnia because of the rebound adrenergic stimulation that continues for several hours after the blood alcohol level declines. Typically, up to two drinks in one evening will not cause a disturbance in sleep, but individuals who have three or more alcoholic drinks often find that their sleep is disturbed. Cigarettes are also characteristically energizing. For this reason, nocturnal smoking can lead to insomnia, as well.

Assessing Multiple Arousals

There are several major causes of multiple arousals, allowing the physician to directly treat many sleep disorders medically while the patient initiates behavioral strategies (Table 1).

The most obvious cause of menopausal arousals is the development of hot flashes. Estrogen has a temperature-regulating function, and women with hot flashes very simply have multiple arousals. This has been documented in multiple studies.

Table 1.
Common Causes of Awakening.

- Sleep apnea/snoring
- Depression/anxiety
- Drug/alcohol/caffeine effects
- Physical discomfort
- Menopause
- Twitching (periodic movements)
- Tooth grinding
- Room environment issues (light, noise, etc.)
- Bladder problems (often this is perceived as the reason but isn't)

Simple therapy with estrogen treats sleep disorders in many women. Although in the current medical climate there are decreasing indications for estrogen, sleep difficulties remain one of the strongest reasons for ongoing estrogen therapy.

Very few studies of estradiol levels and sleep have been conducted.²⁶ Most therapeutic studies have looked at dosages given instead of serum estradiol levels. This may be reasonable, as symptoms may vary widely among individuals. However, measurement of estradiol can be helpful. A low level would imply that higher doses of estrogen can be tolerated and that symptoms may well be related to low estrogen levels. Bedtime dosage can maximize nocturnal estrogen. On the other hand, high levels lead one to look beyond estrogen for treatment options.

Mood Disorders With Menopause

Mood disorders—specifically depression and anxiety associated with perimenopause and early menopause—are a second major cause of sleep disorders in menopausal women. The reason for increased depression at menopause is unclear but may be multifactorial. Sleep deprivation itself is not necessarily associated with depression, but insomnia is very strongly related to it, such that anything that causes insomnia may cause depression. Thus, if hot flashes lead to arousals at night, which lead to secondary psychophysiologic insomnia, a patient who is susceptible to depression will likely become depressed. Sleep diaries of depressed individuals indicate

that depression is preceded by cycles of insomnia.²³ Treatment of sleep disturbances with estradiol may prevent depression by preventing insomnia. One study of older women (average age 67) receiving hormone therapy showed improvement in depression only in patients still experiencing hot flashes.²⁷ Another study showed direct benefit of transdermal estrogen in women with low estradiol levels.²⁸

Adrenocorticotropin hormone (ACTH) and cortisol are both linked to worsening of the sleep cycle and sleep disruptions. Replacement of estrogen lowers both cortisol and ACTH levels, thus illustrating another hormonal basis for improvement of mood disorders.¹⁵

Decreased progesterone may also be a contributing factor in the development of depression and anxiety after menopause. One study suggested that micronized progesterone was more effective for treatment of menopausal mood disorders than the more traditional medroxyprogesterone.²⁹ Both estrogen and progesterone can be manipulated to maximize nocturnal hormone levels.

Sleep-Disordered Breathing After Menopause

Sleep apnea is markedly underdiagnosed in the general population. The Wisconsin Prevalence Study indicated that 93% of women and 92% of men with moderate to severe sleep apnea were not clinically diagnosed.³⁰ Since sleep apnea does increase in prevalence after menopause, physicians treating menopausal patients should be alert to this as a potential cause of change in health status after menopause.³¹⁻³³

Sleep-disordered breathing is much more common in men than premenopausal women. After menopause, the numbers tend to equalize for unclear reasons. Exogenous testosterone has been shown to increase sleep-disordered breathing.¹⁹ Thus, since women have one-tenth of the testosterone of men, they would logically be at lower risk of apnea.

Weight gain is common after menopause and is the most obvious cause of sleep-disordered breathing. Women com-

monly gain weight at menopause for a variety of reasons that are not particularly clear. Increased neck size can lead to greater sleep-disordered breathing. However, this is not the only explanation, since patients matched for body mass index before and after menopause demonstrated increased likelihood of developing sleep-disordered breathing.³⁴

Progesterone also has a positive respiratory stimulatory effect and has been used to stimulate breathing. It is thought that loss of respiratory drive from loss of progesterone in menopause might be one reason for sleep-disordered breathing after menopause. However, menopause is characterized by decreases in all three hormones: estrogen, progesterone and testosterone.

