Management of Hormone Deprivation Symptoms After Cancer

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CME Activity

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Learning Objectives: On completion of this article, you should be able to (1) evaluate lifestyle, mind-body, and over-the-counter remedies for vasomotor symptoms; (2) list the nonhormoneprescription therapies for vasomotor symptom management; and (3) describe management strategies for vaginal dryness and sexual pain in cancer survivors.

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Abstract

Cancer survivors often experience symptoms related to hormone deprivation, including vasomotor symptoms, genitourinary symptoms, and sexual health concerns. These symptoms can occur due to natural menopause in midlife women, or they can be brought on by oncologic therapies in younger women or men. We searched PubMed for English-language studies from January 1990 through January 2016 to identify relevant articles on the management of hormone deprivation symptoms, including vasomotor, genitourinary, and sexual symptoms in patients with cancer. The search terms used included *hormone deprivation, vasomotor symptoms, hot flash, vaginal dryness, sexual dysfunction,* and *breast cancer*. This manuscript provides a comprehensive description of data supporting the treatment of symptoms associated with hormone deprivation.

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As women approach or reach menopause naturally, or if they undergo surgical removal of both ovaries, multiple symptoms related to estrogen depletion can arise. Women with cancer may experience sudden and severe symptoms because certain treatments (eg, gynecologic surgery/radiation, chemotherapy, and gonadotropin-releasing hormone analogs) can abruptly cut ovarian hormone production. In addition, women with cancer, particularly those with breast and other hormonally responsive

cancers, are commonly denied hormone supplementation because of concern regarding recurrence risk. Furthermore, men receiving androgen-deprivation therapy may also have significant symptoms related to hormone deprivation.

We searched PubMed for English-language articles pertaining to the management of hormone deprivation symptoms, including vasomotor, genitourinary, and sexual symptoms, in patients with cancer from January 1990 through January 2016 using search terms that included *hormone deprivation, vasomotor symptoms, hot flash, vaginal dryness, sexual dysfunction,* and *breast cancer*. We identified additional articles by cross-referencing the publications found and included studies for discussion based on judgment, interpretation of the findings, and our collective clinical experience. This article reviews the state of the science regarding the management of symptoms related to hormone deprivation in patients with cancer.

VASOMOTOR SYMPTOMS

Hot flashes (or hot flushes) and night sweats, also called vasomotor symptoms (VMS), are common symptoms associated with hormone depletion, occurring in approximately 75% of women during the menopausal transition.[1] A hot flash is defined as a sudden sensation of intense warmth that often begins in the chest area, may rise to the neck and face, and may be accompanied by red blotches on the skin, profuse sweating, palpitations, anxiety, and embarrassment. A hot flash can last for less than 1 minute or as long as 10 to 20 minutes. They may occur infrequently or more than 20 times per day. Women who have had treatments that cause early menopause may have hot flashes that are more severe and last longer.[2] Women with hot flashes do not have higher body temperatures than other women. Rather, they have a narrowed thermal neutral zone so that as body temperatures slightly rise and decrease in a usual sine wave pattern, women with hot flashes are more likely to start sweating or chilling.[3] The average duration of VMS was previously thought to be only a couple of years, but recent studies reveal the mean duration to be greater than 7 years, with up to one-third of women experiencing moderately severe VMS for 10 years or more.[4,5]

Much has been written about the use of estrogen-based treatment for the control of menopausal symptoms in breast cancer survivors, the discussion of which has been largely influenced by 2 prospective, randomized trials. The Hormonal Replacement Therapy After Breast Cancer Diagnosis—Is It Safe? (HABITS) trial treated women with a history of breast cancer who were experiencing menopausal symptoms with either 2 years of estrogen-based treatment or nonhormonal management.[6] It concluded that estrogen-based therapy should not be used in breast cancer survivors because 26 women in the estrogen-based therapy group, in contrast to only 7 in the nonhormonal treatment group, reported new breast cancer events (relative hazard, 3.3; 95% CI, 1.5-7.4).[6] However, another somewhat similar study, the Stockholm randomized trial, concluded that estrogen-based therapy did not increase the risk of breast cancer recurrence.[7] The Women's Health Initiative trials were particularly influential after they demonstrated an increased incidence of new breast cancer events in women without a history of breast cancer who received combined hormone therapy with oral conjugated equine estrogen and medroxyprogesterone acetate (MPA).[8] Since then, for all practical purposes, menopausal hormone therapy is rarely used in women with a history of breast cancer.

