review

Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer

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Background: The purpose of this study was to provide practical, evidence-based guidelines for evaluating and treating common menopausal symptoms following breast cancer.

Methods: Literature review of the causes, assessment and management of menopausal symptoms in breast cancer patients.

Results: A number of nonhormonal treatments are effective in treating hot flashes. Whether pharmacological treatment is given will depend on the severity of symptoms and on patient wishes. For severe and frequent hot flashes, the best data support the use of venlafaxine, paroxetine and gabapentin in women with breast cancer. Side-effects are relatively common with all these agents. For vaginal dryness, topical estrogen treatment is the most effective but the safety of estrogens following breast cancer is not established. There are limited data on effective treatments for sexual dysfunction during menopause.

Conclusion: Menopausal symptoms after breast cancer should be evaluated and managed as warranted using a systematic approach and may benefit from multidisciplinary input.

Key words: atrophic vaginitis, breast cancer, hot flashes, nonhormonal treatment, sexual dysfunction after breast cancer

introduction

Breast cancer is the most common cause of cancer and the second most common cause of cancer mortality in women, affecting up to one in eight women who survive up to the age of 85 years in developed countries (www.cancer.org). Menopausal symptoms are a frequent and troublesome side-effect of breast cancer therapy in women of all ages. Hot flashes, night sweats, sexual dysfunction, poor sleep and tiredness frequently occur following breast cancer treatment [1]. Vasomotor symptoms, particularly hot flashes, appear to be more severe than in women who have not had breast cancer treatment [2–4]. Atrophic vaginitis affects many women using endocrine therapy for breast cancer, particularly those using aromatase inhibitors [5]. Sexual dysfunction may be related to atrophic vaginitis but also to changes in body image, libido and self-esteem [6, 7]. Across all trials of adjuvant endocrine therapy, vasomotor symptoms such as hot flashes are the most common side-effect [8]. Up to 20% of breast cancer patients consider stopping or actually cease endocrine therapy because of menopausal symptoms, primarily hot flashes [9, 10], despite its established role in reducing recurrence. The recommended duration of initial adjuvant endocrine therapy is 5 years and some patients may benefit from a further 5 years of treatment. With such long-term treatment duration, it is critical to address morbidity associated with treatment side-effects in an effort to optimize adherence to therapy and quality of life (QoL).

We will address how vasomotor symptoms (hot flashes and night sweats), atrophic vaginitis and sexual dysfunction relate to breast cancer and its treatment and will present systematic and evidence-based guidance to the assessment and management of these symptoms.

use of estrogen and progestin in breast cancer patients

Estrogen-containing hormone therapy (HT) is the most effective and well-studied treatment for menopausal vasomotor symptoms and atrophic vaginitis in healthy women [11], but the efficacy and safety of HT following breast cancer is not established. HT was not effective in controlling hot flashes in tamoxifen users in one retrospective study [12]. Long-term use
of combined HT is associated with an increased risk of new breast cancers [13]. The fall in breast cancer incidence seen after 2003 in the United States has been attributed by some to the dramatic drop in HT use following revelation from the Women’s Health Initiative study that the risks of HT were not necessarily outweighed by the benefits for healthy women [13–15]. In breast cancer survivors, one randomized controlled trial (RCT) reports a three-fold increased risk of new primary or recurrent breast cancers in HT users [16]. For the two-thirds of women with hormone receptor-positive cancer, a mainstay of treatment is to block the effects of estrogen or reduce its production, and HT may compromise this effect. In addition, combined HT increases breast density, which may compromise the ability of mammography to detect early cancers [17]. Consequently, many women wish to avoid HT following breast cancer [18]. While progestins are effective for menopausal hot flashes following breast cancer [19–21], their safety is not established. Of concern is that the addition of progestin to estrogen for HT appears to increase the risk of a primary breast cancer [22].

tibolone
Tibolone (Livial™, Organon NL) is a synthetic compound with weak estrogenic, progestogenic and androgenic actions. Tibolone (2.5 mg daily) effectively reduces hot flashes [23] and improves vaginal dryness in healthy postmenopausal women. Tibolone may improve sexual function more effectively than standard HT [24]. In the breast, tibolone inhibits the enzyme sulfatase, which regulates the formation of estrogens and hence decreases estrogen stimulation [25]. Tibolone inhibits proliferation of human breast cells and stimulates apoptosis in breast cancer cell lines [26]. The incidence of breast tenderness is low [27] and mammographic density does not increase with tibolone, in contrast to combined HT [28]. The relationship between tibolone use and breast cancer risk is not established. A large observational study suggested an association between tibolone and breast cancer which was less than that seen with combined HT [29]. A large prospective, randomized, placebo-controlled trial of tibolone after breast cancer has recently been halted following reports that the safety of tibolone was not equivalent to placebo (LIBERATE trial, Organon). Tibolone is available in Europe and Australia, but is not in the United States.

