

Women and Insomnia

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The occurrence of insomnia in women is influenced in great part by the complex hormonal cycles they undergo. Patterns of insomnia in younger women may be physiologically different on a hormonal basis from those found in older women. Although significant objective sleep disturbances have been difficult to demonstrate across the menstrual cycle in normal women, the *International Classification of Sleep Disorders (ICSD)* includes premenstrual insomnia and premenstrual hypersomnia as sleep disorders within the category of menstrual-associated sleep disorder. On the other hand, during pregnancy and after childbirth, profound fluctuations in steroid and hypothalamic-pituitary-adrenal axis-related hormones produce significant physiological changes, including sleep disruption. During the menopausal transition, significant sleep disruptions are provoked by sleep-disordered breathing, vasomotor disturbance, and mood disorders. Regardless of age, women with chronic insomnia are at higher risk for developing or sustaining depression. Thoughtful management approaches must consider known relationships between menstrual or menopausal status and various sleep disorders, and should rely on pharmacologic, nonpharmacologic, or a combination of treatments to achieve successful relief from insomnia. The off-label, first-line use of antidepressants for treating insomnia in the absence of depression is now considered debatable. The long-term efficacy and safety of the newer benzodiazepine receptor agonists (BZRAs) for insomnia, whether taken nightly or episodically, are supported by existing clinical experience. US Food and Drug Administration guidelines limiting the use of hypnotics to only a few weeks predate the newer generation BZRAs, and, as such, the guidelines may no longer be truly appropriate for these new agents. (*Clinical Cornerstone*®. 2004;6[Suppl 1B]:S6-S18) Copyright © 2004 Excerpta Medica, Inc.

INSOMNIA

Insomnia is a complex of symptoms—consisting of difficulty falling asleep, staying asleep, or experiencing nonrefreshing sleep—that result in daytime consequences that significantly impact productivity and quality of life.^{1,2} Up to one third of Americans suffer from some form of insomnia,³ with ~10% having chronic insomnia.⁴ The prevalence of insomnia increases with age and occurs nearly twice as often in women as in men. Although primary insomnia has been estimated to constitute ~15% to 20% of all cases, most insomnia occurs as a result of other conditions, including medical and psychiatric

disorders, lifestyle, and, in women, the hormone cycle, which is most likely why insomnia is both underdiagnosed and undertreated. Despite its enormous societal and economic impact, insomnia is frequently overlooked in the presence of other medical or psychiatric conditions, thus delaying the diagnosis and treatment of this major health problem.

ASSESSMENT

Simple screening questions such as “Are you bothered by sleeping problems?” or “Are your daily activities compromised by daytime fatigue?” should be part of any patient’s history during routine office

visits. Because there are no obvious clinical findings of insomnia, the diagnosis largely depends on subjective patient reports. When patients do mention sleep problems, they generally do not complain of insomnia but of fatigue (“I’m tired all of the time”) or of sleepiness (“I can’t stay awake”). Once

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a potential sleep disorder has been detected, a thorough evaluation should be undertaken to assess the severity of the sleep problem and to determine any readily rectifiable causes.

Appropriate assessment tools are available to evaluate sleep disorders for patients complaining of insomnia or fatigue. A sleep history is an important element in the clinical evaluation of a sleep disorder. In addition to questions about the patient’s other medical conditions and medications, information about smoking, alcohol use, and the home and work environment should be obtained. Specific sleep complaints can be identified by questions such as those in **Table I**.⁵ Having the patient keep a detailed sleep log for 1 or 2 weeks provides valuable supplemental information. If a sleep disorder is present, convenient tools, such as the Epworth Sleepiness Scale (**Table II**), help determine the severity of the problem.⁶

NORMAL SLEEP

Sleep is divided into 2 separate states, rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. NREM (~75%–80% of total sleep) comprises 4 separate stages. Stage 1 NREM sleep (2%–5% of total sleep) is a transitional stage occurring at the onset of sleep and briefly during the transition between other stages. In stage 1 NREM sleep, individuals can be easily awakened. Stage 2 NREM sleep typically lasts for ~10 to 25 minutes, during which there is a higher arousal

TABLE I. QUESTIONS FOR A SLEEP HISTORY.

- Do you have difficulty falling asleep?
- Do you feel excessively sleepy during the daytime?
- What is your sleep/wake schedule during the weekdays/weekends?
- How many hours do you sleep per night?
- How long does it take you to fall asleep after deciding to go to sleep?
- How many times do you wake up during a typical night?
- How long does it take to “get going” after you get out of bed?
- Do you snore loudly or stop breathing at night?
- Do you have crawling or aching feelings in your legs when trying to fall asleep?
- Do you kick or twitch your arms or legs during sleep?
- Do you walk in your sleep?
- Do you act out your dreams?
- How often do you take naps during the day?
- Do you ever tend to fall asleep when talking with someone?
- Do you ever tend to fall asleep while driving?

