A 35-year-old G2P2 woman presented with abnormal uterine bleeding. An endometrial biopsy revealed adenocarcinoma. A total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) was performed. The histologic examination detected an endometrial adenocarcinoma, grade 1/3 with no myometrial or vascular invasion and normal pelvic lymph nodes. Surprisingly, an endometrioid adenocarcinoma of the left ovary also was detected. The patient had a colonoscopy, which demonstrated dozens of ganglioneuromas and hamartomatous polyps of the colon.

Given the detection of tumors in the uterus, ovary, and colon, tissue was tested for Lynch mutations; none were detected. A mutation in the PTEN gene was detected, and a diagnosis of Cowden syndrome was made. Cowden syndrome is caused by an autosomal dominant mutation in the PTEN tumor suppressor gene and is associated with an increased risk of tumors of the breast, thyroid, endometrium, colon, rectum, and kidney.

Following her TAH-BSO, the patient was suffering from insomnia, severe hot flashes, and dry vagina. Her oncologist forbade the use of estrogen or progestins because she believed that Cowden syndrome tumors are estrogen sensitive.

Which nonhormonal options are effective treatments for your patient’s symptoms of insomnia, hot flashes, and dry vagina?

Sleep disorders
Consider sleep hygiene, gabapentin 300 mg nightly, zolpidem 5 mg nightly, or eszopiclone 2 mg nightly

For hypoestrogenic women with sleep problems, three proven interventions are:
- improved sleep hygiene
- gabapentin (Neurontin) prior to bedtime
- gamma-aminobutyric acid type A-receptor agonists, such as eszopiclone (Lunesta) and zolpidem (Ambien).

Interventions to improve sleep hygiene include: keeping the bedroom cool, avoiding naps, exercising daily, sticking to a regular sleep-wake schedule, keeping the bedroom dark and quiet, dimming ambient lighting in the evening, avoiding caffeine after lunch and alcohol late in the evening, stopping smoking, and limiting fluids before bedtime.

Gabapentin is FDA-approved for seizures and postherpetic neuralgia (shingles). The drug also has been used off label to treat diabetic neuropathy, chronic pain, and restless leg syndrome. Clinical trials have shown that gabapentin is also effective for treating insomnia and hot flushes.1,2

In my practice, I prescribe gabapentin 300 mg and instruct patients to take it 1 to 2 hours before bedtime. For some patients, 600 mg of
the drug is needed to produce sleep improvement.

The most common side effects of gabapentin are somnolence, drowsiness, dizziness, and a “spacey” feeling. These effects tend to subside after a month of treatment. Gabapentin has a half-life of 5 to 7 hours, which means that a single dose taken prior to bedtime will have an effect throughout the night.

Eszopiclone and zolpidem are FDA-approved to treat sleep problems. An extended-release form of zolpidem (Ambien CR) is also available. Eszopiclone and extended-release zolpidem are approved for long-term use. Generic zolpidem is less expensive than eszopiclone or extended-release zolpidem.

In a trial of more than 400 perimenopausal women who had symptoms of insomnia, eszopiclone 3 mg nightly for 4 weeks significantly improved sleep onset, sleep maintenance, sleep duration, sleep quality, and daytime functioning, compared with placebo.

In my practice, in order to minimize side effects (see paragraph below), I use either a 5-mg dose of immediate-release zolpidem or a 2-mg dose of eszopiclone.

**Warrn your patients of side effects**

The most commonly reported side effects of these nonhormonal insomnia medications are headache, somnolence, and dizziness. The FDA has recently issued a warning that all drugs taken for insomnia can impair driving and activities that require alertness, including driving.

The recommended dose of immediate-release zolpidem has been lowered from 10 mg to 5 mg. The recommended dose of extended-release zolpidem has been reduced from 12.5 mg to 6.25 mg. The FDA is “continuing to evaluate the risk of impaired mental alertness with other insomnia drugs.”

**Vasomotor symptoms**

**Consider venlafaxine 75 mg daily or gabapentin 600 mg nightly**

Estrogen is a highly effective treatment for menopausal vasomotor symptoms. For women with vasomotor symptoms who cannot take estrogen, however, moderately effective alternative treatments are selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentin.

