Editorial

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MORE COMMON IN PERIMENOPAUSE, POSTMENOPAUSE

Insomnia is a troubling and under-treated problem

Consider gabapentin or eszopiclone to help wakeful women get some sleep at last

It is one of life's treasured pleasures: a peaceful and restful night's sleep from which you awake in the morning refreshed and ready for a new day.

It is one of life's feared miseries: feeling tired but being unable to fall asleep, or waking in the middle of the night and lying there sleepless for hours. A poor night's sleep can leave us ill-equipped to be effective at home or at work the next day.

Insomnia is a constellation of problems:

- difficulty falling asleep
- difficulty staying asleep
- waking too early
- experiencing nonrestorative sleep.

These problems occur in association with impairment of daytime functioning.

In young adulthood, men and women display an equivalent prevalence of symptoms of insomnia. Perimenopausal and postmenopausal women, however, report a rate of insomnia much higher than what is reported by age-matched men.[1]

Our patients who suffer insomnia symptoms—in particular, those perimenopausal and postmenopausal women—would be deeply appreciative if we used our clinical skills to help guide them to a peaceful night's sleep. Here are **1)** strategies for addressing their needs through pharmacotherapy and **2)** useful lifestyle tips to improve their chances of good sleep (see "How you can improve sleep hygiene," page 8).

Hormone therapy

Gynecologists are expert, of course, at using estrogen and progestin hormone therapy to treat menopausal symptoms, such as moderate and severe hot flushes. In perimenopausal and postmenopausal women, these **hot flushes often occur concurrently with insomnia.**

A recent survey, for example, found that the majority of women who reported hot flushes also reported symptoms of insomnia.[2] And another group of researchers showed that women who have moderate-to-severe hot flushes are more likely than women who experience mild hot flushes to have greater nighttime wakefulness and a greater number of long-awake episodes.[3]

Estrogen therapy, in addition to reducing the severity of hot flushes, has been reported to reduce sleep latency and to increase the quantity of rapid eye movement (REM) sleep—thereby improving postmenopausal patients' perception of the quality of their sleep.[4]

Non-estrogen treatment

Many women do not want to take estrogen, however; in others, estrogen therapy is contraindicated. This need not be a roadblock: Women in whom the symptoms of troubling insomnia predominate but who report few hot flushes may, in fact, benefit more from a **non-estrogen treatment for insomnia.** In my gyn practice, I've found that the agents **gabapentin** and **eszopiclone**—each with its own mechanism of action—are of value for treating insomnia in perimenopausal and postmenopausal women.

Gabapentin

Well known by its brand name,

Instant Poll

What are your clinical pearls for treating women who complain of symptoms of insomnia?

Please submit them for publication in an upcoming issue of OBG Management, to obg@qhc.com. Include your name and city and state.

TIPS FOR PATIENTS
How you can improve sleep hygiene

Here are some useful, proven recommendations to increase the likelihood of a good night's sleep.

- **Keep your bedroom cool.** Studies have shown that, at night, the higher the bedroom temperature (and, thus, the higher core body temperature) the greater the likelihood of a sleep disorder.
- **Avoid naps.** Never nap in the evening and try to avoid afternoon napping. Afternoon and evening naps break up the body's natural sleep rhythms, making it difficult for the sleep center to switch central nervous system function to the sleep mode.
- **Exercise daily.** Do so for at least 20 minutes and try to complete your exercise routine more than 4 hours before bedtime.
- **Stick to a regular sleep–wake schedule.** Sleep 7 to 8 hours a night, and then get out of bed.
- **Keep your bedroom dark and quiet.**
- **Avoid caffeine after lunch and avoid alcohol late in the evening and at night.** Caffeine is a stimulant that can reduce the effectiveness of the sleep center.
- **Stop smoking.** Avoid nicotine substitutes, too.
- **Limit fluids before bedtime.** A common cause of nighttime awakening is the urge to urinate; reducing the frequency of awakening to urinate can help to ensure a continuous night's sleep.

Neurontin, gabapentin is approved by the Food and Drug Administration for the treatment of seizures and postherpetic (shingles) neuralgia. The drug has also been used—but is not FDA-approved—to treat diabetic neuropathy, chronic pain, and restless legs syndrome. In addition, clinical trials have shown that gabapentin is effective for treating insomnia[5] and hot flushes—although, again, these are not FDA-approved indications.

