Menopausal Symptoms in Young Survivors of Breast Cancer: A Growing Problem Without an Ideal Solution

Vijayashree Murthy, MS, DNB, MCh, and Ronald S. Chamberlain, MD, MPA, FACS

Background: New breast cancers occur in 25% to 30% of women < 50 years of age. These young women undergo ablative surgery, chemotherapy, or hormonal/targeted treatment. These treatments have resulted in increased survival but at the expense of early menopause, marked by distressing vasomotor symptoms, sexual dysfunction, decreased metabolism, and musculoskeletal and cardiovascular effects.

Methods: A comprehensive literature search was performed using PubMed. This article reviews the evidence-based approaches to the treatment of these distressing symptoms in young breast cancer survivors.

Results: Menopausal symptoms in young patients are typically more severe due to the abrupt and rapid decrease in estrogen, and chemotherapy and hormones worsen these symptoms. Evidence supporting the efficacy of most complementary therapies is scarce. Behavioral modification and yoga may be helpful in mild cases of vasomotor symptoms, whereas newer antidepressants are promising in moderate to severe cases, and stellate ganglion block may be used in refractory cases. Local vaginal moisturizers, and in refractory cases low-dose estrogen creams, may ameliorate most urogenital symptoms. Bisphosphonates, vitamin D, and calcium can treat osteoporosis, and weight-bearing exercises decrease bone mineral density loss and help to control weight. Smoking cessation, exercise, and dietary modifications should be recommended to all young patients to decrease cardiac morbidity. At present, there is insufficient evidence to support any natural agent as a viable alternative to hormone replacement therapy to treat these symptoms.

Conclusions: No single agent can ameliorate vasomotor, cardiac, skeletal, and sexual concerns of young breast cancer survivors coping with menopausal symptoms. Quality-of-life research involving premenopausal breast cancer survivors is lacking. Further study is needed to identify safe and effective treatments for menopausal symptoms and to confirm their long-term safety in young breast cancer survivors.

Introduction

In 2010, approximately 207,090 new cases of breast cancer were diagnosed, with 26.4% occurring in women under the age of 50. Breast cancer death rates have decreased since 1990, with larger decreases occurring in women younger than age 50 (3.2% per year) than in older women (2% per year). Improvement in breast cancer mortality is multifactorial and is at least partly attributable to early detection and improved treatment. The etiology of breast cancer is multifactorial, and surgery is the mainstay for local control of breast cancer. However, the use of adjuvant chemotherapy...
and/or hormonal and targeted therapies has steadily increased in an effort to eradicate micrometastases and expand cure rates. At present, breast cancer survivors represent the largest group of cancer survivors in the United States (22%). Given that over a quarter of all breast cancer patients are premenopausal, in conjunction with a steady decline in mortality rate for this group with the use of adjuvant therapy, the issue of premature menopause warrants increasing attention.

The National Comprehensive Cancer Network (NCCN) defines menopause as a permanent cessation of menses; when applied to breast cancer management, it includes a profound and permanent decrease in ovarian estrogen synthesis (Table 1). In patients receiving adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status, as ovarian function may remain intact or may resume despite anovulation/amenorrhea after chemotherapy. If the use of aromatase inhibitors is considered as a component of endocrine therapy, serial measurements of follicle-stimulating hormone (FSH) and/or estradiol levels are needed to ensure postmenopausal status.

Table 2 summarizes the treatment options of premature menopause. In 1997, the University of California at Los Angeles (UCLA) initiated the Cancer and Menopause Study (CAMS) to evaluate the quality of life and health outcomes of young female breast cancer survivors, focusing on reproductive and late treatment-related effects. Hot flashes and night sweats occurred less often in the youngest women (20% prevalence in those age 25 to 34 years) but increased with age (65% in those age 45 to 51 years). However, weight gain and unhappiness with body appearance were exceedingly common (80% to 85% prevalence in all age groups). Vaginal dryness and dyspareunia were age-related, likely paralleling changes in menopausal status (20% for those age 25 to 34 years and 55% for those age 45 to 51 years).

In a prospective cohort study of 1,011 women treated for breast cancer, Panjari et al found that 70% experienced sexual dysfunction and 77% reported vasomotor symptoms (VMS). Women with VMS were twice as likely to experience sexual dysfunction (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.41–2.63; \( P < .001 \)). Women with body image issues were 2.5 times more likely to report sexual function problems (OR, 2.5; 95% CI, 1.6–3.7; \( P < .001 \)). Complicating the management of menopausal symptoms in breast cancer survivors is the prohibition on the use of hormonal therapies, which may be mitogenic to breast cancer. Management of life-altering menopausal symptoms is an important yet often unaddressed part of the ongoing care of young breast cancer survivors.

### How Common Is Treatment-Induced Menopause, and Who Is Affected?

In normal premenopausal women, FSH produced by the pituitary gland stimulates ovarian follicular granulosa cells to produce estradiol. This process

![Table 1. — The National Comprehensive Cancer Network (NCCN) Criteria for Menopause](image)

<table>
<thead>
<tr>
<th>Prior bilateral oophorectomy</th>
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</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
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<tr>
<td>Age &lt; 60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and coupled with follicle-stimulating hormone (FSH) and estradiol levels in the postmenopausal range</td>
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<tr>
<td>If taking tamoxifen or toremifene and age &lt; 60 years, FSH and plasma estradiol levels should be in the postmenopausal range</td>
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</tbody>
</table>

### Table 2. — Common Menopausal Symptoms and Current Management Options for Premature Menopause

<table>
<thead>
<tr>
<th>Menopausal Symptoms</th>
<th>Current Treatment Options Available</th>
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<tbody>
<tr>
<td><strong>Pharmacologic Treatment</strong></td>
<td><strong>Nonpharmacologic Approach</strong></td>
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<tr>
<td>Vasomotor symptoms (hot flashes)</td>
<td>Vitamin E</td>
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<tr>
<td>Clonidine</td>
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<tr>
<td>Gabapentin</td>
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<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>Stellate ganglion block</td>
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<td>Estrogen cream</td>
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<td>Nonhormonal vaginal moisturizers</td>
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<td>Balanced diet</td>
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<td>Smoking cessation</td>
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<td>Exercise</td>
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<td>Aerobic exercise</td>
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<td>Resistance training</td>
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<td>Calcium</td>
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<td>Vitamin D</td>
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<td>Bisphosphonates</td>
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<td>Aromatase inhibitors</td>
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provide a negative feedback “shutting off” the production of FSH. Premenopausal women typically have low FSH levels (<10 mIU/mL). However, in ovarian failure (either physiological or therapy-induced menopause), estradiol levels decline and FSH levels increase. Menopausal levels of FSH are usually higher than 40 mIU/mL. Drug-induced amenorrhea has been defined as the cessation of menses for at least 3 months during or soon after the administration of adjuvant chemotherapy, the cessation of menses for 6, 8, or 12 months, or the cessation of menses during chemotherapy without subsequent resumption.9,10