Given the evidence for risk or inadequate evidence for safety of available hormonal agents, these are generally avoided following breast cancer. Thus, other options are needed. This presents a clinical conundrum, as nonhormonal therapies have been reported to show only moderate efficacy in treating menopausal hot flashes [30], and there is little research to date to inform the management of other common menopausal symptoms.

evaluation of menopausal symptoms following breast cancer and treatment with nonhormonal therapies
The following guidelines aim to provide clinicians with evidence-based practical guidelines for treatments of hot flashes, symptomatic atrophic vaginitis and sexual dysfunction following breast cancer.

assess the likely cause for the menopausal symptoms

likely causes for hot flashes. Following breast cancer, there are a number of reasons why hot flashes may occur or may worsen (see Figure 1). Breast cancer is the most common malignancy in perimenopausal women, so natural menopausal symptoms may coincide with a breast cancer diagnosis. Stopping HT, the usual recommendation for women diagnosed with breast cancer, will often produce a recurrence of menopausal symptoms [31, 32]. The majority of breast cancers are estrogen and/or progesterone receptor positive and will be treated with endocrine therapies, most may cause hot flashes [9]. In younger women, chemotherapy and endocrine therapy commonly induce temporary or permanent ovarian dysfunction [33] and induce hot flashes [34]. At present, there is no definitive method to distinguish whether menopause will be permanent, although with increasing age permanent ovarian failure is more likely following chemotherapy [35, 36]. In those managed with bilateral oophorectomy, >90% will experience hot flashes as well as other menopausal symptoms which may be particularly severe and long lasting [37].

likely causes for atrophic vaginitis. Low circulating estrogen levels commonly cause atrophic vaginitis. Around 50% of postmenopausal women experience symptoms of vaginal dryness, discomfort, pruritis, dyspareunia, urinary tract infections and urinary urgency attributable to atrophic vaginitis [38, 39]. Unlike menopausal vasomotor symptoms (such as hot flashes), which tend to resolve over time, the number of women affected by atrophic vaginitis may increase over time and symptoms persist indefinitely in some. Premenopausal women who undergo bilateral oophorectomy as treatment for breast cancer or as risk-reducing surgery commonly experience atrophic vaginitis [40]. Reducing circulating estrogens is a cornerstone of treatment for estrogen receptor-positive breast cancer. Both tamoxifen and aromatase inhibitors reduce estrogen exposure to breast tissue, but aromatase inhibitors also inhibit the peripheral conversion of androgens to estrogens by >99% [41]. Tamoxifen has some estrogenic action in the vagina and endometrium and hence causes less vaginal dryness compared with aromatase inhibitors (~8% compared with ~18%) [5, 8]. With the increasing use of aromatase inhibitor (AI), the absolute number of postmenopausal breast cancer patients affected by symptomatic atrophic vaginitis is likely to increase. Symptoms of atrophic vaginitis can have a marked negative effect on QoL in breast cancer patients [42] and may affect cancer treatment compliance.

likely causes for sexual dysfunction. Sexual dysfunction, including problems with lack of lubrication, dyspareunia and decreased libido, and difficulty with orgasm affect at least 50% of women after breast cancer [43]. Sexual dysfunction is common in young women who undergo bilateral oophorectomy for the treatment of breast cancer or as risk-reducing surgery [40]. Sexual and psychological problems are often of complex origin—the diagnosis of breast cancer, change in body image, psychosocial trauma and other.
treatments will affect these. Even in women without breast cancer, the differentiation between poor desire and poor arousal is difficult and often artificial. Direct questioning may be necessary to elicit these symptoms. In younger women, negative body image is linked with mastectomy, hair loss from chemotherapy, concern with weight gain or loss, poorer mental health, lower self-esteem and poor communication with a partner [43]. Sexual difficulties are exacerbated by vaginal dryness, poorer mental health, being married and negative body image [44]. In postmenopausal women, sexual functioning after breast cancer is influenced by age, time since diagnosis, breast conservation, comorbidity, urinary incontinence, perceived health and body image as well as bioavailable testosterone, lutenizing hormone and sex hormone-binding globulin [45]. Sexual function after breast cancer can be assessed in more detail with standardized, validated instruments such as the Sexual Activity Questionnaire [46].

establish the frequency and severity of menopausal symptoms and their impact on QoL

