Managing menopausal vasomotor and genitourinary symptoms after breast cancer

Two cases on selecting safe and useful treatments for survivors of breast cancer experiencing distressing quality-of-life symptoms of menopause

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IN THIS ARTICLE

Breast cancer survivors entering menopause face the risk of several menopausal symptoms:

Hot flashes, the most common symptom, occur in more than 75% of women during menopause and have the potential to persist for as long as 15 years.[1] That lengthy interval becomes a major issue for patients, especially when hot flashes are associated with other menopausal symptoms, including sleep disruption, difficulty concentrating, and emotional instability (crying, irritability).

- **Painful intercourse** and **loss of interest in sexual activity** often develop as a result of vaginal atrophy and dryness.
- **Urinary tract symptoms** include urgency and, compared to the patient's history, more frequent infections.
- **Bone loss** is a concern for many women after breast cancer, especially if they are, or have been, on aromatase inhibitor therapy.
- **Depression** might be related to hormonal changes due to menopause or hormonal therapies, a consequence of merely having a diagnosis of cancer, or an adverse effect of chemotherapy.

In this brief review, I'll examine options for treating symptoms of menopause by strategy—lifestyle modifications, over-the-counter treatments, and prescription drugs. Separately, I'll look at options for managing genitourinary syndrome of menopause (GSM).

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CASE 1

Rose is a 56-year-old woman who presents to clinic with a new breast mass, felt on breast self exam. The mass is about 1 cm, mobile, and firm. Diagnostic mammogram and ultrasound confirm a worrisome mass; biopsy returns positive with a 9-mm invasive, estrogen-receptor positive, ductal carcinoma with negative sentinel nodes at the time of lumpectomy. Radiation therapy was completed. She then met with oncology and decided against chemotherapy. Instead, she began an aromatase inhibitor 3 months ago. Bone density showed osteopenia. She presents to your office reporting frequent bothersome hot flashes and disrupted sleep.

Strategy #1: Lifestyle adaptations

First-line interventions for menopausal women who have had breast cancer usually involve taking a critical look at lifestyle and undertaking modifications that can alleviate discomfort. Because overall health is important for women who have had breast cancer,

Lifestyle strategies to managing vasomotor and genitourinary symptoms after breast cancer

you should, across the spectrum of patients, encourage them to:

- increase physical activity
- reduce body weight by approximately 10% (if overweight or obese)
- reduce alcohol consumption
- stop smoking
- ensure adequate intake of calcium (1,200 mg, preferably by diet)
- optimize the level of vitamin D, including by increasing intake of fresh fish, eggs, and numerous other fortified foods.

The value of nondrug therapy for hot flashes is difficult to prove. Certain lifestyle changes are sensible, even if not evidence-based, and will help some women (but not others). We suggest that patients try lowering the temperature in the home (65–68˚ at night); running a fan; wearing clothing that can be removed in layers; and avoiding triggers such as spicy food, alcohol, cigarettes, and hot drinks. Hypnosis and cognitive behavioral therapy (CBT) have been shown to help in clinical trials. Measures with benefit and minimal risks, but effectiveness not established, include acupuncture (sham worked as well as traditional), exercise, yoga, paced respiration, relaxation training, and mindfulness-based stress reduction.

Strategy #2: OTC compounds

Over-the-counter products—from soy products to black cohosh to flax seed, and including dong quai, evening primrose oil, maca, omegas, pollen extract, ginseng, and red clover,[2] or several compounds formulated in combination—have not been proven to be of more benefit for relieving symptoms of menopause than placebo in randomized trials, and thus might or might not be effective in a given patient. S-equol, a metabolite of a soy isoflavone taken by women who are non-equol producers, is available under the trade name Equelle and has shown some benefit. Note: There is concern that supplements that contain estrogen-like compounds, like soy products, might actually increase the risk of breast cancer. Dietary soy is not felt to be a concern.

Ask questions about the severity of a patient's hot flashes. When a patient reports hot flashes, and is requesting help to relieve her discomfort, inquire 1) how often she has hot flashes, 2) how severe they are, and 3) how bothered she is by them (not all women are equally troubled, of course). The patient's answers to these questions will help you decide

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Weigh hot flash frequency, severity, and the patient's reaction to them when considering an OTC treatment

Newly arrived and on the horizon

Where does this review of available treatments leave us? Regrettably, with many women who experience painful intercourse and vaginal dryness despite what is available for treating their problems, and who continue looking to medical science and women's health care for new options. So, what is coming next for these suffering patients? Here is a quick and selective run-through:

KNDy neurons. For hot flashes, there is the promise of nonhormonal treatment using these neurons, believed to be involved in reproduction by triggering expression of various compounds—particularly neurokinin B, which mediates hot flashes.[1]

Estetrol. In testing for use in treating hot flashes and its effect on GSM is this pregnancy-associated natural hormone that, importantly, did not stimulate breast cancer in a rat model.[2] More evidence of efficacy is needed.