NONPRESCRIPTION TREATMENTS FOR VMS

Lifestyle Measures

Some environmental considerations may help control VMS. The most important of these revolves around keeping the environment cool with moving air. Ambient temperature may affect the frequency and severity of hot flashes. Thus, keeping the room temperature cool, keeping air moving with fans, dressing in layers, and wearing open-weave fabrics are practical strategies that have some scientific basis, even if controlled trials have not demonstrated efficacy.[9] Although clinical trial data are lacking, potential triggers of VMS may include alcohol, tobacco, and caffeine; avoidance of these substances may be of benefit.[10]

Although it is not established that exercise decreases hot flashes,[9] weight loss does seem to be beneficial.[11-13] The Women's Healthy Living and Eating Study, a dietary intervention trial involving women with breast cancer,

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assessed VMS as a secondary analysis. Women whose weight increased by 10% or more after the cancer diagnosis were more likely to experience moderate to severe VMS, whereas those who lost 10% or more of their prediagnosis weight were less likely to report moderate to severe VMS.[14]

Mind-Body Approaches

Three small trials published in the 1990s supported practicing paced respirations (slow, deep-breathing exercises) and participating in applied relaxation exercises (consisting of training and maintenance programs in various techniques of relaxation, eg, progressive, release-only, differential, cue-controlled, and rapid relaxation) to decrease either hot flash frequency or intensity.[15-17] However, 2 randomized trials involving 92 and 218 patients revealed that paced respirations were no more effective than usual breathing for hot flash treatment.[18,19]

Cognitive behavioral therapy (CBT) has been shown to reduce VMS problem ratings, but not VMS frequency, in 2 randomized controlled trials.[20,21] In MENOS 1, women with VMS after breast cancer treatment experienced a significant reduction in VMS problem ratings after 9 weeks of group CBT compared with usual care.[21] MENOS 2 showed a similar benefit with both group and self-guided CBT compared with usual care in perimenopausal and postmenopausal women without cancer.[20]

A recent series of randomized trials has provided convincing evidence that hypnosis can significantly decrease hot flashes. The first of these, based on previous evidence suggesting benefit,[22,23] was a randomized trial that studied 60 breast cancer survivors with bothersome hot flashes.[24] Although this trial had a no-treatment control arm, it did not attempt to blind patients to the proposed hypnosis intervention, which consisted of 5 weekly hypnosis sessions. This trial demonstrated a striking decrease in hot flashes in the hypnosis arm (70% reduction) compared with the control arm (15% reduction). The same group of investigators subsequently reported the results of another randomized clinical trial involving 187 women who had at least 7 hot flashes per day at baseline.[24,25] In a single-blind manner, patients received either structured attention control sessions (designed to match the intervention arm in terms of therapeutic environment, therapist exposure, interpersonal interaction, and encouragement but without hypnosis or cooling suggestions) or hypnosis at weekly intervals for 5 weeks. After 12 weeks, hot flash scores were reduced by 80% with hypnosis vs 15% for the control group ($P<.001$). Correspondingly, physiologically monitored hot flashes were reduced 57% in the hypnosis arm vs 10% for controls ($P<.001$).

Another recent trial randomized patients to receive standard doses of venlafaxine vs hypnosis vs both vs 2 control items (placebo capsules and structured attention control sessions).[26] Hot flash scores decreased by approximately 25% in the double-control arm and by approximately 50% in each of the other 3 arms. A small feasibility study compared gabapentin, at 900 mg/d in 3 divided doses, with hypnotherapy consisting of 3 1-hour sessions at weekly intervals. Although there was not a statistically significant difference between the 2 groups, the authors reported an 80% reduction in hot flash frequency and an 85% reduction in hot flash severity in the hypnotherapy group compared with a 33% reduction in both hot flash frequency and severity in the gabapentin group.[27]

Although studies support CBT and hypnosis as effective therapies for hot flashes, they are not commonly used because the expertise required to provide them has not been well disseminated.