Risk of early menopause with polyagent adjuvant chemotherapy is in the range of 26% to 89%.11 The extent of chemotherapy-induced follicular damage may result in preservation of menses, temporary amenorrhea, irregular menses (perimenopause), or complete ovarian failure (menopause). Although the mechanism is not fully understood, in vitro studies suggest apoptotic changes in pregranulosa cells result in direct follicular damage.12 Simply put, chemotherapy causes destruction of the primordial follicles and impairment of follicular maturation.13

The frequency of chemotherapy-related amenorrhea (CRA) varies with age, cytotoxic agents used, and total cumulative dose.14 The likelihood of premature menopause with alkylating agents is influenced by both the cumulative dose and the duration of therapy.15 A low incidence (9%) of CRA has been reported in regimens without alkylating agents (eg, methotrexate plus 5-fluorouracil [MF]), whereas chemotherapy with cyclophosphamide (12 cycles) has a high percentage of drug-induced amenorrhea (82%).16 Goodwin et al17 reported that 5% to 40% of women younger than 40 years of age who receive cyclophosphamide and MF (CMF) or an anthracycline (such as epirubicin, CEF) for 6 to 9 cycles will develop amenorrhea in 4 to 8 months; in women over the age of 40, the incidence is 20% to 100% within 2 to 4 months (Fig 1).

Three separate studies have investigated the incidence of amenorrhea following doxorubicin (Adriamycin) and cyclophosphamide (AC) × 4 cycles with or without a taxane (T). Stone et al18 analyzed 98 premenopausal women 50 years of age or younger treated with AC or AC + T. They reported an overall incidence of CRA for women older than age 40 receiving AC or AC + T of 43% and 38%, respectively. Swain et al19 analyzed 528 women receiving AC + T with or without tamoxifen. They reported a 14% rate of amenorrhea by 12 months in those < age 30, a 33% rate for women 30 to 40 years of age, and a rate of 70% for women aged 41 to 50 years, again reinforcing that the incidence of CRA increases with age. In an evaluation of 166 breast cancer patients aged 40 years or younger, Fornier et al20 found 15% of women were amenorrheic at 1 year following AC and 17% were amenorrheic when AC was combined with tamoxifen. The median age of women with amenorrhea was 38 years compared with 36 years for women who maintained menses (P < .01).

These findings imply that 4 cycles of AC with or without a taxane is associated with a lower incidence of amenorrhea in younger women (< age 40) than is 6 cycles of CMF. This benefit is limited to those < 40 years of age, as women > 40 years who receive AC with or without a taxane have a > 70% risk of becoming menopausal.18,19 Younger women also appear to require higher cumulative doses of chemotherapy to develop chemotherapy-related menopause. The average dose of single-agent cyclophosphamide received before the onset of amenorrhea was 5,200 mg, 9,300 mg, and 20,400 mg among women 40, 30, and 20 years of age, respectively.21

In premenopausal women with endocrine-responsive tumors, the additive effect of endocrine therapies after locoregional treatment and systemic chemotherapy has been shown to improve recurrence-free as well as overall survival in patients < 50 years.22,23 Cuzick et al24 analyzed 11,906 patients and reported a significant reduction in both disease recurrence (12.7%) and death (15.1%) with the addition of a luteinizing hormone-releasing hormone (LHRH) agonist and tamoxifen to chemotherapy among premenopausal women with estrogen receptor-positive breast cancer. Unfortunately, the combination of chemotherapy along with hormonal manipulation also increased the risk for early menopause and a resultant loss in child-bearing capacity in association with other symptoms in these premenopausal women. Goodwin et al25 reported that use of either CMF or CEF, whether in combination with tamoxifen or not, increased the risk of menopause in 40-year-old women from less than 5% to more than
even after therapy cessation. This finding may be of
Therapy in Breast Cancer Survivors
than 3,000 incident ovarian cancers were detected,
and were followed for 10 years (1995–2005). More
1 million women aged 50 to 79 years who used HRT
motion-based prospective cohort study involving nearly
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cancer but a trend toward increased lung
decrease in fracture rate and a possible decreased risk
further study of HRT in patients with breast cancer. In
of nonhormonal pharmacologic therapies for the
itching occurred in 45.2% vs 36.9% in the placebo
group (RR, 1.23). These results demonstrate that va-
somotor and gynecologic symptoms are consistently
more common in tamoxifen-treated patients.25

Risk vs Benefit of Hormone Replacement Therapy in Breast Cancer Survivors
While hormone replacement therapy (HRT) is com-
monly used in women without breast cancer to pre-
vent or treat menopausal sequelae, its use in breast
cancer survivors is highly prohibitive. The Women's
Health Initiative (WHI) trial and the Hormone Re-
placement Therapy After Breast Cancer: Is It Safe?
(HABITS) trial have both demonstrated an increase in
adverse events among women treated with HRT.26,27

In the HABITS trial, at a median follow-up of 2.1
years, 26 patients in the HRT group and 7 patients in
the non-HRT group had a new breast cancer event
that was considered sufficiently serious to abandon
further study of HRT in patients with breast cancer. In
the WHI trial, women in the estrogen-plus-progestin
group experienced a 26% increase in breast cancer
(38 vs 30 per 10,000 person-years) in addition to an
increased risk of coronary artery disease, stroke, and
pulmonary embolism. Of note, the WHI did report a
decline in fracture rate and a possible decreased risk
of colorectal cancer but a trend toward increased lung
cancer in women receiving HRT.28 At a mean follow-
up of 5.6 years and 2.4 years of additional follow-up,
the hazard ratio (HR) for lung cancer diagnosis was
1.23, with a 95% CI of 0.92–1.63 along with increased
mortality (73 vs 40 deaths, respectively; HR, 1.71;
95% CI, 1.16–2.52; P = .01) with the risk continuing
even after therapy cessation. This finding may be of
greater concern for hormone users who are smokers
or have other risk factors for lung cancer.