Assessment of menopausal symptoms should include the frequency and severity of vasomotor symptoms (hot flashes and night sweats), symptoms of atrophic vaginitis (vaginal dryness, dyspareunia, urinary urgency and pruritis) and associated menopausal symptoms such as sexual dysfunction, reduced libido and sleep disturbance [47]. Standardized scales are useful to establish the range and severity of symptoms, to evaluate changes over time and to discriminate menopause symptoms from those attributable to other common pathologies in this population. The Greene Scale [48] includes an assessment of sexual function, a key issue for young breast cancer patients with menopausal symptoms [49]. A wide range of symptoms are commonly attributed to menopause, but only vasomotor symptoms, atrophic vaginitis, dyspareunia, sleep disturbances and depression are consistently linked to the menopause transition, on the basis of currently available evidence (www.nia.nih.gov). Other symptoms such as poor libido, lethargy and cognitive changes may be related to other psychological disorders such as anxiety and depression or the effects of treatment independent of ovarian function, such as fatigue or cognitive dysfunction secondary to chemotherapy.

The decision whether to treat menopausal symptoms will depend on their severity, impact on activities of daily living and patient preferences. Hot flashes negatively influence QoL in breast cancer patients [50]. Measuring QoL may facilitate treatment decisions, using menopause specific tools such as the MENQOL [51] or tools developed for breast cancer patients such as the FACT-ES [52]. These symptoms may be best assessed within the setting of a menopause service, particularly one with multidisciplinary input from cancer specialists.
The natural history of vasomotor symptoms following breast cancer is not known, but in spontaneous menopause, vasomotor symptoms tend to decrease in frequency and severity following 12 months of amenorrhea [53, 54]. Less is known about the duration of hot flashes following surgical menopause or following breast cancer treatment. However, it seems reasonable to try to discontinue treatments for hot flashes on an intermittent, perhaps annual basis in order to assess whether symptoms recur.

establish what the patient wishes and expects from intervention

Patient goals and expectations from treatment should be assessed. Many women may not be expecting an intervention which totally resolves their hot flashes and a reduction of ~50% in the severity of symptoms may be acceptable in those looking for nonhormonal treatments [55]. Others may largely be seeking information. For those who do request treatment, it is realistic to explain that treatment options are limited and that no intervention is guaranteed to be both safe and effective following breast cancer [47].

provide information about menopausal symptoms and possible treatments

Younger breast cancer patients have identified fertility and menopause as key areas of unmet need regarding information [49]. There is still a paucity of information about menopause and menopausal symptoms following breast cancer and for some women receiving high quality and personalized information may be all that they need [47]. Ideally, a specialist tailored service combining clinical expertise, written information and including a specialist nurse allows coordination of care and avoids patients being given conflicting advice about management of their symptoms. Treatment information should not be biased toward the use of HT and should ideally not be produced by pharmaceutical companies with a conflict of interest. Many national menopause societies (including the North American, British and Australasian menopause societies) produce high-quality information which is available to members. A menopause information booklet for young women following breast cancer is in preparation (Hickey, Saunders, White, in preparation).

assess lifestyle and environmental factors that may be exacerbating hot flashes

Little is known about factors regulating hot flashes arising from endocrine therapy for breast cancer. Following spontaneous menopause, hot flashes may be triggered by stimuli such as spicy food, hairdryers or anxiety. Some women find it helpful to dress in layers so that clothes can easily be removed during hot flashes, to avoid overheating and to wear natural fibers, and use cold packs intermittently. For individual women, identifying potential triggers to hot flashes in a hot flash diary may help in modifying symptoms in the future.

It is uncertain whether lifestyle modifications such as exercise, achieving a healthy weight and stopping smoking will improve hot flashes. However, hot flashes may be more severe in overweight women and in smokers [56]. There is evidence that exercise may reduce the risk or ameliorate hot flashes in some women [57] and improve QoL [58]. Exercise may also reduce the risk of breast cancer recurrence [59].

treatment of menopausal symptoms after breast cancer

Evaluating the cause for menopausal symptoms, assessing their severity and impact on QoL and providing information and understanding patient wishes, all will provide guidance regarding the need for treatment (see Figure 2). For severe symptoms likely to be due to endocrine therapy, there may be a place for modifying or, in some cases, ceasing endocrine treatment. Trials of AI versus tamoxifen suggest a very modest difference in menopausal side-effects, with tamoxifen users reporting slightly more hot flashes [60]. Anecdotally, hot flashes may improve in some women who change from AI to tamoxifen or visa versa, if this is appropriate from a disease treatment standpoint. For many women, hot flashes improve over time and several studies have revealed a marked placebo effect with intervention, possibly because of spontaneous resolution of symptoms over time with ongoing tamoxifen treatment. Since vaginal dryness is more common with AIs [61], changing to tamoxifen may be helpful [62].