A meta-analysis of seven clinical trials of the SSRIs and SNRI antidepressants and three trials of gabapentin provided evidence of the efficacy of these agents for the treatment of vasomotor symptoms. In the meta-analysis, placebo treatment resulted in an average 24% reduction in reported vasomotor symptoms. The active treatments resulted in significantly greater reductions in vasomotor symptoms, compared with placebo. Venlafaxine 75 mg daily resulted in a 33% greater reduction in vasomotor symptoms than placebo. Gabapentin 900 mg to 2500 mg daily resulted in a 35% to 38% greater reduction in hot flashes than placebo. Paroxetine (25 mg daily), fluoxetine (20 mg daily), and sertraline (50 mg daily) also were effective. Desvenlafaxine at a dose of 100 mg daily recently has been reported to be effective for the treatment of hot flashes.

**In my practice,** I use either:

- extended-release venlafaxine, starting at a dose of 37.5 mg daily for 1 week and then increasing the dose to 75 mg once daily, or
- immediate-release venlafaxine, starting at a dose of 37.5 mg daily for 1 week followed by 37.5 mg twice daily.

Immediate-release venlafaxine is less expensive than the extended-release formulations.

**Gabapentin.** Three clinical trials have reported that gabapentin at low doses, 600 mg to 900 mg daily, is effective for the treatment of hot flashes. In two clinical trials, investigators reported that gabapentin 300 mg three times daily reduced hot flashes better than placebo. In a third clinical trial, gabapentin 600 mg—prescribed as a single daily dose prior to bedtime—reduced hot flashes almost as well as low-dosage transdermal estradiol.

**Nonestrogen treatment of dry vagina**

**Recommend vaginal moisturizers and vaginal lubricants**

There are many vaginal moisturizers available for use, including: Replens, Me Again, Vagisil Feminine Moisturizer, Feminease, and K-Y Silk-E. These moisturizers are best used at least one or more times per week. In two small studies, the vaginal moisturizer Replens was reported to be similar in effectiveness to vaginal estrogen treatment.

In my practice, vaginal estrogen is superior to vaginal moisturizers for providing patients with relief from symptoms of dry vagina, but moisturizers are more effective than no treatment.

The vaginal pH levels in premenopausal and postmenopausal CONTINUED ON PAGE 12
women are <4.5 and >5.0, respectively. A new moisturizing gel that contains lactic acid may help create a more acidic vaginal pH, which may decrease vaginal irritation, dryness, and dyspareunia more than a gel without lactic acid.12 Luvena is a “bioengineered” vaginal moisturizer and lubricant that contains ingredients to suppress the growth of anaerobic bacteria and to reduce the development of a harmful vaginal biofilm.

Many postmenopausal women with symptoms of dry vagina use a vaginal moisturizer on a regular basis and also use a lubricant prior to sexual intercourse. Many lubricants are available, including Astroglide, Slippery Stuff, K-Y Jelly, Pjur Eros, ID Millennium, and Elegance Women’s Lubricant.

In my practice I have recommended hydrogenated vegetable oil as a lubricant. For example, Crisco is a hydrogenated vegetable oil that is solid at room temperature and has been reported to be an effective lubricant for vaginal dryness. Application of a small amount of Crisco to the posterior vaginal area creates a protective and lubricated layer over the skin most susceptible to microtrauma during sexual intercourse. To make application easier, the Crisco can be removed from its container and stored in a small decorative glass jar by the bedside or in the bathroom.

My recommendation

Estrogen is typically the most effective treatment of such menopausal symptoms as sleep disorders, hot flashes, and dry vagina. However, many women prefer nonhormonal treatment of these symptoms, and for some women (such as those with estrogen-sensitive cancer) estrogen treatment is contraindicated. Three nonhormonal interventions that I have found useful in my practice are gabapentin for sleep disorders, venlafaxine for hot flashes, and Crisco as a lubricant for symptoms related to a dry vagina.

References

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