Lasers. For vaginal atrophy, many women are choosing treatment with the laser. Keep in mind, however, that, although lasers are FDA-approved devices, they do not have the FDA's endorsement for use in vaginal atrophy, and have not been well-tested for their effectiveness for this indication in women with breast cancer who have taken an aromatase inhibitor. ACOG, NAMS, and the Endocrine Society have urged that additional trials be conducted, and have stated that the laser for vaginal atrophy cannot be recommended until there are more data on safety and efficacy.[2]

Lower-dose soft-gel vaginal estrogen suppositories have recently been approved by the FDA at 4 and 10 µg.[3] The formulations are only minimally absorbed, potentially making them a good option for women who have had breast cancer.

Lasofoxifene, a selective estrogen-receptor modulator not yet approved by the FDA, has been shown to ameliorate vaginal changes.[4] The drug is neutral or protective on the breast, but is now being tested in women with resistant breast cancer and unlikely to become available for GSM.

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which treatment option to offer, based on evidence and your experience.

CASE 1 Continued

Rose tried black cohosh OTC without improvement. She was interested in hypnosis but did not find it effective for her. She returned 3 months later stating that she is miserable, exhausted, not getting enough sleep, and her hot flashes and night sweats are affecting both her work and her relationship.

Strategy #3: Prescription medication

When addressing hot flashes, consider whether they occur more at night or during the day, or do not follow a day–night pattern. For women whose hot flashes occur mostly at night, and might therefore make sleeping difficult and cause fatigue and irritability, gabapentin, taken approximately 1 hour before bed, can be helpful. If tolerated without excessive somnolence the next day, the dose can be increased at night or additional doses provided during the day depending on hot flash response. For women who have hot flashes day and night, we often prescribe a low-dose antidepressant from the selective serotonin-reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) class.

When prescribing an antidepressant, we make a distinction between breast cancer patients who are taking tamoxifen and those who are not, to avoid cytochrome P450 2D6 inhibitors in women taking tamoxifen.[3] Better choices for women taking tamoxifen include desvenlafaxine, venlafaxine, escitalopram, or gabapentin or pregabalin.

For women with breast cancer who are taking an aromatase inhibitor, and who are also experiencing mood changes with their hot flashes, we often choose a trial of a low-dose antidepressant, either an SSRI or SNRI. One drug is approved by the US Food and Drug Administration (FDA) for the treatment of hot flashes (but not for mood disorder). This is low-dose salt of paroxetine, 7.5 mg/d, which has the advantage of exerting no adverse effect on libido or weight (but is sometimes difficult to obtain because it is a branded product that might not be covered, or not covered fully, by a given patient's insurance plan). Other antidepressants can be used in doses lower than needed for depression, with more rapid onset of effect on hot flashes, often within 2 weeks.

Last, transdermal clonidine, an antihypertensive, also has been found to relieve hot flashes.

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Not a recommended strategy: Systemic hormone therapy

Although hormone therapy is, in general, the gold standard for alleviating hot flashes, it is contraindicated in most women with breast cancer.[4] At our institution, we avoid systemic hormone therapy for hot flashes in almost all breast cancer patients.

CASE 2

Sarah first presented with hot flashes that improved while taking escitalopram 10 mg. Her night sweats persisted, however. Gabapentin 300 mg was added to take nightly. With this regimen, she finally felt that she was coping better. Six months later, she reported that she and her long-term partner had not been able to resume vaginal intercourse post–breast cancer treatment because of pain.

The challenge of managing GSM

What if your patient says, "Doctor, I'm really doing OK with my hot flashes, but sex has become painful. I don't have any interest. I have vaginal dryness, and it's affecting my quality of life"?

Studies have shown that GSM affects up to 50% of women, and even more than that among women who have had breast cancer.[5] The condition interferes with sexual intimacy, disrupts quality of life, and can sour a partnership—significant quality-of-life concerns for breast cancer survivors.