Moreover, several recent studies have shown a
small but significantly increased risk of epithelial
ovarian cancer in current and recent users of estrogen
therapy.29 Mørch et al reported a Danish popula-
tion-based prospective cohort study involving nearly
1 million women aged 50 to 79 years who used HRT
and were followed for 10 years (1995–2005). More
than 3,000 incident ovarian cancers were detected,
of which 2,681 were epithelial cancers. When com-
pared with women who never took hormone therapy,
users of HRT had an RR of 1.38 (95% CI, 1.26–1.51)
for all ovarian cancers and 1.44 (95% CI, 1.30–1.58)
for epithelial ovarian cancer. The risk declined after
cessation of therapy. Based on these studies, it is
nearly universally agreed that HRT should not be
used for treatment of menopausal symptoms in breast
cancer survivors.

Current Approaches to Treat Menopausal Symptoms in Breast Cancer Survivors
Currently available treatments for menopausal symp-
toms include hormonal treatment, nonhormonal phar-
maceuticals, and herbal and complementary medi-
cines. The efficacy of each of these approaches is
widely variable. Table 2 outlines the clinical concerns
of premature menopause and the current management
options. The remainder of this article provides an
evidence-based review of these therapies in an effort
to help develop guidelines for appropriate treatment
selection based on severity of symptoms. However,
given the lack of significant information for many
therapeutic approaches such as homeopathy and al-
ternative medicine, it is important to reiterate that
patient demand alone is an inappropriate means to
determine treatment options, and randomized con-
trolled trials are needed to definitively address many
ongoing questions.

Menopausal VMS
Hot flashes are the most commonly perceived and
reported menopausal symptom. Although their pre-
cise pathophysiological mechanism is unknown,
decreased estrogen levels are believed to cause an
induction in noradrenergic hyperactivity, which leads
to a heat loss response and the sensation of warmth
throughout the body followed by sweats. Serotonin
may also play an important role in thermoregulation,
and increased serum levels and upregulation of se-
rotonin receptors in the hypothalamus are associated
with estrogen withdrawal. In a prospective Swedish
population-based cohort study of 6,917 women,
Li et al found that the frequency and severity of
hot flashes in oophorectomized women were 3-fold
higher than in individuals undergoing natural meno-
pause (P < .001). Among breast cancer survivors, the
incidence of VMS has been managed with a variety of
nonpharmacologic estrogen alternatives and phar-
maceutics. The efficacy of each of these approaches is
widely variable. Table 2 outlines the clinical concerns
of premature menopause and the current management
options. The remainder of this article provides an
evidence-based review of these therapies in an effort
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therapeutic approaches such as homeopathy and al-
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patient demand alone is an inappropriate means to
determine treatment options, and randomized con-
trolled trials are needed to definitively address many
ongoing questions.

Table 3 presents all published clinical trials evalu-
ating nonhormonal pharmacologic therapies for the
management of menopausal VMS. Vitamin E has been used
as a treatment of hot flashes as well as a means to
maintain good health, with the belief that it acts as
an estrogen substitute and may result in slightly bet-
ter relief than placebo; hence, it also is called the
“menopausal vitamin.” Barton et al studied 120
breast cancer patients who reported at least 14 episodes of hot flashes per week. These patients were randomized to receive 4 weeks of vitamin E 800 IU daily or placebo followed by a 4-week crossover. Hot flashes were reduced by 25% with vitamin E, compared with 22% with placebo (P = .90). However, the crossover analysis demonstrated that vitamin E significantly reduced hot flashes (17% vs 0.04%; P ≤ .05) and showed no statistically significant differences in toxicity between the two arms.

Miller et al44 conducted a meta-analysis of 19 vitamin E trials, with doses ranging from 16.5 to 2,000 IU daily. They reported that 9 of 11 trials using high-dose vitamin E (≥ 400 IU daily for at least 1 year) showed an increased risk for all-cause mortality. Moreover, the safety of vitamin E at higher doses (>1,000 mg corresponding to 1,100 IU of synthetic vitamin E per day or 1,500 IU natural vitamin E per day) along with other antioxidants such as beta carotene and selenium is related not only to increased mortality but also to an increased risk of heart failure and gastrointestinal cancer.45 As such, vitamin E cannot be recommended as an effective treatment for hot flashes at this time.

**Clonidine:** Clonidine hydrochloride is primarily indicated for the treatment of hypertension and is a centrally acting α-agonist that reduces vascular reactivity. It reduces the release of epinephrine in the brain, raises the sweat threshold, and may ameliorate hot flashes. Clonidine has been tested in doses ranging from 0.1 mg/d to 0.4 mg/d both orally and transdermally. Clayden et al35 studied 100 postmenopausal patients who received clonidine tablets containing 25 μg and then increased to 75 μg for 4 weeks followed by a placebo crossover for 4 weeks. They reported a significant reduction in the frequency of hot flashes (clonidine before placebo, P ≤ .05; clonidine after placebo, P ≤ .001). Pandya et al36 treated 194 breast cancer patients with tamoxifen-induced hot flashes with oral clonidine 0.1 mg/d or placebo for 8 weeks. The frequency of hot flashes decreased by 37% (vs 20% for placebo) after 4 weeks of treatment and by 38% (vs 24% for placebo) after 8 weeks of treatment. Despite a decreased frequency in hot flashes, both studies reported distressing side effects, including sleep difficulties, dry mouth, constipation, and skin reactions. Given its significant side effect profile, clonidine currently has only a limited role as a treatment of menopausal VMS.

**Gabapentin:** This is a gamma-aminobutyric acid used to treat convulsions and postherpetic neurogenic pain. Multiple randomized controlled trials have evaluated the efficacy of gabapentin for the treatment of hot flashes of menopausal vasomotor symptoms (VMS). Table 3 shows selected published trials on the use of nonhormonal pharmacologic therapies for VMS.