complementary and alternative therapies for menopausal symptoms after breast cancer

A large number of studies have been carried out on complementary and alternative treatments for menopausal hot flashes, but overall the published data do not support the efficacy of these products and there are few data on safety [63, 64]. These studies have been extensively reviewed elsewhere [30], but a recent randomized trial comparing black cohosh, multibotanicals with black cohosh or with soy, HT or placebo demonstrated in healthy menopausal women that symptoms worsened with the multibotanical plus soy intervention and that black cohosh was of no benefit. Only estrogen was an effective intervention [65]. The safety of these treatments following breast cancer is not established, and there have now been several reports of liver failure following use of black cohosh [64]. For those with mild vasomotor symptoms who request ‘natural’ treatment, high dose vitamin E (800 IU/day) has shown limited efficacy in reducing hot flashes [66]. However, supplemental vitamin E at >400 IU/day has been linked with an increase in all-cause mortality [67].

nonpharmacological treatments

There are very limited clinical data on nonpharmacological treatments such as behavioral interventions, acupuncture in the management of menopausal hot flashes, and few published RCT of these interventions following breast cancer [30, 63]. Studies with acupuncture have shown mixed results. One RCT suggests that acupuncture is superior to placebo but less effective than estrogen for hot flashes [68] and another that
Acupuncture may improve sleep quality [69]. Recent RCT of 'medical versus sham' acupuncture have failed to demonstrate a benefit [70, 71]. If sterile needles are used, acupuncture is unlikely to cause harm, although breast cancer survivors with prior axillary surgery should avoid the affected arm.

One RCT of paced respiration training versus biofeedback control showed a significant benefit for paced respiration and one RCT of trained relaxation techniques for 20 min/day versus symptom charting (control) also showed a significant beneficial effect [72]. The mechanisms by which these treatments work is not known but adequate training is clearly central to efficacy, and it is unlikely to be helpful to advise patients with hot flashes to 'relax' without structured guidance. A recent pilot study of hypnosis showed a 59% decrease in daily hot flashes and significant decrease in the degree to which hot flashes interfered with daily activities for all measures including work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life and overall QoL [73].

One RCT has demonstrated significant improvements in menopausal symptoms and sexual function in breast cancer survivors following a comprehensive menopausal assessment delivered by a nurse practitioner, focused on symptom assessment, education, counseling and, as appropriate, specific pharmacologic and behavioral interventions for achieving relief of symptoms improved and sexual functioning [42, 74].

**Guidelines for practice**

Vitamin E and/or lifestyle modifications may be appropriate for women with mild or moderate symptoms who wish to avoid pharmacological therapies.

**Pharmacological therapies for vasomotor symptoms**

Estrogen reduces hot flashes by a mean of two to three per day [30]. Relatively few studies have compared nonhormonal therapies with estrogen or directly compared nonhormonal therapies with each other, making it difficult to establish the relative efficacy and tolerability of these treatments. Some studies of nonhormonal therapies have included mixed populations of breast cancer patients, some of whom are taking tamoxifen and some who have experienced a chemotherapy or surgically induced menopause. Differences between these populations may limit meaningful comparisons between treatments. A major consideration is the robust and persistent nature of the placebo response (up to 70% in some studies) in...
the treatment of hot flashes [30]. No conclusions regarding treatment efficacy can be drawn unless studies are of suitable design, size and duration to demonstrate a genuine clinical effect (http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-08-004.html).

**selective serotonin reuptake inhibitors/serotonin noradrenaline reuptake inhibitors**

Selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) are widely used and have been extensively tested for menopausal hot flashes in women who are breast cancer survivors. Their mechanism of action is not clear and appears to be independent and more rapid than their antidepressant effect [75]. Side-effects may include headache, nausea, reduced appetite, gastrointestinal disturbance, dry mouth, anxiety/agitation, sleep disturbance and sexual dysfunction, which are commonly mild and short lived. Adverse events cause ~10% to 20% of individuals to withdraw from treatment [30], but are less likely in women who are taking low doses. Several SSRIs (paroxetine, fluoxetine and citalopram) and SNRIs venlafaxine and desvenlafaxine have been shown to be more effective than placebo in reducing menopausal hot flashes in short-term studies of women with breast cancer [76, 77]. Overall, the clinical efficacy of treatment with antidepressants appears modest compared with estrogen although there are currently no published head to head studies. Further, there is a marked variability of response with some women experiencing an exacerbation of vasomotor symptoms [78]. The popularity of SSRI/SNRI for treating hot flashes is reflected in the rise in prescription of these antidepressants which mirrors a fall in HT use [79]. The optimal duration of treatment is unknown and it is recommended that these agents should be stopped gradually to prevent discontinuation symptoms which are primarily an issue with the short-acting agents (paroxetine and venlafaxine).