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threshold. Stages 3 and 4 (~13%–23% of total sleep) are defined as slow-wave sleep (SWS) and are the periods of deepest sleep. During REM sleep, which is characterized by rapid eye movement, there is a noticeable decrease in muscle tone. Arousal from sleep is most easily accomplished while in REM sleep. A typical night of normal sleep has 4 to 6 cycles, with each cycle lasting ~90 to 110 minutes, alternating between REM and NREM sleep.

BIOLOGIC BASIS OF INSOMNIA AND DEPRESSION

Insomnia is one of the most common complaints of patients with depression, and it may also be a factor in developing or sustaining depression. Clinically, there is little doubt that major depression and insomnia are closely interlinked. Neurotransmitters and steroid hormones interact in an extremely complex and delicately balanced manner. Each system modulates the other, and changes in either system can have marked effects on the other.⁷ The same can be said of the influence of the hypothalamic-pituitary-adrenal (HPA) axis and

TABLE II. EPWORTH SLEEPINESS SCALE.

Situation	Chance of Dozing
0 = Would never doze 2 = Moderate chance of dozing	1 = Slight chance of dozing 3 = High chance of dozing
● Sitting and reading	_____
● Watching television	_____
● Sitting inactive in a public place (eg, 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 _____

A total score >10 is abnormally sleepy. Reproduced with permission.⁶

steroid hormones on each other. Overactivity of the HPA axis is strongly implicated in the pathophysiology of depressive disorders. In the presence of major depression, alterations in sleep electroencephalographic (EEG) patterns and HPA activity have been shown to be influenced by gender, being more prominent in women.⁸ Hormonal therapy in postmenopausal women has been reported to suppress the responses of the HPA axis to emotional stress.⁹ Many studies have been conducted in this area, but because of their small size and great variation in designs and end points, a more definitive answer to the biologic interaction between depression, sleep, and hormonal systems will require much more exhaustive research.

SLEEP IN WOMEN

Multiple extrinsic and intrinsic factors can interfere with normal sleep cycles, resulting in insomnia. The most common factors affecting sleep in women are associated with the life cycle of hormone levels, extending from menarche through and after menopause, including pregnancy. Perimenopausal and immediately postmenopausal years are especially troublesome. The complexity of factors affecting a woman’s hormonal life cycle precludes many generalizations; however, it is possible to look at individual life stages and consider some of the factors that can affect sleep. Although the scope and duration of most studies of sleep and women’s hormonal life cycles substantially limit any defini-

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tive conclusions, sufficient data are available to provide considerable insight into the problems of insomnia associated with these cycles, thus allowing an educated approach to insomnia management.

HORMONAL CHANGES AND SLEEP

The effects of estrogen on sleep are numerous and complicated. Estrogen tends to decrease sleep latency, decrease the number of awakenings after sleep occurs, and increase total sleep time. The number of arousals doubles during the luteal (low estrogen) phase of the menstrual cycle. Temperature regulation in the body is also influenced by estrogen; low levels are associated with increases in both peripheral and central temperature, resulting in the hot flashes characteristic of menopause.⁶

The effects of progesterone on sleep are also marked but more straightforward. Progesterone acts as an anxiolytic agent through its actions as a γ -aminobutyric acid (GABA) agonist. Progesterone peaks sharply during the midluteal phase of a normal menstrual cycle and then drops before menses; these changes are associated with increased arousals and other sleep difficulties. Progesterone also affects breathing by acting as a respiratory stimulant, a mechanism that may explain the remarkably low incidence of obstructive sleep apnea during pregnancy despite the prominent weight gain and changes in body habitus.⁶

SLEEP IN WOMEN WITH NORMAL MENSTRUAL CYCLES

Although many women have “normal” menstrual cycles during the years between menarche and menopause, no 2 women will have the same “nor-

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mal” cycle. The length of the cycle, the timing of different stages that compose the cycle, and the levels of various hormones involved vary significantly among women. These factors introduce difficulties in conducting and, equally important, in comparing studies.

A recent review of studies investigating sleep during the menstrual cycle in women reporting normal cycles¹⁰ noted conflicting results across the studies. The only clear-cut variation in the parameters was in the sleep spindle frequency measured with sleep electroencephalography. In a study of 138 sleep episodes in 9 women, readings were taken and symptoms recorded every other night throughout 1 menstrual cycle, with results analyzed in relation to the phase of the cycle. During NREM sleep, sleep spindle frequency varied noticeably during the menstrual cycle, peaking in the luteal

phase, in parallel with core body temperature. REM sleep, SWS, total sleep time, and sleep efficiency were not affected. Other sleep regulatory mechanisms were not affected.¹¹ There appear to be no definitive major differences in sleep structure during a normal menstrual cycle.