Although most acupuncture trials have not provided much evidence of benefit for the treatment for hot flashes in cancer survivors, a recently published trial provided more promising data. It randomized 120 breast cancer survivors with at least 2 bothersome hot flashes daily to 1 of 4 treatment arms: acupuncture, sham acupuncture, gabapentin, or oral placebo. After 8 weeks, the hot flash composite score fell most with acupuncture (−7.4), followed by sham acupuncture (−5.9), gabapentin (−5.2), and placebo (−3.4) ($P<.001$).[28] However, a systematic review suggests that the data are insufficient to date to support or refute the benefit of acupuncture in the management of hot flashes in patients with cancer.[29]

Over-the-Counter Herbs and Supplements

A variety of supplements and herbs have preliminary data or have enjoyed popularity

without any solid data to suggest that they were helpful for controlling VMS. Several of these agents that have failed the test of placebo-controlled, double-blind clinical trials include magnesium oxide,[30] black cohosh,[31] soy products,[32-34] flaxseed,[35] and vitamin E.[36]

NONHORMONAL PRESCRIPTION TREATMENTS FOR VMS

Extensive studies have evaluated nonhormonal means of treating VMS in women with a history of breast cancer. Some of the women in these trials did not have breast cancer (women who wanted to avoid estrogen-based therapies), and some trials looked at the same treatments in women with and without breast cancer. Some of the women in these trials were taking tamoxifen, and others were not. A pooled analysis and cross-study comparison of the use of individual therapies in populations with and without breast cancer illustrates that the beneficial effects of available treatments seem to be independent of cancer history and tamoxifen use.[37]

Clonidine

Clonidine, an α-adrenergic agonist that results in decreased sympathetic activity, is a relatively old medication that is still occasionally used for treating hypertension. Two relatively large, randomized, placebo-controlled, double-blind clinical trials demonstrated that clonidine significantly decreased hot flashes, with a 20% to 38% reduction in hot flash frequency.[38,39] Toxicities associated with clonidine include constipation, dizziness, drowsiness, dry mouth, fatigue, and weakness. Despite its established efficacy, clonidine is not commonly used for the management of VMS because other nonhormonal agents seem to be more effective and better tolerated.

Antidepressant Agents

A variety of antidepressant agents, both selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, decrease VMS. In the late 1990s, it was independently noted by 4 different clinicians that patients reported a decrease in hot flashes while being treated with 1 of 4 different antidepressants (venlafaxine, paroxetine, fluoxetine, and sertraline), leading to pilot trials of 2 of these drugs[40,41] and randomized, placebo-controlled, double-blind trials for all 4.[42-46]

Venlafaxine was the first of these antidepressant agents that demonstrated clinical efficacy.[43] A 4-arm study revealed that (1) placebo decreased hot flashes by 27% over 4 weeks compared with baseline; (2) venlafaxine 37.5 mg/d decreased hot flashes by 40%; (3) venlafaxine 75 mg/d decreased hot flashes by 60%; and (4) venlafaxine 150 mg/d did not reduce hot flashes any more than did 75 mg/d. Adverse effects included nausea (which usually resolved over time while taking the drug), mild dry mouth, constipation, and decreased appetite. It is known that doses higher than 37.5 mg/d need to be reached gradually via dose titration and that withdrawal symptoms will occur if a patient does not slowly titrate back down to 37.5 mg daily before cessation. Even when weaned slowly, a few patients may have quite bothersome withdrawal symptoms, such as lightheadedness, headaches, and anxiety.

Similar hot flash reductions have been reported with paroxetine, citalopram, desvenlafaxine, and escitalopram in both breast cancer survivors and women without a history of breast cancer.[45-52] Less benefit has been seen with fluoxetine[44] and sertraline[42] compared with these other antidepressant agents. Low-dose paroxetine 7.5 mg/d is the only nonhormonal prescription medication to be approved by the US Food and Drug Administration (FDA) for the management of VMS, and it seems to reduce the frequency of hot flashes to a similar degree as other antidepressant agents; this drug is not associated with significant discontinuation symptoms.[53] Notably, some of these antidepressant drugs interfere with the metabolism of tamoxifen and, thus, should generally be avoided in patients receiving this drug.[54,55] Citalopram 20 mg/d may be the best option given its cross-study comparative efficacy, tolerability, cost, and less interference with tamoxifen metabolism compared with other antidepressant drugs.

Gabapentinoids

Gabapentin is an antiseizure medication commonly used for the treatment of neuropathic pain. Pregabalin, a related compound, seems to be slightly more effective for some

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conditions and requires less frequent dosing than gabapentin.

Two randomized, double-blind, placebo-controlled trials of gabapentin, at a target dose of 300 mg 3 times daily, reported similar results, with an approximately 25% reduction in hot flashes in the placebo arm compared with approximately twice as much on the active treatment, similar magnitudes to what has been seen with the effective antidepressant agents.[56-58] Another much smaller trial, using gabapentin 2400 mg/d, also demonstrated a significant reduction in hot flashes.[59] Gabapentin can cause lightheadedness and drowsiness, especially when first initiated, and may lead to some fluid retention. It is important to slowly adjust the dose when initiating or discontinuing the drug. Pregabalin also reduces hot flashes to a similar degree in women, as illustrated in a 3-arm trial that looked at target doses of 75 mg twice daily, 150 mg twice daily, or placebo. Both doses were equally effective, with fewer adverse effects with the lower dose.[60]

Which Do Women Prefer, Venlafaxine or Gabapentin?