For mild symptoms, encourage patients to apply a lubricant just before intercourse or a vaginal moisturizer twice weekly; moisturizers improve vaginal pH, too. These treatments do not fix the problem of a lack of superficial cells due to estrogen loss, however; to accomplish that, consider prescribing low-dose vaginal estrogen therapy or intravaginal dehydroepiandrosterone (DHEA). This strategy is felt to be safe for many breast cancer survivors, as systemic absorption of estrogen is minimal if dosed low, keeping levels in the postmenopausal range.

The American College of Obstetricians and Gynecologists (ACOG), the North American Menopause Society (NAMS), and the Endocrine Society agree that vaginal estrogen therapy may be a good option for many women with breast cancer for whom moisturizers and lubricants are inadequate.[6] Delivery options include vaginal creams, tablets, suppositories used 2 or 3 times per week, or the low-dose vaginal estrogen ring, replaced every 3 months. We are concerned about using vaginal estrogen in women who have had aromatase inhibitor (AI) therapy; their estrogen levels are so low that absorbing even a small amount might make a difference in terms of effectiveness of AI. For women who need more than lubricants or vaginal moisturizers, particularly those taking anti-estrogen therapy (aromatase therapy), the use of low-dose vaginal hormones may be considered on an individual basis, but should include the oncologist in decision making.[1,3]

Beyond low-dose vaginal estrogen therapies, there are additional options that can be considered but with less supporting data for treating GSM in women with breast cancer.

Oral ospemifene, a selective estrogen-receptor modulator (SERM; Osphena), might be neutral or even protective in its effect on the breast, as demonstrated in preclinical trials.[7] In human trials, the drug is approved only for painful intercourse, not for loss of libido, and has not been tested in breast cancer patients.

Intravaginal DHEA (Prasterone), has been on the market for almost 1 year. The drug is approved for treating painful intercourse, but it also reverses vaginal atrophy and alleviates urinary symptoms. Because DHEA is a prohormone, it is converted to estrogen and androgen in the vagina. Again, absorption appears minimal. Intravaginal DHEA does not have the US Food and Drug Administration (FDA) black-box warning that vaginal estrogen products do, but it is accompanied by a warning that it has not been tested in women with breast cancer.

Tissue selective estrogen receptor modulator is a conjugated estrogen combined with a third-generation SERM bazedoxifene, which treats hot flashes and reverses vaginal atrophy. This new systemic agent is probably neutral on the breast (at least that is the finding in clinical trials at 2 years[8]); again, how-

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Although not well tolerated in breast cancer patients, reassure your patient of the many available and on-the-horizon treatments for their menopause symptoms

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ever, it has not been tested in patients with breast cancer.

Nonhormone therapies

Topical lidocaine for insertional dyspareunia has been studied in postmenopausal women with breast cancer with severe GSM, dyspareunia, increased sexual distress scores, or abnormal sexual function with improvement seen using 4% aqueous lidocaine versus saline applied with a cotton ball to the vestibule for 3 minutes before vaginal penetration.[9]

Vaginal laser therapy has the potential to ameliorate distressing GSM without the need for local hormone intervention; however, placebo or active-controlled trials and long-term safety follow-up are needed.[5]

Treatment begins with a conversation

Most importantly, we need to listen to our patients in discomfort because of their menopausal symptoms. Consider proceeding along these lines: "You've been treated for breast cancer; now, let's look at the medical issues that are affecting your quality of life. Are you depressed? Are you having hot flashes? Are you getting enough sleep? Have you stopped having sex or not restarted after your breast cancer treatment? Are you having painful sex or avoiding sex due to fear of pain? Let's discuss options and work with your oncologist to try to relieve your symptoms and make your life better."

First-line therapy for the treatment of menopausal symptoms in women with a history of breast cancer should start with lifestyle changes and nonhormone therapies. For GSM, lubricants and vaginal moisturizers should be tried first and may be effective. Reassure patients that there are many treatment options, even though not all of them have been well-tested in breast cancer patients, and that new modalities are under investigation and review (see "Newly arrived and on the horizon," page 18). Become familiar with published data on the safety and effectiveness of the range of available treatments; guide patients through the process of finding what works best for them; and invite their oncologist into the therapeutic partnership. If you do not feel comfortable with these issues in women who are breast cancer survivors, find a menopause specialist to help, available by zip code at Find a Provider, http://www.menopause.org. ●

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For a list of menopause specialists, visit menopause.org

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