SSRIs. SSRIs are superior to placebo in treating hot flashes over a 4- to 6-week period. SSRIs that have been evaluated to varying degrees include fluoxetine, citalopram, paroxetine, and sertraline. Mirtazapine is another serotonin-based antidepressant that has undergone preliminary investigation for treatment of hot flashes.

Fluoxetine and citalopram. In breast cancer patients, fluoxetine decreased hot flash composite score by 50% versus 36% for placebo. There was a marked variability in outcome with 42% decreased hot flash composite score by 50% versus 36% for fluoxetine and citalopram. In breast cancer patients, fluoxetine is the optimum dose.

Sertraline. In the general population, mixed results have been seen with sertraline (50–100 mg) for hot flashes [86, 87]. In tamoxifen users, sertraline 50 mg was superior to placebo in reducing hot flashes but did not affect QoL measures [88]. Other studies have suggested that while some women may benefit from sertraline, there is substantial variability in results [78].

Mirtazapine. Pilot studies of mirtazapine (15–30 mg/day) for hot flashes have been encouraging, but tolerance of this SSRI is limited by side-effects, primarily somnolence and weight gain [89, 90].

SNRI—venlafaxine and desvenlafaxine. A placebo-controlled trial of survivors of breast cancer (69% of whom were taking tamoxifen) demonstrated that venlafaxine was more effective than placebo in the treatment of hot flashes after 4 weeks. There was a median reduction in hot flash score of 37% in those taking 37.5 mg/day, 61% reduction in those taking 75 mg/day and 150 mg/day (compared with a 27% reduction with placebo). Side-effects, primarily dry mouth, decreased appetite, nausea and constipation were dose related and it was concluded that 75 mg was the optimum dose [91]. Sexual dysfunction can occur with SSRI/SNRIs but in breast cancer patients libido increased in a trial of venlafaxine for hot flashes [80]. One long-term studies of venlafaxine 75 mg over 12 weeks reported a significant beneficial effect of reducing hot flashes on daily living in the treatment group [92]. In breast cancer patients, a direct comparison demonstrated that short-term venlafaxine is more effective than clonidine in reducing the frequency and severity of hot flashes [93].

A recent randomized controlled trial of desvenlafaxine succinate, the major active metabolite of venlafaxine, demonstrated a significant reduction in hot flashes at 12 weeks of 64% with the 100 mg dose compared with 51% with placebo [77]. Half those in the desvenlafaxine-treated group experienced a 75% reduction in the number of hot flashes at 12 weeks compared with 29% with placebo. Desvenlafaxine showed rapid onset of efficacy and was well tolerated. Clinical trials to evaluate the role of desvenlafaxine in breast cancer survivors are planned.

**possible interaction of SSRI/SNRIs with tamoxifen**

Some SSRIs/SNRIs may interfere with breakdown of tamoxifen to its active metabolite 4-hydroxy-N-desmethyl tamoxifen (endoxifen) by inhibiting the cytochrome P450 2D6 (CYP2D6) enzyme [94]. *In vitro* data indicate that fluoxetine and paroxetine are potent inhibitors of CYP2D6, while desvenlafaxine, venlafaxine, sertraline and citalopram have weak or no effects, and mirtazapine does not inhibit the enzyme [95–97]. Clinical studies have demonstrated that CYP2D6 inhibition is variable and may be related to baseline isoenzyme activity. The clinical effect of tamoxifen is likely to be due to
multiple metabolites and the clinical implications remain unclear but in the light of these concerns SSRI/SNRIs that are strong inhibitors of CYP2D6 should be avoided in patients on tamoxifen where possible. Since citalopram and venlafaxine appear to have less impact on the endoxifen concentration, they may be better therapeutic alternatives in breast cancer patients receiving tamoxifen [76].