SLEEP IN WOMEN WITH DISORDERS OF THE MENSTRUAL CYCLE

Premenstrual syndrome (PMS) is marked by physical and/or mood symptoms that generally begin in the luteal phase of the cycle and usually end at, or shortly after, the onset of menses. When these symptoms are sufficiently severe to interfere with the woman’s ability to function, the diagnosis of premenstrual dysphoric disorder (PMDD) may be indicated, based on the presence of ≥ 5 of 11 designated symptoms, 1 of which is insomnia. Because many clinicians considered PMS to be a variation of mood disorder, and because insomnia represents a major symptom of depressive disorder, a comparison of the sleep patterns between PMS and depression is of interest.

A review of studies of insomnia during the menstrual cycle in women with PMS/PMDD¹⁰ again demonstrated the difficulty in designing and conducting these studies. Definitions, criteria, and end points exhibited wide variations in these areas. Moreover, all of the studies involved small numbers of women, making it difficult to arrive at meaningful conclusions. However, no significant reproducible differences in sleep patterns were found between women with PMS/PMDD and women without PMS/PMDD symptoms who served as controls. One of the largest studies (23 women) had a similar conclusion, but did show significant differences in EEG readings over the menstrual cycle in both PMS/PMDD and control groups, contrary to the results of most other studies.¹² Differences in temperature and sleep parameters were also observed between the groups after being subjected to sleep deprivation, but no changes in sleep architecture were similar to those found in women with major depressive disorder.

SLEEP IN WOMEN USING ORAL CONTRACEPTIVES

Although ~10 million women aged 15 to 44 years in the United States use oral contraceptives (OCs)

regularly,¹³ we know little about their impact on sleep and insomnia. Few studies have been conducted, and almost all involved only a handful of subjects. Anecdotally, physicians may note that women given OCs for birth control or to control symptoms of PMS report improvement in their insomnia and fatigue. However, 1 of the larger studies,¹⁴ involving both depressed and healthy women, suggested otherwise. Included in this study were 68 women with major depressive disorder, 13 of whom were taking OCs and 55 who were not, and a control group of 37 women without depression, 9 of whom were taking OCs and 28 who were not. In the control group, whereas REM sleep increased (from 19.9% to 22.6%), SWS decreased (from 8.8% to 5.3%), and total sleep decreased (from 437.7 min to 413.6 min, NS). Interestingly, similar effects from OC use were noted in the depressed group, but to a lesser degree.

PREMENSTRUAL SLEEP DISORDERS

The *International Classification of Sleep Disorders* lists premenstrual insomnia and premenstrual hypersomnia as sleep disorders within the category of menstrual-associated sleep disorders.¹ Although data from survey studies indicate that women complain about sleep problems most often in the late luteal phase of the menstrual cycle, as mentioned before, essentially no objective data exist to confirm this. In a research study of premenstrual insomnia,¹⁵ menstrual cycle effects were overshadowed by daily irregular variations of insomnia. A number of case studies have reported individuals with hypersomnia just prior to the onset of menses, with most subjects finding relief with the use of OCs.

SLEEP DURING PREGNANCY

Women experience great physiologic and psychologic changes, including significant sleep disruption, with the profound changes in the steroid and HPA axis-related hormones associated with pregnancy and childbirth. Sleep disruptions may develop during the first trimester, and up to 90% of pregnant women are estimated to report some sleep disruption during the third trimester.¹⁰ Sleep studies during pregnancy are limited, but evidence suggests that, compared with women who are not pregnant, women in the third trimester experience increased waking after sleep onset, increased stage 1 sleep,

lower sleep efficiency, and decreased REM sleep. The physical changes in a woman's body during pregnancy obviously play an important role in changes in sleep patterns, but some of these effects may be, in part, the result of psychologic factors. When comparing women in their first pregnancy with multiparous pregnant women, the multiparous women had lower sleep efficiency, due to more frequent awakenings. Experienced mothers had more total sleep, though not significantly more, most likely because they went to bed earlier.

Increased body habitus resulting from pregnancy may compromise breathing, especially during the last weeks. Although studies have documented increases in the incidence of snoring, no studies demonstrate significant sleep apnea. The prevalence of restless legs syndrome (RLS) has been shown to increase during pregnancy, affecting as many as 25% of women during the third trimester, and usually resolving after delivery. Of interest are findings that pregnant women who took supplemental vitamins with folate had a lower prevalence of RLS than women whose vitamins did not contain folate.¹⁶

POSTPARTUM SLEEP DISRUPTION

Childbirth marks the onset of the postpartum period that continues for 6 to 12 months. New mothers frequently experience sleep disruptions, and postpartum mood disorders—psychiatric disorders directly linked to pregnancy and childbirth—are distinct entities recognized by the American Psychiatric Association. Postpartum blues, the mildest of postpartum mood disorders, affects up to three quarters of all women after delivery. Symptoms of mood swings, including anxiety, insomnia, crying, and irritability, typically begin within 1 week after delivery, but usually resolve within 2 weeks. Severe mood disorders, such as major depression and psychosis, are less common. They typically begin later in the postpartum period (2 to 4 weeks after delivery) and may last for up to 6 months.