A practical, nonblinded, crossover trial randomized breast cancer survivors to receive standard doses of gabapentin vs venlafaxine with the primary goal of understanding which treatment women preferred.[61] Although the average decrease in hot flashes was virtually identical in each treatment arm, and the toxicity profiles looked similar (different adverse effects but similar-appearing magnitude), the women chose venlafaxine by a 2:1 margin, 68% vs 32% (P=.01). However, some patients experienced better hot flash control and fewer adverse effects with gabapentin therapy. These data support using an antidepressant drug as first-line treatment of VMS and then trying gabapentin in patients who do not achieve adequate symptom control with an antidepressant agent.

Oxybutynin

Oxybutynin, an anticholinergic agent that is most commonly used for overactive bladder symptoms, may also manage VMS.[62] Of 52 patients who were prescribed oxybutynin, 90% of whom were refractory to previous hot flash treatments, 70% had a favorable response lasting weeks to years. More than half of the patients used it for more than 6 months, although 12% of responding patients stopped taking the drug owing to adverse effects.

Additionally, a prospective, double-blind clinical trial was developed to address the utility of oxybutynin for treating menopause-related hot flashes. Although the results of this clinical trial do not seem to be published in the usual format, an Internet patent report regarding this trial describes that 148 patients were randomized and that there were significant reductions in both of the primary end points (daily frequency of moderate to severe VMS and daily severity of all VMS) at week 12 compared with baseline (P<.001).[63]

Stellate Ganglion Blockade

Stellate ganglion blockade (SGB) is a selective block of the cervical sympathetic chain designed to reduce autonomic reactivity. It has been used with mixed results to treat complex pain syndromes,[64-67] and there are preliminary data suggesting that SGB may help treat posttraumatic stress disorder.[68] Lipov et al[67,69] proposed that SGB might be helpful for alleviating hot flashes after experiments showed that injection of a modified rabies virus in the stellate ganglion of an animal led to viral spread to areas of the brain thought to be related to temperature regulation: the amygdala, insulate, and hypothalamus. He reported positive-appearing, nonrandomized pilot trials including 2 groups of women with[70] and without[71] a history of breast cancer; similar results were seen in pilot trials from other institutions.[72-74] Subsequently, a small sham, placebo-controlled, randomized trial reported that the frequency of moderate to severe hot flashes was decreased in the SGB arm by 50% at 4 to 6 months vs 0% in the sham arm (P<.001), although there was not a significant difference in subjective total hot flashes between the 2 study arms.[75] In addition, the total number of objective hot flashes (determined by skin conductance testing to measure sweating episodes) from baseline to 3 months was reduced more in the active vs sham arm (relative risk=0.71; 95% CI, 0.64-0.99; P<.05).

Another trial randomized 40 patients to be treated by SGB vs pregabalin 75 mg twice daily. Nineteen of the 20 patients randomized to SGB had a single procedure, and 1 patient had a repeated SGB procedure 15 days later. This trial reported that hot flashes decreased more

during the third month with SGB than with pregabalin therapy (P=.006).[76] This is impressive because pregabalin has also been shown to be an active agent for decreasing hot flashes.

Although additional randomized trials would be welcome, the current SGB data seem quite promising for hot flashes. Complications related to SGB are rare in experienced hands and with the use of image-guided procedures, but concerns exist because of the proximity of the stellate ganglion to critical structures such as spinal nerves and the vertebral, internal carotid, and inferior thyroid arteries. Inadvertent intravascular injection may result in seizures related to the local anesthetic.[75] Also, it is unclear what the optimal frequency and duration of SGB therapy is for hot flash management.