gabapentin

Gabapentin is a gamma-aminobutyric acid currently licensed for the treatment of epilepsy and chronic pain in several countries. There have been fewer studies of gabapentin for hot flashes compared with SSRI/SNRIs, but the current evidence suggests that gabapentin may be at least as effective, though head to head studies are lacking. Gabapentin (900 mg/day) is effective in reducing hot flashes in breast cancer patients [98–100] in women with a chemically and/or surgically induced menopause [101] and in symptomatic women during spontaneous menopause [102, 103]. In women with spontaneous menopausal symptoms, gabapentin had a rapid onset of action reducing hot flashes by 51% compared with 26% on placebo flashes from 8.5 to 4.5/day over 4 weeks [103]. These findings are similar to those seen in women with chemically or surgically induced menopause (54% versus 31% with placebo) and in breast cancer patients, the majority of whom are taking tamoxifen (49% compared with 21%). Gabapentin is the only nonhormonal treatment to have demonstrated equivalent efficacy to estrogen in the treatment of hot flashes [102]; however, this study included only 20 subjects in each arm. Unlike the SSRI/SNRI, gabapentin has no known drug interactions, no absolute contraindications, does not cause sexual dysfunction and appears to be well tolerated for this indication [101, 103]. Further, it does not have a withdrawal syndrome like some SSRI/SNRIs (paroxetine and venlafaxine). Side-effects including dizziness, unsteadiness and drowsiness affect up to 20%, but appear to markedly improve after the first week of treatment and are largely resolved by week 4 and these did not appear sufficient for women to discontinue gabapentin [103].

guidelines for practice. For breast cancer patients with moderate to severe hot flashes, it is reasonable to consider either SSRI/SNRIs or gabapentin as first-line approach. There are few head to head studies between preparations, but venlafaxine (37.5 mg daily increasing to 75 mg daily after 1 week) or paroxetine (10 mg daily increasing to 20 mg daily after 1 week if symptoms persist) have been extensively studied and appears effective, at least in the short term and adequately tolerated (see Table 1). If venlafaxine is not effective, it is reasonable to consider trying paroxetine and vice versa. In those who are taking tamoxifen, preparations which induce CYP2D6 (e.g. paroxetine and fluoxetine) should be avoided. SSRI and SNRI are contraindicated in women taking monoamine oxidase inhibitors and should be used cautiously or potentially avoided in women with bipolar disorder/manic depression because of the risk of inducing mania. If there is no response in 4 weeks, then the treatment is unlikely to be effective. Gabapentin appears to be an effective alternative and may be used as an alternative first-line treatment or instead of SSRI/SNRIs in women who did not respond to or who cannot take SSRI/SNRIs. There does not appear to be a benefit of adding gabapentin to SSRI/SNRI [99]. Gabapentin may also be considered if sexual dysfunction is a problem before SSRI/SNRIs or develops on this therapy.

clonidine

Clonidine is a centrally acting α-agonist agonist licensed for the treatment of hypertension that reduces vascular reactivity. A range of doses and delivery systems (oral and transdermal) have been studied and clonidine appears to have a mild to moderate efficacy in the treatment of menopausal hot flashes, reducing hot flashes by up to 46% [30]. In tamoxifen users with a history of breast cancer, a reduced frequency and severity of hot flashes has been seen with 0.1 mg/day of transdermal clonidine [104] or 0.1 mg/day oral clonidine [105]. Adverse

Table 1. Relative efficacy and tolerability of nonhormonal preparations for menopausal hot flashes

<table>
<thead>
<tr>
<th>Efficacy: mean difference in daily number of hot flashes versus placebo (95% confidence interval)</th>
<th>Clonidine</th>
<th>SSRI/SNRI</th>
<th>Gabapentin</th>
</tr>
</thead>
<tbody>
<tr>
<td>[30]**</td>
<td>-0.95 (-1.44 to -0.47)</td>
<td>-1.13 (-1.70 to -0.57)</td>
<td>-2.05 (-2.80 to -1.30)</td>
</tr>
<tr>
<td>Speed of onset</td>
<td>Rapid (&lt;1 week)</td>
<td>Rapid (&lt;1 week)</td>
<td>Rapid (&lt;1 week)</td>
</tr>
<tr>
<td>Duration of action</td>
<td>Up to 8 weeks</td>
<td>Up to 6 weeks</td>
<td>Up to 12 weeks</td>
</tr>
<tr>
<td>Discontinuation due to side-effects in clinical trials for hot flashes</td>
<td>40% [105]</td>
<td>10%–20% [106]</td>
<td>10% [103]</td>
</tr>
<tr>
<td>Common side-effects</td>
<td>Dry mouth and insomnia or drowsiness</td>
<td>Dry mouth, blurred vision, sexual dysfunction</td>
<td>Dizziness, drowsiness, unsteadiness</td>
</tr>
<tr>
<td>Efficacy in the treatment of concurrent depression</td>
<td>Not established</td>
<td>Good</td>
<td>Not established</td>
</tr>
<tr>
<td>Efficacy in the treatment of concurrent neuropathic pain</td>
<td>Not established</td>
<td>Not established</td>
<td>Good</td>
</tr>
</tbody>
</table>

*Interpretation of the findings from this meta-analysis is limited by the fact that baseline hot flash data were not collected.
effects are common with clonidine including dry mouth and insomnia or drowsiness. Doses used for treating hot flashes do not appear to affect blood pressure [30].