The association of insomnia with the many changes that occur postpartum is complex, with hormonal and mood disturbances, the mother-infant relationship, and the household environment all contributing to sleep disruption. The interrelationship of these factors makes it difficult to arrive at definitive conclusions as to cause and effect, and sleep studies

conducted during this time period often produce conflicting data. First-time mothers experience a greater decrease in sleep efficiency after delivery than multiparous mothers, although total sleep time is essentially the same. Novice mothers may be more susceptible to sleep disruptions by their infant during the night, but can catch up with their sleep when the infant naps during the daytime, an opportunity that might not be available to mothers with older children. Women who breast-feed their infant are also subject to more frequent awakenings than mothers who bottle-feed their infant. Few data exist for treating postpartum insomnia, primarily because many factors cannot be controlled. Mothers are generally advised to “catch sleep when you can.”

SLEEP DURING PERIMENOPAUSE AND MENOPAUSE

The menopausal transition is triggered by major hormonal fluctuations and accompanied by substantial physiologic and psychologic alterations. Hormonal changes begin 7 to 10 years before menses cease, marking the onset of perimenopause, an interval that can last until 1 year postmenopause. During this time, insomnia becomes increasingly common and is a primary menopausal complaint with up to 60% of women reporting insomnia or symptoms of insomnia.¹⁷ Many women complain of fatigue during the day, completely unaware that they are having sleeping problems at night. Aside from the physiologic changes, it is also a time of great social and psychologic adjustment. Women experience a peak incidence of depression and anxiety with shifting of their self-image and body image, which can have a negative impact on sleep patterns. The fact that many menopausal women have improvement in sleep when they are given estrogen also suggests that insomnia patterns in older women are physiologically different on a hormonal basis from those found in younger women.

Physiologic Symptoms

Among the physiologic symptoms that cause sleep disruption during the perimenopausal and postmenopausal years are hot flashes, mood disorders, and sleep-disordered breathing. Between 75% and 85% of perimenopausal and postmenopausal women report having hot flashes; these may occur

for as long as 5 years in as many as 25% of women.¹⁰ The actual roles that hot flashes and mood play in insomnia associated with menopause are controversial. Subjective and objective data assessing the role of hot flashes in disrupting sleep are conflicting. Uncertainty also exists as to how mood disorders such as depression and anxiety act to disturb sleep, and whether or not they are a result of vasomotor symptoms associated with menopause. Polysomnographic measurements during sleep studies have not resolved the association of hot flashes with sleep disruption in menopause. Although hot flashes have been reported to be associated with nocturnal awakenings and decreased sleep efficiency in some studies, no such association was found in other studies. Estrogen is generally considered the drug of choice for treating hot flashes, but its efficacy in treating nocturnal hot flashes (night sweats) and associated insomnia is unclear and debatable, because most data supporting its role during sleep are subjective.

Sleep-Disordered Breathing

Sleep-disordered breathing also plays a role in poor sleep in postmenopausal women, and, while markedly less than in men, probably has a greater prevalence than is generally believed. Recent polysomnographic data show that the prevalence of mild sleep apnea (apnea-hypopnea index [AHI] = 5–10 incidences/h of sleep) increases from 6.5% to 8.7% in women aged 30 to 39 and 40 to 49 years, respectively, to 16% in women from 50 to 60 years of age. While the data are not broken down by menopausal status, they suggest that there is an increase associated with menopause (**Figure**).¹⁸ The exact mechanism for this increase is unknown, but several causes have been suggested. The increase in body weight that may occur after menopause may play a role, and the postmenopausal decrease in levels of progesterone, a known respiratory stimulant, have also been implicated. Studies investigating both proposed mechanisms have yielded conflicting data.

MANAGEMENT

Management of insomnia is probably a better term to use than treatment, because most cases of insomnia are not truly cured, but are, for want of a better term, in remission. The first step in managing insom-