Table 3. — Selected Published Trials on the Use of Nonhormonal Pharmacologic Therapies for Menopausal Vasomotor Symptoms

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Treatment</th>
<th>Sample; Duration</th>
<th>Results</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barton et al34 (1998)</td>
<td>Vitamin E 800 IU/d</td>
<td>120 breast cancer patients; 8 wks</td>
<td>Reduction in hot flashes by 25% vs 22% with placebo</td>
<td>No statistically significant difference in toxicity between the treatment arms</td>
</tr>
<tr>
<td>Clayden et al35 (1974)</td>
<td>Clonidine 25 μg to 75 μg b.i.d.</td>
<td>100 postmenopausal women; 4 wks</td>
<td>Decrease in frequency of hot flashes (clonidine before placebo, P ≤ .05; clonidine after placebo, P ≤ .001)</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Pandya et al36 (2000)</td>
<td>Clonidine 0.1 mg/d</td>
<td>194 postmenopausal women; 8 wks</td>
<td>Reduction in hot flashes by 38% vs 24% with placebo</td>
<td>Dry mouth, difficulty sleeping</td>
</tr>
<tr>
<td>Guttuso et al37 (2003)</td>
<td>Gabapentin 900 mg/d</td>
<td>59 postmenopausal patients; 12 wks</td>
<td>Reduction in hot flash frequency by 45% and hot flash composite score (frequency and severity) by 54%</td>
<td>Dizziness, skin reaction, and excessive sleepiness</td>
</tr>
<tr>
<td>Pandya et al38 (2005)</td>
<td>Gabapentin 300 mg/d or 900 mg/d</td>
<td>420 breast cancer patients; 8 wks</td>
<td>Reduction in hot flash severity score by 31% for patients on 300 mg and 46% for those on 900 mg</td>
<td>No side effects reported</td>
</tr>
<tr>
<td>Biglia et al39 (2009)</td>
<td>Gabapentin 900 mg/d or vitamin E 800 IU/d</td>
<td>115 breast cancer patients; 12 wks</td>
<td>Reduction of hot flashes by 67% for gabapentin and 57% for vitamin E (P &gt; .05)</td>
<td>Somnolence, dizziness, and dry mouth in patients on gabapentin</td>
</tr>
<tr>
<td>Evans et al40 (2005)</td>
<td>Venlafaxine 75 mg/d</td>
<td>80 postmenopausal women; 12 wks</td>
<td>Reduction in hot flashes by 51% vs 15% with placebo</td>
<td>Dry mouth, decreased sleep and appetite</td>
</tr>
<tr>
<td>Loprinzi et al41 (2000)</td>
<td>Venlafaxine 37.5 mg/d, 75 mg/d, or 150 mg/d</td>
<td>191 postmenopausal women; 4 wks</td>
<td>Reduction in hot flashes by 37%, 61%, and 61% in the 3 treatment arms, respectively, vs 27% with placebo</td>
<td>Dry mouth, constipation</td>
</tr>
<tr>
<td>Bordeleau et al42 (2010)</td>
<td>Venlafaxine 37.5 mg/d × 1 wk then 75 mg/d × 3 wks vs gabapentin 300 mg once daily × 3 d then 300 mg b.i.d. × 3 d then 300 mg t.i.d. × 22 days</td>
<td>66 breast cancer patients; 4 weeks</td>
<td>Reduction in hot flash severity by 66% in both arms</td>
<td>Dizziness and negative mood changes in patients on gabapentin</td>
</tr>
<tr>
<td>Loprinzi et al43 (2002)</td>
<td>Fluoxetine 20 mg/d</td>
<td>81 breast cancer patients; 4 weeks</td>
<td>Reduction in hot flashes by 50% vs 36% for placebo</td>
<td>No side effects reported</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily, t.i.d. = three times a day
flashes. Guttuso et al\textsuperscript{37} evaluated 59 postmenopausal women who were treated with 900 mg of gabapentin orally or placebo for 12 weeks. They reported a 45\% reduction in hot flash frequency and a 54\% reduction in hot flash composite score (frequency and severity). Pandya et al\textsuperscript{38} evaluated 420 breast cancer patients treated with gabapentin 300 mg/d, gabapentin 900 mg/d, or placebo for 8 weeks. The hot flash severity score was 15\%, 31\%, and 46\%, respectively. Biglia et al\textsuperscript{39} studied the efficacy and tolerability of gabapentin (900 mg/d) vs vitamin E (800 IU/d) in the treatment of VMS among 115 breast cancer patients. The hot flash frequency score decreased by 66.9\% and 57.1\%, respectively ($P > .05$), suggesting that gabapentin was more effective than vitamin E while also having a favorable effect on the quality of sleep.

All of these studies reported light-headedness, excessive sleepiness, and rash with gabapentin. At present, although gabapentin can be considered effective in the management of hot flashes, additional clinical information is needed regarding its side effects and safety.

**Selective Serotonin Reuptake Inhibitors and Selective Noradrenergic Reuptake Inhibitors**

**Venlafaxine:** Venlafaxine affects the reuptake of serotonin and norepinephrine. Evans et al\textsuperscript{40} studied oral venlafaxine (75 mg/d) vs placebo in 80 postmenopausal women over a 12-week period. There was a corresponding 51\% reduction in the hot flash score in the venlafaxine group compared with 15\% reduction in placebo. The difference between the groups linearly increased from $P < .001$, respectively, with venlafaxine. Loprinzi et al\textsuperscript{41} treated 191 breast cancer patients with oral venlafaxine (37.5 mg/d, 75 mg/d, or 150 mg/d) vs placebo for 4 weeks. Hot flashes were reduced with venlafaxine by 37\%, 61\%, and 61\%, respectively, compared with 27\% for placebo.