HORMONE TREATMENTS FOR VMS

Megestrol acetate, a progesterone analog used to treat breast cancer (160 mg/d), uterine cancer (320 mg/d), and appetite loss (400-800 mg/d), has also been studied as an agent to decrease VMS. The first report of a placebo-controlled, double-blind, randomized clinical trial demonstrated that a low dose (40 mg/d) of megestrol acetate reduced hot flashes by 85% compared with a 21% reduction with placebo use.[77,78] Despite exploring many potential adverse effects, withdrawal menstrual bleeding in some women was the only one noted. Adverse events with higher doses of megestrol acetate used for other indications can include increased appetite, weight gain, thromboembolic events, and even death.[79] Another trial comparing megestrol acetate at doses of 20 mg/d vs 40 mg/d illustrated equivalent benefits over placebo.[80]

A related agent, MPA, is a progesterone analog similar to megestrol acetate that has been used in relatively high doses to treat breast cancer and appetite loss. In low oral doses, it has been used for endometrial protection in menopausal hormone therapy regimens.

A hot flash trial randomizing patients to receive intramuscular MPA vs oral megestrol acetate showed marked similarities between the 2 agents.[81] Another trial randomized women to receive a single dose of MPA 400 mg intramuscularly vs venlafaxine 37.5 mg/d for a week, then 75 mg/d for the remainder of the trial.[82] The venlafaxine in this trial performed remarkably similarly to the same dose of venlafaxine in the previously discussed placebo-controlled, multidose trial,[43] with approximately a 60% reduction in hot flashes after 6 weeks, and the MPA performed similarly to megestrol acetate, with approximately an 85% reduction in hot flashes.

The MPA intramuscular dose is a slow-release preparation with a half-life of approximately 50 days. Although the data from these trials were measured only for limited periods, the effect on VMS seems to be quite prolonged, frequently lasting for months or years. In women who experience a recurrence of VMS, a repeated dose is again effective.[83]

Although these progesterone analogs are not estrogen, there are theoretical concerns that 1 or both of them might affect breast cancer risk, although there are not good data that demonstrate harm. One of the reasons for concern is that daily oral MPA, when combined with estrogen, increases the incidence of breast cancer in patients who had not previously had breast cancer.[8] Another potential concern regarding MPA is its association with decreased verbal memory, an early predictor of Alzheimer's disease.[84]

WHAT IS KNOWN ABOUT TREATING VMS IN MEN?

Vasomotor symptoms are a substantial problem in up to 80% of men with prostate cancer who undergo androgen deprivation therapy.[85] There are fewer hot flash treatment studies in men than in women. Nonetheless, the trials conducted in men support that some, but not all, of the treatments that are helpful in women are also helpful in men.

Trials of progesterone analogs and estrogens in men reveal that they are associated with a marked reduction in hot flashes, just as they are in women.[77,86-88] However, there are concerns about the use of both estrogens and progestogens in male cancer survivors owing to high rates of cardiovascular and thromboembolic disease, particularly if metastatic disease is present.[89] Also, there are reports that men taking low doses of megestrol acetate can experience a rise in prostate-specific antigen levels that decrease on drug discontinuation.[90,91] However, this should not be an absolute contraindication to the use of these agents (oral megestrol acetate or intramuscular MPA) because progestogens have demonstrated anticancer

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activity, and another agent that is used to treat prostate cancer, bicalutamide, is also associated with increased prostate-specific antigen levels that decrease on drug discontinuation.[92] This phenomenon is also seen with hormone treatments in patients with breast cancer, whereby an agent can cause initial tumor regression. After tumor growth with continued treatment, tumor regression can happen on withdrawal of the same hormone therapy with no other change in treatment.[93,94] Given the previously noted concerns, some providers are not comfortable using progesterone analogs for the treatment of VMS in men, but others commonly use this approach.

Gabapentin can decrease hot flashes related to androgen-deprivation therapy in men[95] to a similar degree as that observed with gabapentinoids in women.[56-60]

In contrast to estrogen, progesterone analogs, and gabapentinoids, which seem to have similar effects in women and men with hot flashes, clonidine has not been associated with a reduction in hot flashes in men as it has in women.[38,96]

There are conflicting data regarding whether antidepressant agents work as well for hot flash control in men as in women. Four pilot trial reports support that these drugs decrease VMS in men to a similar degree as in women,[97-101] but a placebo-controlled, randomized trial, with a 2 × 2 study design to also assess a soy compound, found that neither venlafaxine nor the soy product significantly decreased hot flashes more than placebo.[101] Ideally, additional information will become available to determine the true value of selected antidepressant agents for treating VMS in men. See Table 1 for a summary of options for VMS management.