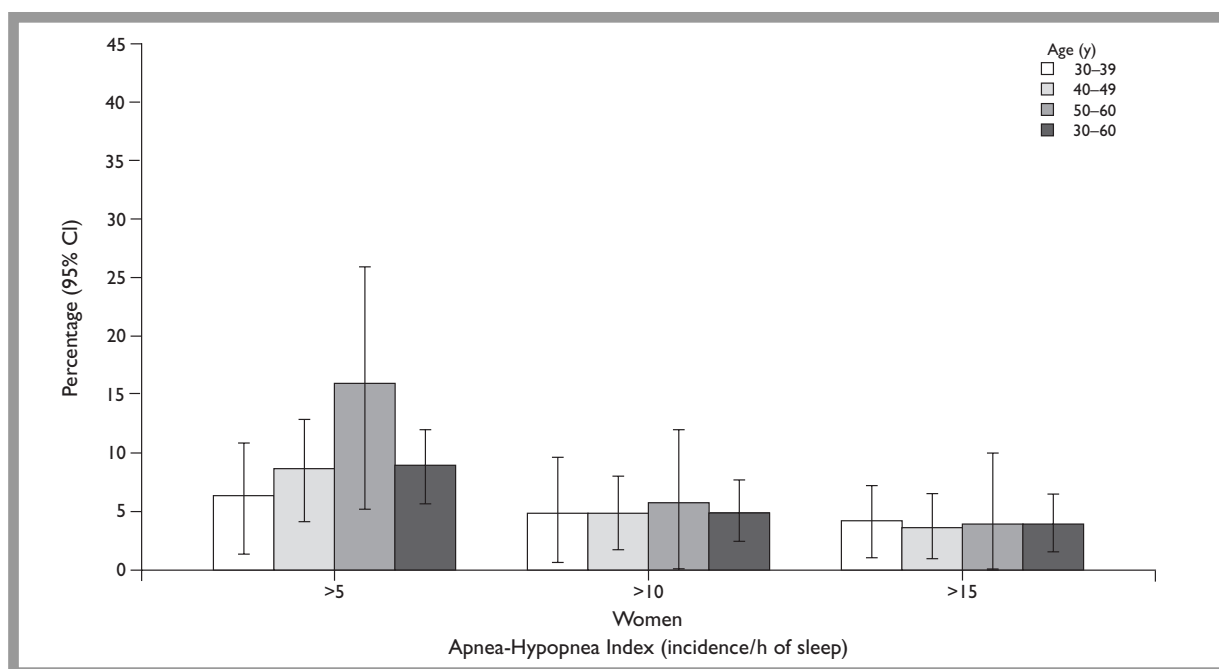


Figure. Sex-specific prevalence of sleep-disordered breathing.¹⁸

nia is a complete assessment of the patient, the sleep disorders that are present, and any possible causes. If specific causes can be determined, elimination of them can go a long way in controlling the patient's insomnia. Because many sleep disorders in women have as their basis the balance of various hormonal systems, management approaches must strongly consider known relationships between menstrual status and sleep disorders. Fortunately, in contrast to clinical studies investigating most other medical or mental conditions (with the exception of depression), clinical studies involving sleep disorders have included enough women to ensure that the findings apply equally to both sexes without "extrapolation" of the data. Indeed, many studies include a majority of women. However, in managing sleep disorders, as in treating most other health problems, pharmacologic and nonpharmacologic approaches, or a combination of the 2, must be considered, especially in women.

PHARMACOLOGIC MANAGEMENT OF INSOMNIA

Antidepressants

Antidepressants, especially the newer selective serotonin reuptake inhibitors (SSRIs), play an important role in the management of major depression and may alleviate many of the associated symptoms, including insomnia. However, the use of these

agents to treat insomnia when depression is not present is debatable. Tricyclic antidepressants, especially amitriptyline, have been commonly prescribed in the past for their sedating properties. However, these agents have a high profile of potential adverse effects (AEs), and, when treating insomnia in the absence of depression, may result in excessive residual daytime sedation, owing to their long half-lives. The newer SSRIs have a better safety profile, but there is no substantial clinical evidence that they are effective in treating insomnia when no underlying depression is present. For some patients, the SSRIs can have activating AEs, including insomnia.

The off-label use of antidepressants for treating insomnia has increased markedly over the past 20 years, primarily the result of the introduction of trazodone, a nontricyclic antidepressant commonly prescribed for insomnia. For selected patients, trazodone is beneficial because of its mild-to-moderate sedating properties. It is effective as an antidepressant and can reduce depression-related insomnia.¹⁹ However, there are issues associated with its use in patients who are not depressed. Residual morning sedation or difficulty in concentrating frequently occurs after the bedtime use of trazodone. Patients may report that they fall asleep more easily, but this does not mean they necessarily wake up feeling more refreshed. Trazodone use may result in ortho-

static hypotension due to postsynaptic alpha antagonism, an AE that may be clinically significant, especially in elderly patients or in patients taking antihypertensives.

Trazodone is frequently given as a sleep aid in conjunction with other antidepressants. Serotonin syndrome has been reported when trazodone was coadministered with other serotonergic medications (eg, fluoxetine, paroxetine, monoamine oxidase inhibitor antidepressants). Serotonin syndrome is a potentially fatal condition whose symptoms include confusion, agitation, restlessness, hyperreflexia, autonomic instability, fever, and coma. Also, as a substrate of cytochrome P450 isoform 3A4 (CYP3A4), trazodone is subject to possible drug interactions with other agents that are substrates, inhibitors, and inducers of CYP3A4. Trazodone has been reported to induce or aggravate cardiac arrhythmias.²⁰

Although it is widely prescribed for insomnia, little research or evidence supports the safety or efficacy of trazodone in treating insomnia. One 14-day, placebo-controlled, double-blind study compared trazodone 50 mg, zolpidem 10 mg, and placebo in patients who were not depressed but had primary insomnia. During the first week, both drugs resulted in shorter sleep latencies than placebo, with zolpidem notably better than trazodone. During the second week, the zolpidem group continued to have reduced sleep latency, but the trazodone group was comparable to placebo. Estimated total sleep was the same in all groups.²¹ Thus, it appears that trazodone offers a higher risk of AEs and substantially less evidence for efficacy than prescription hypnotic agents.