In a recent multicenter randomized crossover clinical trial for the treatment of hot flashes, 66 patients were randomly assigned to 4 weeks of venlafaxine (37.5 mg daily for 7 days followed by 75 mg daily for 21 days) or gabapentin (300 mg once per day for 3 days, then 300 mg twice per day for 3 days, then 300 mg 3 times per day for 22 days), with patient preference as the primary outcome.\textsuperscript{42} In this group of patients, 32\% preferred gabapentin and 68\% preferred venlafaxine ($P = .01$). Both agents reduced hot flash scores to a similar extent (66\% reduction); however, treatment with venlafaxine was associated with fewer negative mood changes ($P = .01$) and less dizziness ($P = .005$). Venlafaxine appears to be effective in the management of hot flashes among breast cancer survivors. A decrease in libido is a common adverse effect of selective serotonin reuptake inhibitors (SSRIs), and their efficacy when used over a prolonged period (more than 12 weeks) remains unknown.

Boekhout et al\textsuperscript{43} evaluated 102 patients randomized to receive venlafaxine 75 mg, clonidine 0.1 mg, or placebo orally for 12 weeks. They found that hot flash scores were significantly lower with clonidine vs placebo and venlafaxine vs placebo ($P = .03$ and .07, respectively) but were equal in both arms. They concluded that venlafaxine and clonidine are equally effective in the management of hot flashes.

**Fluoxetine:** Fluoxetine is another distinct SSRI that has been evaluated in a randomized placebo-controlled crossover trial in the United States ($N = 81$).\textsuperscript{46} Fluoxetine 20 mg/d was associated with a 50\% decrease in hot flash scores at the end of the first 4-week treatment period compared with a 36\% decrease in those receiving placebo. Subsequent analysis of the crossover data indicated that patients reported median improved reductions of 1.5 hot flashes per day (19\%) and 3.1 score units per day (24\%) on fluoxetine compared with those seen with the placebo ($P < .01$ and .02, respectively). Women taking fluoxetine were also less likely to complain of insomnia. Given that mood disorders are a common presentation among breast cancer survivors, antidepressants may provide relief for more than just hot flashes, although their long-term efficacy and toxicity need to be addressed.

**Paroxetine:** Paroxetine is another SSRI used for the treatment of hot flashes. In a randomized placebo-controlled crossover trial, Stearns et al\textsuperscript{47} randomized 151 women to receive either 4 weeks of paroxetine 10 mg or 20 mg followed by placebo. They found that paroxetine 10 mg reduced the frequency of hot flashes by 40.6\% compared with 13.7\% for placebo ($P = .0006$) and 20 mg reduced hot flash frequency by 51.7\% compared with 26.6\% for placebo ($P = .002$).

**Citalopram:** The antidepressant citalopram is a moderate inhibitor of CYP2D6 and has minimal effect on tamoxifen metabolism. Barton et al\textsuperscript{48} randomized 254 women to receive placebo or citalopram 10, 20, or 30 mg orally for 6 weeks. Reductions in mean hot flash scores were 23\% (placebo), 49\%, 50\%, and 55\%, respectively, with no significant side effects. The advantages of citalopram over other agents are that unlike paroxetine, it can be given with tamoxifen and only 10 mg/dL of citalopram is needed for a 46\% reduction in the daily frequency of hot flashes.

**Stellate Ganglion Block**

This procedure aims to interrupt parts of the sympathetic nervous system involved in temperature regulation. The stellate ganglion block has been used to treat sleep dysfunction, which is often reported by patients on antiestrogen therapy. Lipov et al\textsuperscript{49} conducted a pilot study on 13 breast cancer survivors who reported severe hot flashes and night awakenings. The block was performed at the anterolateral aspect of the C6 vertebra under fluoroscopy, and 7 mL of 0.5\% bupivacaine was injected to produce a sympathetic block. Hot flashes decreased from a mean of 79.4 (standard deviation [SD], 37.4) per week prior to the procedure to a mean of 49.9 (SD, 39.9) per week during the first 2 weeks after the procedure ($P \leq .07$).
At present, the use of a single homeopathic medicine is not the gold standard in homeopathic care, as the numbers in these trials were too small to provide meaningful results. Although no major adverse events were reported with the use of these drugs, homeopathic medicine cannot be recommended as effective treatments of VMS until well-controlled, high-quality clinical trials assessing the safety and efficacy of these therapies in breast cancer patients have been conducted.

Chinese Herbs: Dong quai is a traditional Asian herbal preparation made from the root of *Angelica sinensis* and used to treat menopausal symptoms. It can be employed as a general blood tonic for purifying and increasing blood flow and as a valuable remedy for anemia. It is also a common traditional

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**Complementary/Alternative Therapies**

The percentage of breast cancer survivors who receive alternative therapies during or after definitive treatment for breast cancer is unknown. In addition to minerals, multivitamins, antioxidants, and acupuncture, several herbal anticancer preparations, homeopathic remedies, and plant estrogens (such as phytoestrogens, black cohosh, and dong quai) have been tested as treatments for VMS. Although the mechanism of action of these plant preparations is not clear, their estrogenic characteristics have induced endometrial hyperplasia and lowered FSH levels in experimental animals. In addition, they may also have an antiproliferative effect on breasts and a positive effect on bone mineral density (BMD).

**Homeopathy:** Many homeopathic medicines have been used in the treatment of VMS, including *Lachesis mutus*, *Belladonna*, *Sepia officinalis*, *Sulphur*, *Sanguinaria canadensis*, and *Amylum nitrosum*. To date, two randomized placebo-controlled studies have evaluated the use of homeopathic medicine either alone or in combination. Jacobs et al analyzed 83 breast cancer survivors (mean age, 55 years), and Thompson et al evaluated 45 breast cancer survivors (mean age, 52 years) who received either an individualized medicine, a formulaic complex remedy containing three medicines — *Amyl nitrate* 3 × [1:1,000 dilution], *Sanguinaria canadensis* 3 × [1:1,000 dilution], and *Lachesis* 12 × [1:1,000,000,000,000 dilution] — or a placebo. They reported no significant difference in the severity or frequency of hot flashes. Of note, women taking the combination homeopathic remedy did experience increased headaches.

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**Fig 2.** Proposed algorithm for the management of vasomotor symptoms in young breast cancer survivors.
Chinese medicine for gynecologic indications, including irregular menstruation, premenstrual symptoms, and menstrual cramps, and for relief of peri- or post-menopausal syndrome.

In a double-blind trial of 71 women randomized to receive dong quai (4.5 g/d of aqueous extract standardized to 0.5 mg/kg of ferulic acid) or placebo for 24 weeks, there was no difference noted in hot flashes between the two groups. Dong quai has been reported to have estrogen agonist activity, and at this point, a lack of efficacy makes it an inappropriate choice for the management of VMS in breast cancer patients.