GENITOURINARY SYNDROME OF MENOPAUSE

The symptoms of genitourinary syndrome of menopause (GSM) (formerly termed vulvovaginal atrophy or atrophic vaginitis), such as vaginal dryness and discomfort with sexual activity, occur in nearly half of postmenopausal women and in more than 60% of breast cancer survivors.[102,103] Multiple surveys of postmenopausal women suggest that GSM has a detrimental effect on sexual health and quality of life.[102,104,105] Women are unlikely to discuss the problem with their health care providers and frequently do not associate the issue with hormone changes or the menopausal transition.[104]

Treatment of GSM can follow a stepwise approach, beginning with meticulous vulvar skin care, including the avoidance of irritants (eg, soaps, detergents, and other products with perfumes or dyes). The use of lubricants (water, silicone, or oil based) as needed for sexual activity is advised to reduce friction and promote comfort and pleasure. Vaginal moisturizers can be used on a regular basis (2-5 times per week) to increase vaginal moisture. It is important to advise patients that it may take 2 months to realize the full effect.[2] There are limited data on the safety of various over-the-counter lubricants and moisturizers, and testing on a small patch of skin for 24 hours before using a product vaginally is recommended.[102] Regular, painless sexual activity may also promote vaginal health, as may the use of a vibrator to increase blood flow.[102] The use of vaginal dilators with or without pelvic floor physical therapy may also be of benefit.

Hyaluronic acid gel is a biopolymer that releases water molecules to the tissues and helps alleviate vaginal dryness. A recent multicenter, randomized, controlled, open-label trial compared hyaluronic acid and estriol cream vaginally applied every 3 days. After 10 applications, there was significant improvement in both groups (84% and 89%, respectively) as measured by patient grading of vaginal dryness and other vaginal symptoms, with no significant difference between the 2 arms.[106] Possible benefit in cancer survivors has been suggested in a pilot trial involving women treated for cervical and endometrial cancers.[107] Further study is needed in cancer survivors.

If conservative measures do not adequately relieve symptoms of GSM, the use of low-dose vaginal estrogen can be considered after consultation with a woman's oncologist. Low-dose vaginal estradiol (eg, 25-μg estradiol vaginal tablets and the low-dose vaginal ring) may result in transient elevations in estradiol levels in women taking aromatase inhibitors.[108,109] The lower 10-μg estradiol vaginal tablets resulted in significant improvements in symptoms and sexual dysfunction without a statistically significant increase in serum estradiol levels after 12 weeks of treatment in 1

TABLE 1. Treatment Options to Consider for Vasomotor Symptoms in Cancer Survivors[a]

Treatment type and specific therapy	Examples and recommended target dose	Notes	References
Lifestyle			
Avoidance of triggers and reduction of body heat	Keeping the room cool; using fans; dressing in layers; wearing open-weave fabrics; avoiding spicy foods, alcohol, and other hot flash triggers	Low cost and nontoxic	9,10
Mind-body			
Cognitive behavioral therapy	Group or self-guided	Reduces hot flash severity, not frequency; requires expertise not widely available	20,21
Hypnosis	Weekly for 3-5 wk	Requires expertise not widely available	22-25
Nonhormone			
Antidepressants (SSRIs and SNRIs)	Venlafaxine 75 mg/d	Can be considered as first-line therapy; escalate and taper dose slowly to avoid adverse effects	40-53,86,97-101
	Desvenlafaxine 150 mg/d	More expensive and less well-studied than venlafaxine	
	Paroxetine 7.5 mg/d	Only FDA-approved therapy for treatment of hot flashes; best to avoid in patients taking tamoxifen due to inhibition of CYP2D6	
	Citalopram 20 mg/d	Preferred first-line therapy for many patients because of low cost, low toxicity, and minimal CYP2D6 inhibition	
	Escitalopram 20 mg/d	Reasonable first-line therapy, but more expensive than citalopram	
Clonidine	0.1 mg/d	Rarely used because of toxicities and availability of alternative options	38,39,96
Gabapentinoids	Gabapentin 900 mg/d	May be particularly helpful for patients with prominent night sweats	56-61,95
	Pregabalin 150 mg/d	More expensive and less well-studied than gabapentin	
Oxybutynin	5 mg twice daily	Recommendation based on published pilot data; placebo-controlled trials needed	62,63
Stellate ganglion blockade	Optimal frequency and duration are unclear	Carries a small risk of damage to vessels and nerves in the neck	64-76
Hormone[b]			
Estrogens	—	Usually not used in survivors of hormonally responsive cancers	6,7,88,89
Progesterone analogs	Megestrol acetate, medroxyprogesterone acetate	Lack of well-defined risk-benefit data in survivors of hormonally responsive cancers	77-84,86,87

[a]CYP2D6 = cytochrome P450 2D6; FDA = Food and Drug Administration; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
[b]Use with caution in survivors of hormonally responsive cancers.