Despite these drawbacks, there has been an increase in the number of trazodone prescriptions written for insomnia, whereas its use in depression has decreased with the advent of the SSRIs. In fact, trazodone is prescribed for sleep difficulties more often than zolpidem, the most commonly prescribed hypnotic.³ The reasons for this prescribing pattern might be that many clinicians are proponents of trazodone because of its sedative properties, but are unaware of its safety profile. Another factor is that physicians are heavily regulated in several states, limiting the number of prescriptions, the number of pills, and the duration of use of hypnotics for sleep disorders. (They may

also be reluctant to prescribe a sedating antidepressant as the first choice for a pure sleep disorder, partly owing to concern about the long half-lives of these agents.) A short-acting nonbenzodiazepine hypnotic would be preferable for the patient with insomnia who is not depressed.

Selective Serotonin Reuptake Inhibitors

SSRIs are among the most widely prescribed drugs in the world. Originally developed to treat major depression, they have been found to be effective in a number of anxiety disorders, including social phobia as well as obsessive-compulsive, panic, and posttraumatic stress disorders. Recently, fluoxetine was approved for the treatment of the symptoms of PMDD. One definitive study involving 313 women demonstrated that fluoxetine may be effective in decreasing the psychologic symptoms of tension, irritability, and dysphoria in women with PMDD.²² However, among the most commonly reported AEs were insomnia or disturbed sleep, fatigue or lethargy, and somnolence or decreased ability to concentrate. It appears that there is no real justification to use an SSRI outside of labeling to treat insomnia or sleeplessness.

Hormonal Therapy

The role of hormone replacement therapy (HRT) in perimenopausal and postmenopausal women became even more controversial with the February 2004 National Institutes of Health (NIH) decision to stop the estrogen-alone Women's Health Initiative (WHI) trial after 7 years of follow-up. In healthy postmenopausal women, this study assessed the efficacy of long-term use of estrogen alone for the prevention of heart disease and hip fracture, and the associated change in risk for breast cancer. The short-term risks and benefits of hormones for the treatment of moderate-to-severe menopausal symptoms were not examined.²³ The trial was discontinued based on the NIH conclusion that estrogen alone does not appear to have any effect on heart disease, a key question of the research. Whereas there was a decrease in the risk of hip fracture and no increased risk of breast cancer, the use of estrogen alone appeared to increase the risk of stroke. This increased risk paralleled the finding in another WHI study (discontinued in July

2002), in which for every 10,000 women, those taking estrogen plus progestin had 8 more strokes per year than those taking placebo.

The NIH advises women to follow US Food and Drug Administration (FDA) guidelines regarding HRT. Either estrogen or estrogen with progestins is an approved therapy for moderate-to-severe hot flashes and symptoms of vulvar and vaginal atrophy. Although HRT is effective for prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis who cannot take nonestrogen medications. The FDA advises postmenopausal women who use or are considering using these products to discuss the benefits and risks with their physicians, and recommends that estrogens and progestins be used at the lowest doses for the shortest duration needed to achieve treatment goals.

Despite the conflicting and often confounding results of clinical trials investigating its effects on mood, sleep, and hot flashes, HRT has had a profound, positive effect on perimenopausal or postmenopausal women. Many of the women whose therapy was discontinued after the first WHI study report asked to restart HRT because they could not tolerate the symptoms that resumed. Evidence suggests a role for HRT in managing the mood disturbances associated with menopause, whether or not the benefits are an indirect result of reduction of hot flashes. Although HRT appears to have less effect on insomnia, the addition of psychotherapy improves insomnia. This, and the WHI findings, suggest there

may be benefits to including behavioral therapy as part of the management plan for insomnia in perimenopausal or postmenopausal women.

Benzodiazepine and Nonbenzodiazepine Hypnotics

In the United States, hypnotic drugs that are indicated for the treatment of insomnia are those that function as benzodiazepine receptor agonists (BZRAs), enhancing the normal inhibitory activity of the GABA(A) receptor complex.²⁰ The BZRAs used to treat insomnia have multiple effects, acting as anxiolytics, hypnotics, muscle relaxants, and anticonvulsants. They increase total sleep time, decrease sleep latency and the frequency and duration of awakenings, and reduce the time spent in SWS and REM sleep.³

Five traditional benzodiazepines and 2 newer nonbenzodiazepine medications function as BZRAs (Table III). Traditional benzodiazepines, in use as hypnotics since the 1960s, are agonists for all of the identified benzodiazepine receptor subtypes, whereas the newer-generation BZRAs preferentially bind to the type-1 receptor. This specificity of binding may be the reason the newer nonbenzodiazepine agents, zaleplon and zolpidem, are not associated with the tolerance, withdrawal, and dependence difficulties demonstrated by the traditional BZRAs, and hence have a much lower potential for abuse.