**Black Cohosh:** Black cohosh (Actaea racemosa) is a perennial plant native to eastern and central parts of North America that contains triterpene glycosides, phenolic acids, flavonoids, tannins, and volatile oils. It has been used to treat premenstrual symptoms, dysmenorrhea, induction of menopause, and more recently hot flashes. Its mechanism of action is not fully understood, and data are conflicting regarding the estrogenic effect of black cohosh (as a partial agonist at the 5-HT1A [5-hydroxytryptamine] and µ-opiate receptors with possible affinity to dopamine 2 receptors).

In a series of 136 breast cancer survivors randomized to receive either 20 mg of the herbal preparation or placebo for 12 months, Hernández Muñoz et al. found a reduction in the severity and frequency of hot flashes, which were reported by 24.4% of patients in the intervention group and 73.9% in the usual-care group (P < .01) with no adverse events. However, in a separate study, Jacobson et al. studied 85 patients randomized to receive black cohosh or placebo for 60 days, with reports of no effect on the severity of hot flashes (P = .04). It may also be hepatotoxic in the long term, thus it is not an ideal alternative for the treatment of hot flashes.

**Soy Phytoestrogens:** These naturally occurring plant estrogens activate human estrogen receptor-alpha and -beta and have been shown to have estrogenic and antiestrogenic properties due to their structural similarity with mammalian estrogens. Soy and flax are considered the richest sources. The three most abundant isoflavones in soybeans are genistein, daidzein, and glycitein. The effects of these compounds in vitro have led to the hypothesis that soy isoflavones may be associated with a decrease in some cancers, especially hormone-dependent cancers such as breast and prostate, by inhibiting several key enzymes involved in carcinogenesis as well as providing protective effects on BMD loss.

Quella et al. studied 177 breast cancer patients who were randomized to receive 150 mg of isoflavones daily for 9 weeks or placebo. No difference in the symptoms was seen between the two groups.

Van Patten et al. conducted a double-blind randomized controlled trial in 125 breast cancer patients on tamoxifen therapy who reported moderate hot flashes. Women received either a soy beverage containing 90 mg of isoflavones daily or a placebo rice beverage. No difference in hot flashes or hot flash scores was identified. Currently, no convincing evidence has been reported to suggest any substantial benefit of phytoestrogens for VMS.

**Yoga and Relaxation:** Yoga is an increasingly popular mind/body discipline that holds promise for reducing menopausal symptoms in breast cancer survivors. Increased sympathetic activation and psychological distress are common triggers for hot flashes, and through increased relaxation, vigor, and acceptance, yoga may have a beneficial impact on VMS in breast cancer survivors.

Meditation, deep breathing, and relaxation techniques of yoga have been evaluated not only for controlling hot flashes but also for reducing stress and anxiety. Carson et al. randomized 37 disease-free breast cancer patients experiencing hot flashes to an 8-week yoga program or a wait-list control. The primary aim of this study was to test whether changes in hot flash total scores would be significantly different in the yoga vs the control group after treatment and at subsequent follow-up. Following treatment, women who participated in the yoga program showed significantly greater improvements relative to the control group in hot flash frequency, severity, and total scores (P < .001) as well as in the levels of joint pain (P < .001), fatigue, sleep disturbance, symptom-related bother (P < .001), and vigor (P < .05). At 3-month follow-up, patients maintained their treatment gains in hot flashes (P < .001) and showed significant gains in mood, relaxation, and acceptance.

Chattha et al. analyzed 120 patients who participated in the 8-week yoga program or regular physical exercises and found a significant decrease in VMS in the yoga program group (P < .05). Yoga significantly decreased climacteric symptoms, perceived stress, and neuroticism in perimenopausal women compared with physical exercise. The results of these two trials provide promising support for the beneficial effects of a comprehensive yoga program to treat hot flashes and other menopausal symptoms in early-stage breast cancer survivors. An integrated approach to yoga therapy potentially represents a preferred nonhormonal, lifestyle-modifying regimen for symptomatic perimenopausal women.

**Behavioral and Lifestyle Modification:** Simple strategies such as wearing lighter clothes, dressing in layers, keeping the room temperature low, avoiding alcohol and spicy foods, and drinking cold beverages all help to alleviate VMS. Studies have repeatedly demonstrated that climacteric symptoms are related to lifestyle habits such as diet, exercise, and rest. Moreover, the quality of life of women who exercise regularly may be better in terms of psychological health, life satisfaction, and social participation and support than that of those who do not. Several authors have reported that even low-intensity aerobic exercise 3 times a week for 10 to 12 weeks alleviated...
most climacteric symptoms. A group of 35 women with VMS who were 40 to 60 years of age were randomized to undergo a 12-week structured education and 60-minute aerobic exercise program or asked to refrain from the same to ascertain the effects of this program on climacteric symptoms, quality of life, and attitude toward exercise. Ueda observed that the structured education and exercise program had significant effects on climacteric symptoms without any adverse events ($P < .05$).

**Genitourinary Symptoms and Sexual Function**

Young women who experience abrupt menopause as a result of ovarian suppression or chemotherapy are at risk for sexual dysfunction. Dyspareunia is the most frequent sexual dysfunction in young breast cancer survivors, resulting in decreased sexual desire (the second most common sexual problem reported). Both aromatase inhibitors and gonadotropin-releasing hormone (GnRH) analogs are associated with similar degrees of vaginal dryness and dyspareunia; however, these effects are reversible upon withdrawal of the drug. Tamoxifen does not interfere with sexual function because its mild estrogenic action on the vagina prevents postmenopausal vaginal dryness. One study, however, reported a mild decrease in sexual desire in women taking tamoxifen.

Unlike hot flashes, which dissipate and resolve spontaneously in time, atrophic vaginal symptoms and lower urinary tract symptoms require ongoing treatment. Untreated vaginal dryness leads to itching, burning, and compromised sexual activity. Preparatory information about these changes and the provision of resources for coping early in the treatment phase are often helpful. Nonestrogenic water-based vaginal lubricants or polycarbophil moisturizers moderately decrease the symptoms of both vaginal dryness and dyspareunia.