To treat insomnia in my perimenopausal and postmenopausal patients, I start gabapentin at a dosage of 100 mg nightly, increasing it by 100 mg to 300 mg nightly. Occasionally, a patient reports the need to take as much 600 mg nightly before the quality of her sleep improves.

The most common side effects reported with gabapentin are somnolence, drowsiness, dizziness, and a "spacey" feeling—most often, during the first 1 to 3 weeks of treatment or when the dosage is escalated. Side effects tend to subside after 4 weeks of treatment.

Because gabapentin reaches it peak serum level 2 to 3 hours after ingestion of an oral dose, it is best to recommend that your patient take the drug a few hours before going to bed.[6] Gabapentin has a half-life of 5 to 7 hours, allowing a single dose taken near bedtime to last throughout the night.

For cooling hot flushes. In addition to being effective for the treatment of insomnia, gabapentin has been reported, as I noted, to alleviate hot flushes. Dosages required to achieve this effect are greater than what is typically prescribed for insomnia:

- In two clinical trials[7,8] in which gabapentin was evaluated for treating hot flushes, researchers reported that a dose of 300 mg, three times daily, reduced hot flushes better than placebo did.
- In a third clinical trial, gabapentin was prescribed as a single, 600-mg dose at bedtime. Investigators reported that gabapentin reduced hot flushes almost as well as low-dosage transdermal estradiol.[9]

Eszopiclone

This drug (sold as Lunesta) is a non-benzodiazepine gamma-aminobutyric acid (GABA) type A-receptor agonist that is FDA-approved for treating both sleep-onset and sleep-maintenance insomnia. A typical starting dosage is 2 mg at night, increased to 3 mg as needed. Note: If your patient is simultaneously taking a drug that inhibits the cytochrome P_{450} 3A4 (CYP3A4) enzyme system (e.g., ritonavir and other protease inhibitors, ketoconazole, verapamil, dilitiazem, fluconazole), begin the dosage of eszopiclone at 1 mg nightly and do not increase it!

For comparison, consider the half-life of four of the most commonly prescribed sleep medicines:

- eszopiclone, 5 to 7 hours
- zolpidem (Ambien), 1.5 to 2.4 hours
- extended-release zolpidem (Ambien CR), 1.5 to 2.4 hours (although the active drug is released from its matrix over a longer duration)
- zaleplon (Sonata), 1 hour.

Because eszopiclone and extended-release zolpidem have the longest-lasting effects, they are most likely to maintain sleep throughout the night.

The most common side effects of eszopiclone are a persistent metallic taste, somnolence, headache, dizziness, and unpleasant dreams.

Eszopiclone (as well as extended-release zolpidem) is approved for long-term use. Non-benzodiazepine

$GABA_A$ agonists such as eszopiclone are not considered addictive.

Notable research. In a 6-month trial, eszopiclone, 3 mg nightly, was associated with improvements in sleep, quality of life, and work performance, compared with placebo.[10] In a trial of more than 400 perimenopausal women who had symptoms of insomnia, eszopiclone, 3 mg nightly for 4 weeks, improved sleep onset, sleep maintenance, sleep duration, sleep quality, and daytime functioning, also compared to placebo.[11] Eszopiclone also improved depressive symptoms as recorded by the Montgomery-Åsberg Depression Rating Scale.[11]

The latter finding is significant. Investigators have reported that insomnia and mood disturbances, such as depression and anxiety, exhibit an association in some mid-life women.[12,13] The two problems may influence each other: Insomnia increases the risk of daytime mood disturbance while emotional distress increases the chance that a woman will experience insomnia.[14]

In a study, perimenopausal and postmenopausal women who experienced the combination of hot flashes, insomnia, and mild depression with or without anxiety were randomized to eszopiclone, 3 mg nightly for 11 weeks, or to placebo pill.[15] Compared with placebo, eszopiclone alleviated insomnia, nocturnal (but not daytime) hot flushes, and symptoms of depression and anxiety and improved quality of life.

Note: During nights that follow cessation, for any reason, of eszopiclone treatment, sleep latency and episodes of wakefulness may increase.

"… and in the morning wake … new-created"

Literature is filled to overflowing with reflections on the nature of sleep. D. H. Lawrence depicted it as a profound restorative in the poem "Shadows." Here is an excerpt:

> And if tonight my soul may
> find her peace
> in sleep, and sink in good
> oblivion,
> and in the morning wake like
> a new-opened flower
> then I have been dipped again
> in God, and new-created.

As I said: How appreciative your patients will be if you can help them feel like a "new-opened flower," come morning!

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The author reports no financial relationships relevant to this article.

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