**guidelines for practice.** Clonidine may be useful in the treatment of mild to moderate hot flashes. Clonidine may also be suitable for those who wish to avoid other agents (see Table 1).

**side-effects of treatment**

When treating hot flashes with pharmacological agents, the risks and benefits of treatment, including the impact on QoL, need to be fully considered by both the health provider and the patient. SSRI, SNRI and gabapentin are commonly associated with side-effects. However, side-effects are typically transient and dose related and doses used to treat hot flashes are generally lower than those used for the conventional indications. Further, a distinction should be made between the percentage of subjects who experience side-effects and those for whom the balance of benefit and unwanted effects is such that they chose to withdraw from treatment. While side-effects have limited the use of clonidine for hot flashes [75], in trials of SSRI, SNRI for hot flashes side-effects have lead ~10% to 20% of subjects to withdraw from treatment [106]. Common unwanted effects include asthenia, constipation, dry mouth, nausea, dizziness, insomnia and somnolence. One recent large study of desvenlafaxine over a 52-week period showed no difference in discontinuation due to side-effects between active treatment and placebo after the first week of treatment [77]. However, an increased incidence of hypertension and cardiovascular events in the active treatment group is not fully accounted for. Discontinuation syndromes may also occur when some SSRI and SNRI are abruptly discontinued and are most marked with the short-acting agents (desvenlafaxine, venlafaxine and paroxetine). In large studies of gabapentin for hot flashes, withdrawal from treatment due to side-effects (primarily somnolence and dizziness) seem to be less frequent [100]. Discontinuation symptoms with gabapentin may occur but are uncommon [107].

Clinicians should discuss with women the potential benefits and side-effects of specific agents. A woman who starts a nonhormonal agent may recognize within days whether the agent is effective in alleviating her symptoms or whether it is associated with bothersome side-effects or both.

**treating other common menopausal symptoms after breast cancer**

Depending on the cause for the menopausal symptoms and the nature of concurrent endocrine treatments, breast cancer patients may experience a range of menopausal symptoms. Two of the most common associated symptoms are vaginal dryness and sexual dysfunction.

**atrophic vaginitis following breast cancer**

Symptomatic atrophic vaginitis affects around one-third of postmenopausal women [108]. Unlike hot flashes, these symptoms may get worse with time since menopause. Following breast cancer, use of aromatase inhibitors is associated with a significantly greater incidence of vaginal dryness compared with tamoxifen [61]. Increasing use of AIs means that the number of women complaining of vaginal dryness following breast cancer treatment is likely to increase [109].

**treating atrophic vaginitis following breast cancer**

Both systemic and vaginal estrogens are effective in relieving symptomatic atrophic vaginitis, and there is some evidence that vaginal estrogens may be superior to systemic treatment for vaginal dryness [110]. Vaginal treatment does not alter liver metabolism and this allows the use of lower doses of estrogen compared with systemic therapy [111]. Nonhormonal vaginal lubricants such as Replens® are also helpful for some women but are not as effective as topical estrogens [108].

While systemic estrogens are avoided following estrogen receptor-positive breast cancer, vaginal estrogens have been widely used to treat symptoms of atrophic vaginitis [112]. Small retrospective studies in breast cancer patients suggest that vaginal estrogens do not adversely affect outcome [113]. Similarly, vaginal estrogens were permitted in the placebo–controlled MA.17 trial of letrozole as extended adjuvant therapy following 5 years of tamoxifen without seeming to interfere with the observed efficacy [114].

Vaginal estrogens can be administered in the form of an estradiol-releasing vaginal ring, estrogen-based vaginal creams, pessaries-containing estriol and a slow-release 17β estradiol tablet. Recently, Kendall et al. [41] have shown that Vagifem increases circulating estradiol in AI users within 2 weeks of use. They propose that vaginal estradiol may reverse the efficacy of AI in suppressing estrogens and hence should be avoided. More information is needed about the safety of vaginal estrogens following breast cancer. Vaginal preparations containing estriol are as effective as those containing estradiol in treating symptomatic women [115]. Estradiol is a much more potent estrogen than estriol [116]. In the steroid pathway, estriol arises from estrone and cannot be converted to estradiol. Hence, if vaginal estrogens are to be used following breast cancer, particularly in AI users, then estriol-containing preparations may be preferable. New approaches such as pilocarpine are under investigation [117].