The elimination half-lives, and subsequent durations of action, of the traditional benzodiazepines differ greatly, ranging from a few hours to several

TABLE III. BENZODIAZEPINE RECEPTOR AGONIST HYPNOTICS.

Generic Name	Brand Name	Elimination Half-life (h) (including active metabolites)
Benzodiazepine		
Estazolam	ProSom®	10–24
Flurazepam	Dalmane®	40–250
Quazepam	Doral®	40–250
Temazepam	Restoril®	3.5–18
Triazolam	Halcion®	1.5–5.5
Nonbenzodiazepine		
Zaleplon	Sonata®	1
Zolpidem tartrate	Ambien®	2.5

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days. Agents with a longer half-life are more commonly associated with residual daytime sedation, cognitive impairment, and increased risk of falls and other accidents, including automobile accidents. In view of these daytime effects, shorter-acting medications are almost always recommended.

Of special concern to the premenopausal women who suffer from insomnia is that benzodiazepines are contraindicated during pregnancy, and are either contraindicated or not recommended while breastfeeding. Zaleplon and zolpidem are not contraindicated during pregnancy or nursing, but their use is not recommended during pregnancy.

Zolpidem has been available in Europe since 1988 and in the United States since 1993. Zaleplon became available in the United States in 1999. Pharmacologic receptor-binding specificity helps to explain the benefits attributed to these agents. The short elimination half-lives of zolpidem (~2.5 h) and zaleplon (1 h) leave little risk of daytime sedation or cognitive impairment the day after bedtime use. With its longer elimination half-life, zolpidem is more likely to improve sleep during the entire night than is zaleplon, whereas the ultrashort half-life of zaleplon allows a single repeat dose during the night if necessary. Both medications should be taken just before bedtime, because their onset of action can be rapid. Reduced starting doses are recommended for elderly patients or those with impaired liver or kidney function. Common AEs include headache, dizziness, drowsiness, and nausea, but serious reactions are rare.

Long-term Use and Abuse Potential

The safety and efficacy of zolpidem and zaleplon are well established for short-term use. Long-term safety and efficacy have not been tested in double-blind, placebo-controlled studies, but the continued effectiveness and safety of these agents with long-term use—whether taken nightly, on a frequent intermittent basis, or episodically—are supported by existing clinical experience.^{24,25} Open-label 1-year studies of zaleplon²⁶ and zolpidem²⁷ have demonstrated continued efficacy with no evidence of tolerance and without rebound effects when the drugs were discontinued.

Because of concern for possible abuse, some physicians may avoid or limit their use of hypnotics

for patients with insomnia, partly owing to the safety and abuse problems observed with the older agents. Other physicians may hesitate to prescribe the newer hypnotics because they believe that patients will become psychologically dependent on them. Regulatory issues may also be a factor in prescribing hypnotic medications. Although most insomnia patients may take hypnotics for many years, many of them do so for only a few days or weeks at a time, with only a minority (10%–15%) using them regularly on a chronic basis, and then not necessarily every night. FDA guidelines limiting the use of hypnotics to only a few weeks predate the newer-generation BZRAs, and, based on recent data on the long-term use of zolpidem and zaleplon, the guidelines might not be appropriate for these new agents. BZRA hypnotics are rarely abused by insomnia patients, who tend to exhibit therapy-seeking behavior and are unlikely to self-escalate dosage with successful therapy.

KEY POINT

In the United States, hypnotic drugs that are indicated for the treatment of insomnia are those that function as BZRAs, enhancing the normal inhibitory activity of the GABA(A) receptor complex.

OVER-THE-COUNTER TREATMENTS

Antihistamines

Many over-the-counter (OTC) sleep aids are first-generation histamine blockers, with diphenhydramine most commonly used. First-generation antihistamines may provide mild to moderate sedation for some individuals; however, the elimination half-life is relatively long (≤ 8 h) with residual “hangover” effects possible the day after bedtime use. Nonsedating second-generation antihistamines are not a consideration for treating insomnia. Tolerance to the sedating effects of antihistamine has not been well studied, but evidence suggests

that diphenhydramine-induced sleepiness diminishes over time.

As a CYP2D6 inhibitor, diphenhydramine is subject to possible drug interactions with other agents that are substrates of CYP2D6. Because antihistamines also have potential anticholinergic effects, consideration should be given to elderly patients or patients taking drugs with anticholinergic properties (eg, bladder control agents, antidepressants, and antipsychotics). Diphenhydramine, alone and in combination with other medications, has been associated with constipation, urinary retention, blurred vision, confusion, and delirium, all possible symptoms of excessive anticholinergic activity. Whereas few data show that bedtime administration of first-generation antihistamines results in improved sleep in patients with insomnia, significant data demonstrate that they can cause daytime sleepiness and decreased cognitive function.