Treatment of Menopausal Sleep Problems

HRT decisions. Sleep and mood disturbances are perhaps the most important reasons for prescribing hormone replacement therapy (HRT). With the advent of drugs to improve bone density as well as cardiovascular risk, many clinicians are moving away from HRT, especially in light of concern over the potential for increased breast cancer.³⁵ The risk-benefit ratio changes when there are fewer biologically complicated therapeutic agents to reduce heart and bone risk. Other factors also need to be considered. Depression is clearly linked to mortality. Similarly, insomnia is a major negative predictor of quality of life, and sleep-disordered breathing has very significant cardiovascular and other risks. All these factors need to be considered in the HRT decision.

HRT has been shown to be useful in the treatment of depression in early menopausal women, as well as in older women with persistent climacteric symptoms. However, in asymptomatic older women, the benefits are less clear.²⁷

HRT is an appropriate consideration for most women with sleep disorders who experience symptoms of hot flashes. Obviously, the symptoms themselves should be adequately controlled and may require higher varying doses of estrogen, ranging

from low-dose phytoestrogens to higher-dose synthetic products. Estradiol measurements can be helpful, especially for identifying patients who can tolerate higher doses of estrogen and those in whom disturbed symptoms are caused by something other than estrogen deficiency.

Unfortunately, other than recording subjective complaints of patients, there is no way of monitoring whether sleep arousals are caused by hot flashes. If a woman continues to report waking repeatedly, it should be assumed that the problem is not hot flashes if her serum estradiol level is >50 pg/ml (untreated is usually <20 pg/ml). Progesterone is an anxiolytic and stimulates GABA receptors. It therefore would be appropriate for nocturnal use. One can switch from the usual medroxyprogesterone to a micronized progesterone empirically.

Treatment of depression. If insomnia and arousals persist despite absence of hot flashes, depression and mood-related arousals should be considered (including history) and appropriately treated. Depression commonly causes insomnia that is characterized by arousals with sleep-maintenance difficulty. Unfortunately, several antidepressant medications can exacerbate insomnia.

Virtually all of the SSRIs have been linked to insomnia, and if a sleep disorder persists, this interaction should be considered. More than half of all patients taking fluoxetine (Prozac) require secondary medications to aid sleep. Initiating treatment with a sedating antidepressant in patients with insomnia would be reasonable. Paroxetine (Paxil) is sedating, as are several other antidepressants. Often bupropion (Wellbutrin), taken during the daytime, is relatively more neutral, as are several of the SSRIs, such as sertraline (Zoloft) and citalopram (Celexa). However, all antidepressants have been associated with sleep disturbances, including all three of the above-mentioned medications. The atypical antidepressants have variable effects on sleepiness. Adding a benzodiazepine or zolpidem (Ambien) to SSRI treatment may be necessary.

Mirtazapine (Remeron) is a predictably sedating antidepressant with alpha-2-blocking properties. This makes it useful as a sleeping pill in addition to its antidepressant effects. Unfortunately, mirtazapine increases appetite in most people, causing them to gain weight. This side effect may prohibit its use in some people. However, the effect may be blocked by the addition of topiramate (Topamax). Mirtazapine is a good choice for spontaneously thin patients or patients with loss of appetite related to depression or anxiety.

Treatment of sleep-disordered breathing. Treatment approaches for sleep-disordered breathing can include continuous positive airway pressure (CPAP), dental appliances or surgery. Estrogen therapy also seems to improve sleep-disordered breathing. Women treated in an initial small pilot trial and followed up after 1 month showed a 50% reduction in sleep-disordered breathing with addition of estradiol plus medroxyprogesterone.³² A large epidemiologic study indicated that postmenopausal women on HRT had significant improvements in prevalence of sleep-disordered breathing.³¹ Men had a sleep apnea prevalence of 3.9% versus 1.2% for premenopausal women. After menopause, prevalence of sleep apnea in women rose to 2.7%, which still remains significantly lower than in men when controlling for age and BMI, perhaps because of different body-fat distribution between men and women. Postmenopausal women treated with HRT continued to have a very low prevalence of sleep apnea.

It is appropriate to prescribe HRT for patients with mild sleep-disordered breathing and follow them to observe improvement. Behavioral therapy, including an exercise program that leads to weight loss, might be appropriate in some patients, particularly those with excessive fat around the neck.

Treatment of RLS. RLS should be considered a treatable cause of both insomnia and arousals. Patients will generally mention this to their physicians, and it is not a standard part of the

history and physical exam. Patients with RLS have nocturnal periodic leg movements that may need to be treated. The initial treatment for restless legs is a dopamine agonist, such as pramipexole (Mirapex), which is effective in approximately 80% of patients. Clonazepam (Klonopin) is a second-line therapy for both RLS and periodic leg movement disorder (PLMD). It does not eliminate nighttime twitching, but it does allow patients to sleep through the twitching. The majority of patients with RLS/PLMD can be treated with pramipexole and clonazepam. Some recalcitrant patients will require additional drugs, which may include gabapentin (Neurontin) or long-term narcotic use, both of which are very effective.