trial,[2] although another trial, using sensitive estrogen testing, supported that all vaginal estrogen preparations are absorbed to some degree.[110] An exploratory study involving 16 postmenopausal breast cancer survivors with vaginal atrophy on aromatase inhibitors looked at the effect of a combination of ultra-low-dose vaginal estriol and lactobacilli on the sexual functioning domain of quality of life and found improvements in vaginal dryness scores and an increase in sexual activity after 12 weeks of treatment.[111]

Because the goal of aromatase inhibitors is to decrease circulating estrogen levels, some

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providers are averse to the use of any form of estrogen in women taking these medications. However, because tamoxifen works in premenopausal women and actually increases estrogen concentrations in these women, giving low-dose vaginal estrogen is unlikely to be harmful concurrent with tamoxifen.

Vaginal dehydroepiandrosterone (DHEA) has been studied in a randomized, double-blind, placebo-controlled, phase 3 clinical trial examining the effect of a DHEA 6.5-mg vaginal suppository vs a DHEA 3.25-mg suppository vs placebo given daily over a 12-week time frame. The 6.5-mg dose was found to be effective after 12 weeks, with improvements in the 4 primary objectives (decrease in parabasal cells, increase in superficial cells, decrease in pH, and decrease in dyspareunia). Vaginal dryness also improved significantly, and serum steroid levels (estradiol, testosterone, and DHEA) remained well within postmenopausal levels; endometrial biopsies at 12 weeks revealed atrophy.[112] In another study, 6.5 mg of intravaginal DHEA used daily for 2 weeks and then decreased to twice per week resulted in loss of the effectiveness achieved with daily dosing when dosing was decreased to twice weekly.[113] Although not yet published in a peer-reviewed journal, a 2014 abstract by Barton et al[114] revealed that survivors of breast and gynecologic cancer experienced improved sexual functioning with intravaginal DHEA therapy, and there was no associated rise in estradiol level for those taking concurrent aromatase inhibitors (presumably because DHEA could not be converted into estrogen without aromatase activity). Two patients experienced facial hair growth, suggesting that androgen levels increased, but this was not thought to be detrimental if it did not lead to increased estrogen levels. However, long-term safety studies of intravaginal DHEA are still needed in women with hormone-responsive cancers.

Ospemifene is an oral selective estrogen receptor modulator that is FDA approved for the treatment of moderate to severe dyspareunia associated with vaginal dryness related to menopause.[115,116] The most frequent adverse effect is hot flashes (6.6% with the 60-mg dose vs 3.6% with placebo). Although no cases of venous thromboembolism were noted during the safety studies, ospemifene has a black box warning due to the known thrombogenic potential of other selective estrogen receptor modulators.[117] Ospemifene seems to block estrogen activity in breast cells in preclinical studies, but there are no human data to support the safety of ospemifene in women with, or at high risk for, breast cancer.[118]

A carbon dioxide laser was recently cleared by the FDA and is marketed for the treatment of vaginal dryness and other symptoms related to GSM. Note that devices are not required to go through the same stringent process involving rigorous scientific study for efficacy and safety that is required of new drugs. Initial small studies using 3 treatments spaced a few weeks apart reported improvements in vaginal symptoms and sexual function.[119,120] However, there is a lack of comparison studies and data regarding long-term safety, and cost is a concern.

Intravaginal oxytocin has been investigated for the treatment of GSM in a recent study involving 64 women who were randomized to receive 400 IU, 100 IU, or placebo gel nightly for 7 weeks. The 400-IU dose improved the percentage of superficial cells and the maturation index and significantly reduced the most bothersome symptom compared with placebo without stimulating the endometrium.[121] Additional study is needed to determine whether this is a safe alternative to low-dose vaginal estrogen for women with a history of breast cancer, although oxytocin has been found to be inhibitory to breast, ovarian, and endometrial cancer cells.[122-124]

Lidocaine used topically at the introitus may be helpful for women with insertional dyspareunia. A small randomized, placebo-controlled study involving 46 women with a history of breast cancer demonstrated relief of sexual pain with the application of 4% aqueous lidocaine to the vulvar vestibule 3 minutes before sexual activity.[125] This may be a practical treatment combined with vaginal lubricants and moisturizers for women who are unable to use hormone treatment options. See Table 2 for treatment options for vaginal dryness and sexual pain in cancer survivors.