If vulval pruritis is a problem, systemic dermatological disorders should be excluded. Enquire specifically about vaginal discharge, e.g., whether it has a specific odor or is pruritic, and take swabs from vulva and vagina to exclude infection if suspected. Intermittent vulvovaginal soreness may indicate a herpetic lesion which requires a special culture medium and fluid from the lesion to make the diagnosis. If urinary frequency or recurrent urinary tract infection are a complaint, bladder hygiene protocols may be helpful [118].

**guidelines for practice.** Nonhormonal agents such as Replens™ or Sylk™ may be effective. If not, vaginal estrogens can be considered. In those taking AI, an agent containing estriol (such as Ovestin™) will not increase circulating estradiol. However, their safety is still not established and patients should be informed that vaginal estrogens may partly counteract the effects of AI.
sexual dysfunction following breast cancer

Both the diagnosis and treatment of breast cancer may impact negatively on sexual function in women [43]. These are likely to vary according to age, menopausal status and relationship factors as well as the nature of surgical and endocrine treatments [8]. Despite the prevalence of female sexual dysfunction after breast cancer, there is a paucity of data showing effective intervention strategies and lack of approved treatment options for hypoactive sexual desire disorder (HSDD) in women. Sensitive but direct questioning about sexual function may be needed since patients may be reluctant to raise these issues themselves. Where vaginal dryness contributes, vaginal estrogens can be considered as discussed above or simple lubricants such as Replens or Sylk may be helpful [119]. Consider stopping SSRI/SNRIs since these may cause/complicate sexual dysfunction by reducing libido and causing anorgasmia. Testosterone therapy is offered by some clinicians for HSDD but its safety and efficacy have not been well established [120] in healthy women or after breast cancer [121]. Testosterone may not be effective without adequate circulating estrogen. For these reasons, testosterone or other androgens cannot be recommended after breast cancer. There is some evidence that sexual problems after breast cancer tend to decrease over time [43]. Type 5 phosphodiesterase inhibitors such as sildenafil have undergone extensive study in the setting of female sexual dysfunction with mixed results. Although animal and human studies have shown increases in vaginal blood flow, this has not translated into a perception of improved sexual response in placebo-controlled studies in women [122]. Small studies suggest that the antidepressant bupropion may improve sexual function in breast cancer survivors [123] but larger trials are needed to confirm this. Sex therapy may be helpful when to consider using estrogen for menopausal symptoms following breast cancer

For all women, the use of hormonal treatments for menopausal symptoms is an issue of balancing QoL against risk. For women with no history of breast cancer, the risks of HT appear minimal, particularly for low-risk women taking HT for ≤5 years [13]. Following breast cancer, current guidelines are to avoid estrogen and tibolone since these may increase the risk of breast cancer recurrence [124]. However, for some women, the benefits of estrogen in terms of symptom reduction and QoL may outweigh these risks. Ultimately, the decision to take estrogen for severe menopausal symptoms should rest with the patient who is fully informed regarding the potential adverse effects on disease prognosis. A benefit of multidisciplinary care is the ability to calculate individual patient recurrence risks and to use this information in decision making about treatment choices. In addition, if endocrine therapies are producing severe menopausal symptoms with relatively small benefits in terms of recurrence or survival, the multidisciplinary (MD) team may advise that these can reasonably be stopped or adjusted. For women with advanced breast cancer, the issues of QoL are paramount and HT may be considered following discussion with her carers.

conclusions

Menopausal symptoms, in particular hot flashes, night sweats, vaginal dryness and sexual dysfunction, are common following breast cancer treatment. Increasing numbers of studies are reporting treatments for menopausal hot flashes following breast cancer, but relatively few studies have addressed the management of other common menopausal symptoms. Of the prescribed and available medications, venlafaxine, paroxetine and gabapentin appear to be effective in reducing the frequency and severity of hot flashes. The SNRI desvenlafaxine is currently being investigated for treatment of VMS in women with breast cancer, but this agent is not yet approved for use. Side-effects are relatively common with all these agents but in most studies side-effects have not been an indication for women to discontinue medication when hot flashes are effectively being managed. It is disappointing that despite the prevalence of hot flashes in all women, the mechanisms regulating flashes are so poorly understood. There appears to be a gap in clinical service provision for women with menopausal symptoms following breast cancer and further research is warranted.

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references