Melatonin

The use of melatonin as a sleep-inducing agent is unsupported by substantial evidence, and it is not FDA approved for the management of insomnia. However, melatonin levels have been found to decrease with age, and patients with insomnia and depression characteristically have low levels. In addition, menopausal insomnia patients have been noted to have a shift of the melatonin peak to either an earlier or later time than usual, which may disrupt sleep architecture.⁶ Although subjective or objective improvement in sleep with melatonin has been equivocal, evidence shows it may benefit selected patients by modulating the intrinsic circadian system.

Alcohol

People with insomnia frequently self-medicate with alcohol or OTC medications. A survey of adults aged 18 to 65 years ($n = 1324$) reported that 10% drank alcohol exclusively as a means to sleep, another 10% used only OTC medications, and 8% took prescription medications. Subjects who drank alcohol to induce sleep reported greater daytime sleepiness than the other groups.²⁸ The detrimental effects of alcohol include worsening of insomnia and breathing disturbances during sleep. Although unstudied in women, the influence of nocturnal alco-

hol ingestion on cardiorespiratory function has been reported in healthy men.²⁹ The AHI increased in men under the influence of alcohol, and men who did not snore showed an increase in the incidence of hypopnea. Mean oxygen saturation decreased during NREM4 sleep in snoring men, and in both REM and NREM3 sleep in men who did not snore. Nighttime alcohol resulted in significantly increased nocturnal heart rate in both groups.

A remaining concern is that patients who use OTC medications for their insomnia may delay seeking appropriate medical care and not receive accurate assessment and effective treatment.

NONPHARMACOLOGIC MANAGEMENT

Recent studies have shown that nonpharmacologic management of insomnia can be as effective as pharmacologic management in the short term, and has more durable effects in the long term. Behavioral approaches have begun to be appreciated for their effectiveness and acceptance by physicians and patients. Sleep specialists agree that a systematic data-driven program of cognitive behavioral therapy (CBT) for the treatment of insomnia is most effective. Such a treatment plan might contain any or all of the following: stimulus control therapy; sleep restriction; cognitive therapy; relaxation techniques; and phototherapy. Many nonsleep specialists mistakenly believe that behavioral treatment is merely sleep hygiene education. Sleep hygiene should certainly be considered part of a treatment plan for insomnia, but by itself does not provide significant benefit for extended periods of time, except in a few selected cases. Some clinicians also have the misperception that CBT involves a protracted, time-intensive process when, generally, only 4 sessions are involved, with evidence that as few as 2 sessions can provide enduring benefit for many individuals.

Sleep restriction and stimulus control techniques are designed to help eliminate behavioral patterns that maintain or exacerbate chronic insomnia. The goal of relaxation therapy is to reduce the “somatic hyperarousal” thought to be associated with chronic insomnia. Cognitive therapy is directed toward eliminating irrational beliefs and fears people may have about the consequences of insomnia, factors resulting in the “cognitive hyperarousal” that is also thought to be related to chronic insomnia. In clinical

practice, these procedures can be treatment strategies instituted as part of an individual comprehensive treatment program or as part of a group therapy process.³⁰

An extensive meta-analysis of 59 studies of non-pharmacologic insomnia treatment outcomes involving >2000 patients demonstrated that patients with insomnia who received psychologic treatment for chronic insomnia had significantly improved sleep induction and sleep maintenance compared with untreated subjects.³¹ A mean of only 5 hours of therapy time per patient was involved. Follow-up monitoring for a mean of 6 months after the treatment program showed that clinical benefits were well maintained.

A randomized, placebo-controlled, 8-week clinical study involving 78 older adults (mean age, 65 years) with chronic and primary insomnia compared the clinical efficacy of CBT (consisting of stimulus control, sleep restriction, sleep hygiene, and cognitive therapy) with pharmacologic therapy (temazepam), both singly and combined. Follow-up evaluations were conducted at 3, 12, and 24 months.³² Behavioral, pharmacologic, and combined therapies were all more effective than placebo at the end of the treatment phase, with no significant differences between the 3 treatment groups. Subjects who received CBT maintained clinical benefits at follow-up evaluations; those who received drug therapy alone did not. Combined therapy results were more variable. The results from this study suggest that both behavioral and pharmacologic therapy provide clinical benefits for the short-term treatment of insomnia, whereas behavioral treatment provides better long-term benefits.

CONCLUSIONS

Insomnia is a pervasive problem that is multifactorial in its presentation and in its causes. This is especially true in women, in great part owing to the complex hormonal cycles they undergo. There is no question that insomnia is greatly underdiagnosed and undertreated. Primary care providers must become aware of the problem by being proactive in recognizing insomnia and using the best available means to manage it. Although no single treatment is best, many approaches—pharmacologic, nonphar-

macologic, or a combination of the 2—can achieve successful relief of insomnia.

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