A prospective randomized open-label trial compared a nonhormonal local bioadhesive vaginal moisturizer (Replens) and a vaginal estrogen cream (Premarin). The moisturizer (typically prescribed 3 times a week for at least 1 month) improved vaginal moisture, fluid volume, elasticity, and pH despite a lack of cornification, although to a lesser extent than did the cream.

In an overview on topical estrogen therapy for the management of postmenopausal vaginal atrophy, Al-Baghdadi and Ewies concluded that nonmedicated vaginal lubricants and moisturizers were no better than placebo and less effective than estrogens. Vaginal estrogen preparations not only reversed atrophic changes and relieved associated symptoms but did so while avoiding systemic effects.

Biglia et al evaluated the efficacy and safety of two low-dose vaginal estrogen treatments and a nonhormonal vaginal moisturizer in patients with urogenital atrophy. At 4 weeks, the vaginal symptom scores were significantly better with both vaginal estrogen treatments, with further improvements noted at 12 weeks ($P = .02$). The authors concluded that both low-dose vaginal estrogen treatments were effective at relieving urogenital atrophy and resulted in minimal to no increase in systemic absorption. Nonhormonal moisturizers provided only transient benefit at best.

In a contrasting study, Santen et al and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial suggested that virtually all local estrogen preparations are absorbed systemically to at least some extent (approximately 3%), raising concern about their use in hormone-positive breast cancer patients, especially those receiving aromatase inhibitors. In view of this finding, the International Menopause Society writing group recommends nonestrogenic vaginal preparations to treat vaginal dryness in hormone receptor-positive breast cancer survivors. If the symptoms are refractory to these measures, local lubricants containing low-dose topical estrogen in the form of a slow-release ring or a suppository with the lowest dose possible may be used with appropriate patient counseling.

**Cardiovascular Effects**

Although systemic therapies in early-stage breast cancer treat the tumor effectively and significantly reduce the risk for recurrence, they may be associated with increased cardiovascular risks. Radiation fields including the internal mammary nodes result in a higher radiation dose to the heart and an increased incidence of cardiac mortality. As more node-negative women receive adjuvant chemotherapy, we must acknowledge the possibility that early chemotherapy-mediated gains in survival from breast cancer may be overshadowed by later increases in mortality from cardiovascular events.

Coronary artery disease is also an insidious and potentially fatal consequence of menopausal estrogen decline. Cardiovascular complications related to cancer therapy may be even more prominent among women with existing cardiovascular disease and in those who are at high risk for developing cardiovascular disease. The increased risk for cardiac toxicity in women receiving radiation, anthracyclines (dose-limiting cardiac toxicity), and/or trastuzumab for the adjuvant treatment of breast cancer is well established, especially when these therapies are used concomitantly.

The risk of thromboembolic disease is higher among estrogen receptor-positive early-stage breast cancer patients receiving tamoxifen in the adjuvant setting, regardless of whether it is given before or instead of an aromatase inhibitor. Current data suggest no substantial differences in the risk for ischemic cardiovascular events between aromatase inhibitors and tamoxifen, although investigations are ongoing.

Because of the multimodal treatment of early-stage breast cancer patients, their care requires a multidisciplinary approach to reduce not only the risk for breast cancer recurrence, but also the risk for treat-
ment-related cardiac toxicities, which includes risk assessment, management, and long-term follow-up care. The most important lifestyle modifiers include cessation of smoking, a healthy, lipids-lowering diet, and moderate exercise to control weight. A balanced diet low in saturated fats helps to control blood lipid levels, and consumption of 400 to 800 IU of vitamin E daily exerts a protective effect against coronary artery disease.85

Dexrazoxane is a cardioprotective agent to decrease cardiomyopathy induced by an anthracycline (both doxorubicin and epirubicin) without affecting the response rate to anthracyclines. Marty et al84 evaluated breast cancer patients using anthracyclines with and without dexrazoxane and found that the incidence of cardiac events was 13% and 39%, respectively (P < .001). Routine use of aspirin or antioxidants in low-risk women is not recommended.

Changes in Metabolism

Weight gain appears to occur when women lose fat-free mass after menopause, tend to exercise less, and experience greater increases in fat mass, fasting insulin levels, and waist-hip ratio. Postmenopausal women burn fewer calories at rest than do premenopausal women, suggesting that estrogen helps to control weight.85

Given the negative effects of a breast cancer diagnosis and its treatments on body weight and bone mass, Irwin et al86 randomized 75 breast cancer survivors to either a 6-month controlled aerobic exercise intervention or usual care. Exercisers experienced significant decreases in percent body fat (P = .0022) and increases in lean body mass (P = .047) compared with the usual-care group. BMD was also maintained among exercisers, compared with a loss in BMD among usual-care participants (P = .043).

Schmitz et al87 investigated a resistance training program on body composition. They observed significant increases in lean body mass (0.88 for exercisers vs 0.02 for controls; P < .01) and decreases in body fat (−1.15% for exercisers vs 0.23% for controls; P = .03) with a twice-weekly year-long resistance training program in 81 pre- and postmenopausal breast cancer survivors. In summary, moderate-intensity aerobic exercise produces favorable changes in body composition, which may improve quality of life in young breast cancer survivors.

Musculoskeletal Symptoms

Chemotherapy-induced ovarian failure results in significant bone loss, which can be a debilitating problem for breast cancer survivors. Estrogen exerts a protective effect on bone by stimulating new bone formation and inhibiting resorption.88 The World Health Organization definition of osteoporosis is a BMD of 2.5 or more standard deviations below normal peak bone mass (T score ≤ 2.5), which results in a 4- to 5-fold increased risk of nontraumatic fracture. Osteopenia is defined as a BMD between 1 and 2.5 standard deviations below normal bone mass (T score ≤ 1.0 and ≥ 2.5).89

In a study of 27 premenopausal breast cancer patients receiving CMF chemotherapy, BMD was 14% less among 16 patients who developed amenorrhea than in the remaining 11 patients who resumed menstruation.90 Although tamoxifen stimulates bone formation as a result of its estrogen agonist activity, in premenopausal women it prevents stronger osteogenic activity on bone and leads to bone loss.91 Patients using aromatase inhibitors are at increased risk of bone loss and fractures, and one-third of women treated with aromatase inhibitors suffer from joint pain (arthralgia) and muscle pain (myalgia).92 Although the exact reason for musculoskeletal symptoms is uncertain, it is often attributed to estrogen depletion.