Nonspecific Treatments

Hypnotics. With the emergence of the newer classes of "nonbenzodiazepines," such as the GABA receptors zolpidem and zaleplon (Sonata), medications are now available that selectively target the benzodiazepine "sleep receptor" (class 1 GABA) without significantly affecting breathing or anxiety receptors. Both medications are indicated for sleep-onset insomnia difficulties. Zolpidem and zaleplon tend to be short-acting drugs. Zaleplon is the shorter-acting of the two and might be a good choice for women who are waking in the middle of the night. In menopausal insomnia, women find this type of arousal during the night to be the most disturbing. No significant tolerance or withdrawal is associated with either zaleplon or zolpidem when used on a fairly regular basis, although it is reasonable to recommend that patients not use them every night. Zolpidem every other night has been used successfully without any withdrawal or tolerance reported.³⁶

The older benzodiazepines used for sleep, such as temazepam (Restoril), triazolam (Halcion) and estazolam (Prosom), offer the benefit of a somewhat longer half-life, such that they can be taken at bedtime and still be effective should arousals occur in the middle of the night. However, they increase the

risk for respiratory depression and the potential for grogginess the next day.

Antidepressants as hypnotics. Another way to address both onset and maintenance insomnia is with a longer-acting sedating antidepressant. The most commonly used of these is trazodone (Desyrel). In 50- to 100-mg doses, trazodone is commonly used to induce sleep. It lasts long enough through the night to promote reinitiation of sleep. This is a popular drug, partly because of patients' (and their physicians') inordinate fear of the benzodiazepine-receptor class of medications. Trazodone likely works because of its effects on the histamine receptors. Other antidepressants, such as mirtazapine and the older tricyclics (e.g., amitriptyline [Elavil] and doxepin [Sinequan]) can be used, but they are sedating and have anticholinergic side effects.

OTC agents. Over-the-counter (OTC) antihistamines are reasonable choices to aid in sleep. They act by suppressing histamine, which is an arousal chemical in the brain. The value of OTC antihistamines is their safety, although they can create sleepiness the next day. The disadvantage is that they lose effectiveness over time, and after taking them for a while patients may find these drugs are simply leaving them groggy the next day. Antihistamines are therefore good intermittent drugs to use as an alternative to the benzodiazepine-receptor class. A rotation of antihistamine, trazodone and zolpidem might be a reasonable approach.

Melatonin levels decrease with age, and low levels are characteristic of patients with insomnia and depression. This leads one to consider using melatonin, at least in some patients with insomnia. Menopausal insomnia patients have a pattern of disruption of melatonin that involves shifting of the melatonin peak away from its usual time frame of between 1 a.m. to 5 a.m. to either an earlier or later time. This shifting causes disruption in the sleep architecture. Short-acting melatonin may be one treatment consideration for nighttime arousals (e.g., those occurring between 1 a.m. and 3 a.m.).

Behavioral therapy. Primary care phy-

Table 2.
Behavioral Treatment of Insomnia.

- Stimulus response therapy (includes bedtime rituals and "sleep hygiene" environment)
- Relaxation therapy (and biofeedback)
- Cognitive behavioral therapy: "Inner Dialogue"

sicians need to bear in mind that behavioral therapy for insomnia is the most effective therapy in the long term (Table 2). Effective behavioral therapies include stimulus response therapy, cognitive behavioral therapy, sleep restriction and relaxation therapies. Trained therapists can use all of these, and there are good references that describe their use.^{37,38} Patients need to find a therapist who specifically has an interest in sleep induction, however. Thus, the treating physician should have a referral list of psychologists with special interest/training in sleep medicine.

Summary

The development of sleep disorders in menopause is an extremely common issue that is germane to all physicians who treat menopausal women. The three major issues that develop at menopause in association with sleep include: (1) increasing nocturnal arousals, with resulting sleep deprivation and secondary insomnia; (2) menopause-related mood shifts; and (3) menopausal increase in sleep-disordered breathing.

The treating physician must sort out the primary differences between insomnia (the inability to fall asleep) and arousals that lead to sleepiness. Predisposing factors to insomnia may be specifically treated (e.g., restless legs), but insomnia commonly is treated in nonspecific ways with medications and behavioral therapy. Arousals, on the other hand, can be treated in a specific way with HRT, medications for specific sleep disorders and appropriate therapy for sleep-disordered breathing. Recognition of menopausal and

other sleep disorders can have profound effects on patients' quality of life. ■

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