SEXUAL DYSFUNCTION

Sexual health is considered an important part of survivorship, and sexual problems are a widespread concern in patients with cancer.[126]

TABLE 2. Treatment Options to Consider for Vaginal Dryness and Sexual Pain in Cancer Survivors[a]

Treatment type and specific therapy[b]	Examples and dosages	Notes	References
Nonprescription			
Lubricants	—	Used as needed for sexual activity	—
Moisturizers	—	Used several times per week to maintain vaginal moisture	102
Hyaluronic acid gel	—	Used intravaginally every 3 d	106,107
Nonhormone			
Topical lidocaine	4% aqueous lidocaine	Applied to the vulvar vestibule as needed several minutes before penetration	125
Hormone[c]			
Low-dose vaginal estrogen	Available in vaginal cream, 10-μg tablet, or ring	Low-level systemic absorption of unclear clinical significance is possible with existing local vaginal estrogen products; not recommended in patients with a history of breast cancer taking aromatase inhibitors	102,108-110
Intravaginal DHEA	3.25 or 6.5 mg of 0.5% intravaginally daily	Long-term safety data in breast cancer survivors are lacking, but no evidence of increased estradiol levels in patients taking aromatase inhibitors	112-114
Ospemifene (oral SERM)	60 mg/d by mouth	Not FDA approved for use in women with or at high risk for breast cancer	115-118

[a]DHEA = dehydroepiandrosterone; FDA = Food and Drug Administration; SERM = selective estrogen receptor modulator.
[b]Nonprescription treatments are first-line therapies; nonprescription and nonhormonal treatment options are preferred in survivors of hormonally responsive cancers.
[c]Use with caution in survivors of hormonally responsive cancers.

However, patients frequently do not communicate with their health care providers about sexual health concerns, despite wanting their providers to ask about it.[127] The treatments commonly used to treat breast cancer, including surgery, chemotherapy, and endocrine therapy, can have a significant effect on sexual function and quality of life.[128-130] The sexual health challenges facing women with breast cancer are well-described and include body image concerns, infertility, relationship issues, lack of sexual desire, difficulty with orgasm, sexual pain, and vaginal dryness.[55] Women may enter menopause abruptly as a result of chemotherapy or hormone blockade, and even those who were already menopausal may lose some residual ovarian androgen production, resulting in new or worsening VMS, which can be severe and persistent.[2,131]

In addition to the treatment of vaginal dryness with the measures described previously herein, women may benefit from a multidisciplinary approach to sexual dysfunction that incorporates a biopsychosocial model of the female sexual response.[132] This model addresses the biological, psychological, sociocultural, and relational components that might be affecting a woman's sexual health (eg, vaginal dryness, sexual pain, concerns about body changes, family stressors, mood disorders, and relationship factors). A woman may also benefit from working with a psychologist or sex therapist, particularly if there are relationship concerns, body image issues, changes in sexual functioning or sexual pain, or mood disorders. Physical therapy with a therapist trained in the management of pelvic floor disorders can be helpful for the management of tight, tender pelvic floor muscles and to improve kinesthetic awareness, promote relaxation of the pelvic floor muscles, direct dilator therapy, and decrease fear of penetration.[132,133]

CONCLUSION

There are a variety of treatment modalities that can help alleviate bothersome VMS in cancer survivors, including antidepressant agents, gabapentinoids, and clonidine. Other therapies, including CBT and hypnosis, have been found to be efficacious but are underused owing to the additional expertise required. Stellate ganglion blocks and therapies directed toward men with VMS show promise but require additional study.

Genitourinary function and sexual health are also important considerations in cancer

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survivorship care. Vaginal lubricants and moisturizers, vaginal dilators, physical therapy, and sometimes even low-dose vaginal estrogen can be considered as treatment options for GSM. New and novel therapies for the treatment of vaginal dryness and sexual pain that require more study in this population include intravaginal DHEA, intravaginal oxytocin, carbon dioxide laser treatment, ospemifene, and lidocaine. Using a multidisciplinary approach to the management of sexual health concerns can be beneficial.

Abbreviations and Acronyms: **CBT** = cognitive behavioral therapy; **CYP2D6** = cytochrome P450 2D6; **DHEA** = dehydroepiandrosterone; **FDA** = Food and Drug Administration; **GSM** = genitourinary syndrome of menopause; **MPA** = medroxyprogesterone acetate; **SERM** = selective estrogen receptor modulator; **SGB** = stellate ganglion blockade; **SNRI** = serotonin norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **VMS** = vasomotor symptoms

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The Symposium on Neoplastic Hematology and Medical Oncology will continue in an upcoming issue.

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