Identification and appropriate management of women at risk for osteoporosis and fractures are essential to prevent skeletal morbidity during chemotherapy and hormonal therapy for breast cancer. Management of osteoporosis is an extensive and detailed topic and beyond the scope of this article. However, general recommendations include regular physical activity as well as impact (walking, running, and aerobics) and nonimpact (resistance training and weight lifting) exercises. Both forms of exercise have been shown to decrease BMD loss by 1% to 1.6%.93 Smoking, alcohol, and caffeine appear to have a negative impact on bone loss. Adequate intake of calcium (1,000 mg/d to 1,500 mg/d) and vitamin D (oral dose of 1,000 U/d) is recommended to provide building blocks for bone deposition.88

Strontium ranelate is an oral antosteoporotic drug that has been shown to increase bone formation in vitro by enhancing osteoblastic cell replication and osteoblastic differentiation, and it also decreases bone resorption by inhibition of osteoclast resorbing activity and osteoclast differentiation.94 In a randomized controlled trial, 1,649 postmenopausal women received 2 g of oral strontium ranelate daily or placebo for 3 years. A relative risk reduction in vertebral fracture was seen in favor of strontium (49% after 1 year and 41% over 3 years), concluding that treatment of postmenopausal osteoporosis with strontium ranelate leads to an early and sustained reduction in the risk of vertebral fractures.95

Gnant et al86 evaluated the effect of zoledronic acid to prevent BMD loss in premenopausal breast cancer patients. The authors observed that bisphosphonates significantly reduced BMD loss at 3 years. To date, however, no trials have shown any benefit to the administration of bisphosphonates to premenopausal patients prophylactically. Hence, until well-conducted studies assess these results, we recommend that alternative measures be adopted for the management of bone function and that bisphosphonates be reserved for the treatment of osteoporosis or pronounced osteopenia.
Fatigue is another common side effect with respect to breast cancer survivors. Although the exact physiology of fatigue in this group is not well understood, it has been proposed that the lack of an efficient hypothalamic-pituitary-adrenal axis following chemotherapy is the cause, resulting in an inability to fight physiological stress with increased proinflammatory cytokines and a flattened cortisol response.

Direct analysis of T lymphocyte receptor (TLR) expression and signaling will provide important avenues for clarifying the basis for aberrant inflammatory signaling in fatigued cancer survivors, which will help define specific molecular targets for interventions that ameliorate fatigue by addressing its inflammatory basis. Development of such therapies could markedly enhance quality of life in the significant fraction of breast cancer survivors who suffer from persistent fatigue.

Conclusions

Given the critical role of reproductive hormones in the initiation and promotion of breast cancer, targeted endocrine therapies form an integral part of breast cancer care. As adjuvant treatment (chemotherapy and/or hormonal therapy) is used more often among patients with early-stage breast cancer at low risk of recurrence, the beneficial effects of such treatment must be balanced against treatment-related detrimental effects, including loss of child-bearing capacity and menopausal complications.

Menopausal symptoms are typically more severe in young breast cancer survivors than in older patients due to the abrupt change in hormonal environment and rapid decrease in estrogen. Research has demonstrated an integral relationship between quality of life, chemotherapy-induced menopause, sexuality, psychosocial distress related to fertility concerns, and uncertainty about the effects of premature menopause on cardiovascular disease and bone loss experienced by many of these young patients. Young breast cancer survivors perceive menopausal symptoms as having a markedly negative impact on their quality of life.

Although hormone replacement therapy may mitigate many of these symptoms, both the Women’s Health Initiative (WHI) trial and the Hormone Replacement Therapy After Breast Cancer: Is It Safe? (HABITS) trial have demonstrated an increase in adverse events among women treated with hormone replacement therapy, and hence they cannot be recommended for managing menopausal symptoms at this time.

Based on current evidence, behavioral modification and yoga may be helpful in mild cases of vasomotor symptoms. Newer antidepressants such as venlafaxine, gabapentin, and fluoxetine are the most promising first-line agents for the management of hot flashes in moderate to severe cases, whereas a stellate ganglion block may have a role in refractory cases. The duration of therapy should be based on the natural history of vasomotor symptoms, which typically resolve within 2 to 3 years of menopause, after which consideration may be given to tapering off or discontinuing these agents. Clinical evidence supporting the role and efficacy of most alternative and complementary therapies for menopausal symptom relief is scarce. Local vaginal moisturizers are useful for the amelioration of most urogenital symptoms. If urogenital symptoms are refractory, moisturizers with low-dose estrogen may be considered with appropriate risk counseling. Bisphosphonates, vitamin D, and calcium supplements are useful in treating osteoporosis, and weight-bearing exercise helps both in decreasing bone mineral density loss and in controlling weight. Patients receiving anthracycline therapy or trastuzumab should be closely monitored for cardiac morbidity, which may be decreased by exercise and dietary modifications aimed at reducing fat and cholesterol levels. Smoking cessation should be recommended to all patients.

Despite these recommendations, many questions remain unanswered. As we seek to help young breast cancer survivors manage menopausal symptoms, there is no single agent that can ameliorate vasomotor, cardiac, skeletal, and sexual issues. It remains unclear whether there is a safe dose or duration of hormone replacement therapy that may be used in these young patients without increasing the risk of recurrence. An improved understanding of who is most likely to develop menopause would help to facilitate decision-making by women and physicians facing these trade-offs. As in all cancer treatments, communication and interaction are central. In our efforts toward personalized medicine, the multidisciplinary treatment team must include not only primary breast surgeons and oncologists but also gynecologists, counselors, and others with expertise in managing physical, psychological, and sexual symptoms as well as fertility concerns. The current level of research into the treatment of menopausal symptoms in young breast cancer survivors needs to be expanded. At present, there is insufficient evidence to support any one agent as a viable alternative to hormone replacement therapy to treat these symptoms. Further study is required into safe and effective treatments for menopausal symptoms and their long-term safety in young breast cancer survivors.

References


